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Review Article

Overview of systematic reviews with meta-analyses on acupuncture in post-stroke cognitive impairment and depression management

Caroline Yik-fong Hung^{a,b}, Xin-yin Wu^{c,*}, Vincent Chi-ho Chung^{b,d},
Endy Chun-hung Tang^{a,b}, Justin Che-yuen Wu^a, Alexander Yuk-lun Lau^{a,b}

^a Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

^b The Hong Kong Institute of Integrative Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

^c Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, Changsha, China

^d Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, School of Public Health, Prince of Wales Hospital, Shatin, Hong Kong

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ABSTRACT

Background: Acupuncture has been using as an alternative non-pharmacological therapy in the management of post stroke depression and cognitive impairment but its effectiveness and safety remain controversial. We conducted an overview of systematic reviews with meta-analyses to evaluate the evidence on the effect of acupuncture in the treatment of stroke with conventional medicine intervention. **Methods:** Systematic reviews summarized the treatment effects of acupuncture for post stroke cognitive impairment and post stroke depression were considered eligible. Methodological quality of included systematic reviews was assessed using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2).

Results: Four systematic reviews on post stroke cognitive impairment and ten systematic reviews on post stroke depression with good methodological quality were included. Meta-analyses revealed that acupuncture plus cognitive rehabilitation; and acupuncture or moxibustion plus cognitive rehabilitation, versus cognitive rehabilitation demonstrated statistically significant increase in Mini-Mental State Examination scores in compared to cognitive rehabilitation after 4 weeks treatment [Pooled weighted mean difference (WMD) = 3.14, 95% confidence interval (CI) = 2.06 to 4.21, I² = 36%]; and (Pooled WMD = 3.22, 95% CI = 2.09 to 4.34, I² = 0%). Furthermore, acupuncture versus antidepressant demonstrated statistically significant improve depression measured by increasing in 17-item Hamilton Depression Rating Scale in comparing to cognitive rehabilitation after 2 weeks treatment (Pooled WMD = -2.34, 95% CI = -3.46 to -1.22, I² = 5%). Acupuncture usage was not associated with increased risk of adverse events.

Conclusions: Acupuncture is safe and improves cognitive function and depressive disorder without obvious serious adverse events for post stroke patients.

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1. Introduction

Incident stroke could lead to emotional changes and an acute decline in cognitive function.^{1,2} The emotional changes after stroke are thought to result from disruption of prefrontal system and

lesions damaging the striato-pallido-thalamo-cortical pathways^{3–5} while the decline in cognitive function after stroke is due to the reduction of regional blood flow blocked by recurrent and multiple infarctions.⁶ Post stroke depression (PSD) is associated with poor functional outcomes, and consistently high mortality rates^{7,8} and post-stroke cognitive impairment is associated with increase mortality,⁹ hospitalization,¹⁰ disability,¹¹ and poorer quality of life.¹² It has been found that cognitive performance was associated with symptoms of depression and with self-reported cognitive function on patient after stroke.¹³

In the management of post stroke depression, it has been suggested that Selective Serotonin Reuptake Inhibitors (SSRIs) is the

* Corresponding author at: 5/F, Xiang-Ya School of Public Health, Central South University, Kai-Fu District, Chang-Sha, Hu-Nan, China.

E-mail addresses: carolinehyf@gmail.com (C.Y.-f. Hung), xinyin.wu@csu.edu.cn (X.-y. Wu), vchung@cuhk.edu.hk (V.C.-h. Chung), endytang@gmail.com (E.C.-h. Tang), justinwu@cuhk.edu.hk (J.C.-y. Wu), alexlau@cuhk.edu.hk (A.Y.-I. Lau).

first line treatment.⁸ It has been proven that SSRI (Fluoxetine) had lower rates of depression and better motor function as compared to the placebo group at 3 months.¹⁴ Whereas, drug therapy of post-stroke cognitive impairment remains unclear.⁶ Currently, there are no evidence-based interventions that can successfully treat post-stroke cognitive decline. Alternatives therapy such as cognitive rehabilitation may be beneficial for enhancing their attention deficits and activities of daily living (ADL) immediately following less than 3 months and 6 months of treatment respectively.¹⁵ However, there is still insufficient evidence and unclear effectiveness of cognitive rehabilitation for improving individuals cognitive function.^{16,17}

Acupuncture has been using as an alternative non-pharmacological therapy that involves the insertion of needles into acupuncture points in the skin as to correct imbalances of the flow of Qi through meridians.¹⁸ Preclinical evidence demonstrated that acupuncture associates with the potential of DNA methylation and histone modifications of brain-derived neurotropic factor in epigenetic mechanism that may produce antidepressant effect in animal study.^{19,20} Acupuncture incorporation with electrotherapy also improves cognitive function and synaptic plasticity²¹ by attenuating left cortex, hippocampus, corpus striatum, and thalamus lesions and increasing the density of dendritic spines and number of CA1 synapse in the hippocampus of middle cerebral artery occlusion induced cognitive deficit rats.^{22,23} Many clinical studies have suggested the use of acupuncture in the management of post stroke depression^{24–32} and cognitive impairment.^{33–38} These trials were implemented with different methodologies and outcome measures. The treatment effects of acupuncture on post-stroke cognitive impairment and depression were inconclusive from systematic reviews.^{39–42} Systematic reviews have been conducted to examine the potential relative benefits or harms of acupuncture in the treatment of post-stroke cognitive impairment and depression. However, the treatment benefits of acupuncture on post-stroke cognitive impairment and depression are still unclear due to the differences of methods, and quality of systematic reviews. We conduct an overview of systematic reviews to overcome the gaps by composing, appraising, and summarizing all relevant systematic reviews into a single document, which has potential usefulness for therapeutic and policy decision-making. Furthermore, there has been no overview of systematic reviews to analyze the effectiveness and safety of acupuncture for improving cognitive function and depression in post-stroke patient. In this overview of systematic reviews, we aim to summarize the best available clinical evidence on the effectiveness and safety of acupuncture on post-stroke cognitive impairment and depression management. This study will provide a comprehensive synthesis of clinical evidence on acupuncture on post-stroke cognitive impairment and depression receiving routine stroke care, which may help in identifying treatment alternatives with acupuncture on post-stroke cognitive impairment and depression management so as to provide a basis to develop an integrative medicine model for post-stroke cognitive impairment and depression.

2. Methods

2.1. Search strategy

A literature search of online databases MEDLINE, Excerpta Medica dataBASE (EMBASE), Cochrane Database of Systematic Reviews (CDSR) and Database of abstracts of reviews of effects (DARE) and Chinese databases [Chinese Biomedical Database (CBM), Wan Fang Digital journals and Taiwan Periodical Literature Databases] from inception to August 2017 was performed. Specialized search

filter for reviews was used for MEDLINE and EMBASE.^{43,44} Detailed searching strategies were reported in [Supplement 1](#).

2.2. Eligibility criteria

2.2.1. Types of studies

We included systematic reviews (SRs) with meta-analysis of randomized controlled trials (RCTs) in this overview. RCTs are trials that group patients by simple random methods. We excluded SRs with meta-analysis of observational studies, which included case-control studies, cross-sectional studies, longitudinal studies, and cohort studies. We used the Cochrane Collaboration definition for systematic review, that is a form of publication that searches, identifies, appraises, and collates all empirical evidence according to the pre-specified eligibility criteria to answer the objectives or specific research questions, using systematic methods to minimize risk of bias.⁴⁵ We only included the SRs that used validated method to measure the outcome. We evaluated all possible clinical evidence in the use of acupuncture versus conventional intervention for post-stroke cognitive impairment management and the use of acupuncture versus anti-depressant for post stroke depression treatment.

2.2.2. Subjects

We included patients diagnosed with any type of stroke by World Health Organization stroke criteria⁴⁶ (ischemic stroke, acute ischemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, acute stroke, progressive cerebral infarction, acute cerebral infarction, cerebral haemorrhage, and cerebral ischemic stroke) or America stroke association criteria⁴⁷ (ischemic, haemorrhagic, transient ischemic) and received acupuncture along with conventional intervention (cognitive rehabilitation and conventional therapy) in post-stroke management. The participants in the included reviews were not limited by gender, age, course of the disease, and treatment duration.

2.2.3. Intervention and control

We included peer-reviewed full articles published in English and Chinese language. Subjects were defined by a diagnosis of stroke^{46,47} and were using acupuncture and conventional intervention. Acupuncture included (needle) acupuncture, electroacupuncture, and moxibustion therapy. The specific types of (needle) acupuncture and moxibustion referred to 'Acupuncture and moxibustion law, 7th edition' as the selection criteria.⁴⁸ We included acupuncture interventions regardless of needle material, treatment points (e.g., single head acupuncture treatment or scalp), the implementation of techniques, selected points to implement the hands of time, leaving the needle time and treatment is not limited. Cognitive rehabilitation, which included physiotherapy, occupational therapy, speech therapy, and nursing care, was used in the management of post-stroke cognitive impairment. Conventional therapy included use of drugs, such as antiplatelet agents, anticoagulants, fibrinogen-depleting agents, and volume expansion and vasodilators, and neuroprotective agents; but not including thrombolytic agents. Conventional care also included treatment for stroke related complications, such as brain edema, seizures, dysphagia, pneumonia, voiding dysfunction and urinary tract infections, and deep vein thrombosis. Anti-depressants were included monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs) and SSRIs for the treatment of post stroke depression. In the management of post-stroke cognitive impairment, two types of comparisons were considered to be included in this overview of SRs: (1) acupuncture plus cognitive intervention versus cognitive intervention only; and (2) acupuncture plus cognitive intervention versus placebo of acupuncture plus cognitive intervention.

For the treatment of post stroke depression, two types of comparisons were considered to be included in this overview of SRs: (1) acupuncture versus anti-depressant only; and (2) acupuncture versus placebo of acupuncture plus anti-depressant.

2.3. Selection of systematic reviews

2.3.1. Data extraction

We extracted the following data from full-text articles: (i) basic characteristics of the SRs, searching date of the study, number of included studies, total number of patients and bibliographic information; (ii) detail information on study design and patient, intervention, control and outcomes; (iii) meta-analysis results of the including pooled effects of each comparison for each outcome; and (iv) results of methodological quality assessment.

2.4. Quality assessment of systematic reviews

Methodological quality of all included SRs was assessed using Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2).⁴⁹ The judgments were given in 11 items as 'yes', 'no', 'cannot answer' or 'not applicable' based on the information provided. The detail description of AMSTAR 2 is provided in Table 2. Two researchers conducted literature selection, data extraction and methodological quality assessment independently. Any disagreement was discussed with consensus. A third reviewer assessed unresolved discrepancy when necessary.

2.5. Data analyses

The acupuncture treatments were assessed at SRs level. The pool effect estimates were extracted from each meta-analyses. We extracted pooled relative risk (RR) or pooled odds ratio (OR) for dichotomous outcomes, and pooled weighted mean difference (WMD) for continuous outcomes with 95% confidence interval (CI). For publication bias, funnel plot results would be reported if it was being mentioned in the included SRs. Heterogeneity across RCTs was reported by describing I^2 values reported in included meta-analysis; I^2 values of 0–25%, 26–50%, and above 50% represented low, medium and high heterogeneity, respectively.⁵⁰

2.6. Outcome

We evaluated all possible clinical evidence in the use of acupuncture along with conventional medicine intervention for post-stroke cognitive impairment and depression. Cognitive function and depressive disorder were the two major outcomes for evaluating the effectiveness of acupuncture. The primary clinical outcomes were cognitive function improvement and depression symptoms improvement. Cognitive function was assessed at the end of treatment course by Mini-Mental State Exam (MMSE).⁵¹ Depression were assessed at the end of treatment course by Hamilton Rating Scale for Depression (HAM-D).⁵² We also reported on other outcomes, including ADL,⁵³ change of P300 amplitude,⁵⁴ change of P300 latency,⁵⁴ and change of neurobehavioral cognitive status examination⁵⁵ total scores, change of BI,⁵⁶ Mangled Extremity Severity Score (MESS)⁵⁷ reduction rate, change of Fugl-Meyer scales,⁵⁸ change of Sandoz clinical assessment geriatric scale,⁵⁹ change of functional independence measure,⁶⁰ and change of the antidepressant side-effect checklist.⁶¹

3. Results

3.1. Study characteristics

A total of 2305 citations were retrieved from the electronic databases, among which 14 SRs^{42,62–74} fulfilled the inclusion criteria (Fig. 1). These eligible SRs were published between 2010 and 2018. The characteristics of included SRs have been summarized in Table 1. All SRs^{42,62–74} that provided a cutoff date on literature search, 13 of SRs^{42,62–66,68–74} (92.9%) conducted literature search after 2010 with the most recent search conducted in 2016.

The percentage of male participants was ranged from 53.5% to 61.4% (from three SRs^{64,65,73}). The reported age of participants was ranged from 30 to 79 years (from two SRs^{63,64}). The range of duration of disease since onset was ranged from 12 days to 1 year from one SR.⁶⁴ The treatment during of disease since onset was ranged from 2 to 24 weeks from thirteen SRs.^{42,62–67,69–74}

Four SRs^{42,62–64} focused on post-stroke cognitive impairment and ten SRs^{65–74} summarized the evidence on post stroke depression.

3.2. Methodological quality of included SRs

All SRs^{42,62–74} performed comprehensive literatures search and evaluated the scientific quality of the included studies (Table 2). All SRs^{42,62–74} included the components of Population, Intervention, Comparator group, and Outcome (PICO) and timeframe for follow-up in the research questions and inclusion criteria, explained their selection of RCTs for inclusion in the review, involved at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include and also which data to extract from included studies, and used appropriate methods for statistical combination of results. Eleven SRs^{42,63–65,67,68,70–74} provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of review. Nine SRs^{42,62–64,66,67,69–71} only included low risk of bias RCTs in individual studies on the results of the meta-analysis. Seven SRs^{42,62–64,66,67,71} reported on the sources of funding for the studies included in the review. Six SRs^{63,67,69–71,74} assessed risk of bias in individual studies that were included in the review. Six SRs^{63,65–67,70,71} included only low risk of bias RCTs when interpreting or discussing the results of the review. Five SRs^{63,64,69,70,74} described the details of populations, interventions, comparators, outcomes, and research design. Three SRs^{65,66,72} performed graphical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias. Three SRs^{42,66,72} reported their funding sources and any potential sources of conflict of interest. Two SRs,^{42,70} used a comprehensive literature search strategy. None of SR provided a list of excluded studies and justify the exclusions.

3.3. Outcome measures

The types of outcomes measures used across the SRs were summarized in Table 3. Other reported outcomes were listed in Appendix II. Four (28.6%) SRs^{42,62–64} provided meta-analytic results on cognitive function. Ten (71.4%) SRs^{65–74} reported meta-analytic results on depression.

3.4. Outcomes

3.4.1. Post-stroke cognitive impairment

Four SRs^{42,62–64} evaluated the evidence of acupuncture for improving cognitive function in post-stroke patient versus cognitive rehabilitation. Two SRs^{42,63} showed significant clinical benefit in cognitive impairment improvement after acupuncture treatment when compared to cognitive rehabilitation. Acupuncture

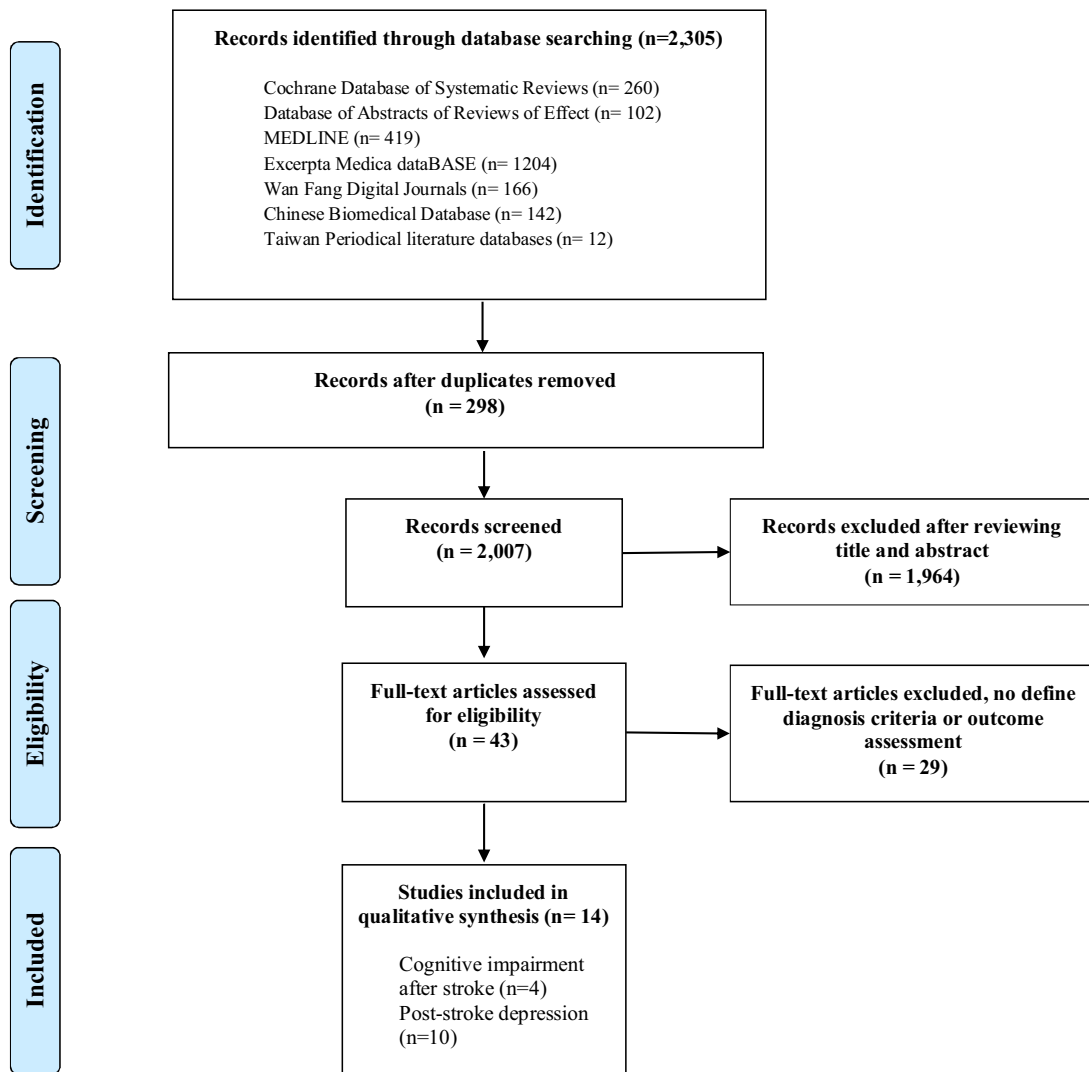


Fig. 1. Flowchart of literature selection on meta-analyses of acupuncture in post-stroke cognitive impairment and depression management.

plus cognitive rehabilitation versus cognitive rehabilitation demonstrated statistically significant increase in MMSE scores in compared to cognitive rehabilitation after 4 weeks treatment with medium heterogeneity (Pooled WMD=3.14, 95% CI=2.06 to 4.21, 4 RCTs, $I^2=36\%$).⁴² Acupuncture or moxibustion plus cognitive rehabilitation versus cognitive rehabilitation demonstrated statistically significant improvement in MMSE scores in compared to conventional stroke after 4 weeks treatment with low heterogeneity (Pooled WMD=3.22, 95% CI=2.09 to 4.34, 3 RCTs, $I^2=0\%$).⁶³ Acupuncture or moxibustion plus cognitive rehabilitation versus cognitive rehabilitation or Nimodipin showed clinical benefit in MMSE scores improvement after 4–8 weeks treatment with low heterogeneity (Pooled WMD=2.64, 95% CI=1.78 to 3.50, 5 RCTs, $I^2=0\%$).⁶³ Three SRs^{42,62,64} studied the clinical effect of acupuncture, electro-acupuncture, or scalp acupuncture plus cognitive rehabilitation on post-stroke cognitive impairment. The clinical benefit of cognitive function improvement was inconclusive due to heterogeneity across the underlying studies. None of the four SRs^{42,62–64} reported adverse events (AE) of acupuncture or moxibustion plus cognitive rehabilitation versus cognitive rehabilitation.

3.4.2. Post stroke depression

Ten SRs^{65–74} evaluated the evidence of acupuncture for improvement of depression in post-stroke patient versus

antidepressants. One SR⁶⁶ showed acupuncture versus antidepressants demonstrated statistically significant improve depression measured by increase in HAMD 17 items in compared to cognitive rehabilitation after 2 weeks treatment with low heterogeneity (Pooled WMD=−2.34, 95% CI=−3.46 to −1.22, 4 RCTs, $I^2=5\%$). The clinical benefit of depression improvement from two SRs^{67,70} was inconclusive due to heterogeneity across the underlying studies and inclusion a single study result. Three SRs^{66,67,69} measured HAMD 24 items reduction rate of acupuncture versus antidepressants in post-stroke patient. One SR⁶⁹ reported electro-acupuncture versus antidepressants demonstrated statistically significant improvement in HAMD 24 items reduction rate after 8 weeks or 4 to 8 weeks of treatment with low heterogeneity (Pooled OR=1.72, 95% CI=1.05 to 2.28, 5 RCTs, $I^2=0\%$) (Pooled OR=1.61, 95% CI=1.09 to 2.38, 12 RCTs, $I^2=0\%$).

Eight SRs^{65–67,69–72,74} reported AE of acupuncture versus antidepressants. One SR⁷⁴ reported electro-acupuncture treatment was associated with fewer AEs in comparing to antidepressants (Pooled RR=0.21, 95% CI=0.14 to 0.33, 8 RCTs, $I^2=0\%$). Two SRs^{65,70} showed acupuncture versus antidepressants demonstrated statistically significant reduction in the incidence of AE (Pooled RR=0.32, 95% CI=0.19 to 0.53, 8 RCTs, $I^2=0\%$) (Pooled OR=0.10, 95% CI=0.05 to 0.19, 9 RCTs, $I^2=42\%$) respectively. Five SRs^{66,67,69,71,72} reported AE were described generally in SRs level. Most AE were reported in patients who received antidepressants which included dizziness,

Table 1
Characteristics of Included Meta-analyses on Acupuncture in the Treatment of Cognitive Impairment and Post-Stroke Management

First author and year of publication	Search until (year)	Age (year-old)	Treatment duration	No. of studies (no. of patients)	Nature of acupuncture	Nature of control interventions	Outcomes reported
Treatment of cognitive impairment							
Liu, 2014 ⁴²	2012	18–80	2–24 weeks	21 (1421)	Acupuncture	Cognitive rehabilitation (physiotherapy, occupational therapy, speech therapy)	Cognitive function [*]
Liu, 2015 ⁶²	2013	NA	4–8 weeks	9 (325)	Electro-acupuncture	Cognitive rehabilitation/conventional intervention (Nimodipin)	Cognitive function [†]
Xiong, 2016 ⁶⁴	2014	53–78	4 weeks–1 year	13 (1113)	Scalp acupuncture	Cognitive rehabilitation/conventional intervention	Cognitive function [‡]
Zhang, 2015 ⁶³	2015	30–79	4 weeks–3 months	11 (395)	Acupuncture/moxibustion (Acupuncture, scalp acupuncture, electro-acupuncture)	Cognitive rehabilitation/conventional intervention (Nimodipin)	Cognitive function, [§] activities of daily living (ADL)
Treatment of depression							
Li, 2012 ⁷¹	2011	NA	4–8 weeks	13 (1062)	Electro-acupuncture	Antidepressants (tricyclic antidepressants, primary serotonin reuptake inhibitors)	Level of depression , [¶] , ADL ^{**}
Li, 2018 ⁷⁴	2016	NA	4–12 weeks	18 (1536)	Electro-acupuncture	Antidepressants (selective 5-HT reuptake inhibitors)	Level of depression, adverse events
Niu, 2014 ⁶⁹	2014	NA	4–8 weeks	20 (1372)	Electro-acupuncture	Antidepressants (selective 5-HT reuptake inhibitors, monoamine oxidase inhibitors)	Level of depression, [¶] cognitive function, [†] sensorimotor function, ^{††} ADL ^{**}
Que, 2018 ⁷⁰	2014	NA	4–8 weeks	18 (1813)	Acupuncture/ Electro-acupuncture	Fluoxetine hydrochloride (formulation, route of administration, and dose were not limited)	Level of depression , [¶] , ^{‡‡} cognitive function, [†] ADL, ^{**} function independent measure, ^{§§} adverse events
Wu, 2015 ⁷³	2011	NA	2–6 weeks	5 (728)	Acupuncture	Fluoxetine hydrochloride	Level of depression , [¶]
Xiong, 2010 ⁶⁷	2009	NA	1–8 weeks	20 (2031)	Acupuncture/ moxibustion	Antidepressants (type were not limited)	Level of depression , [¶] , ^{‡‡} , adverse events
Xu, 2014 ⁶⁸	2013	NA	2–8 weeks	20 (2083)	Acupuncture/ moxibustion	Antidepressant (type were not limited)	Level of depression , [¶]
Zhang, 2014 ⁶⁵	2013	NA	4–8 weeks	13 (845)	Acupuncture	Antidepressants (type were not limited)	Level of depression, [¶] adverse events
Zhang, 2014 ⁶⁶	2012	NA	2–8 weeks	17 (1132)	Acupuncture (Filiform needle)	Antidepressants (type were not limited)	Level of depression, , [¶] adverse events
Zhan, 2016 ⁷²	2015	NA	4–8 weeks	14 (1180)	Electro-acupuncture	Antidepressants (type, dosage form, and dose were not limited)	Level of depression , [¶] , ^{‡‡}

^{*} Change of Mini-mental state examination (MMSE) scores; Change of P300 amplitude; Change of P300 latency, Change of Neurobehavioral cognitive state examination total score.[†] Change of MMSE.

[‡] Change of MMSE, Change P300 latency.

[§] Change of MMSE scores, Change of P300 amplitude, Change of P300 latency.

^{||} Change of Hamilton Depression Rating Scale (HAMD).

[¶] The reduction score rate of HAMD = [(total score pretreatment - total score post-treatment)/total score pretreatment] × 100%.

^{**} Change of Barthel index (BI).

^{††} Change of Fugl-Meyer scales (FMS).

^{‡‡} Change of Self-rating depression scale (SDS).

^{§§} Change of Sandoz clinical assessment geriatric scale (SCAG).

drowsiness, nausea, abnormal electrocardiogram, sweating, constipation, nausea, loss of appetite, abdominal pain, insomnia, elevated alanine aminotransferase, urinary retention, dry mouth, constipation, rash, and headache. The main AE from acupuncture group were soreness at the needle site, dizziness, sweating, gastrointestinal discomfort, skin allergy, and fatigue. None of these eight SRs^{65–67,69–72,74} showed that acupuncture usage would increase the risk of AE. No life-threatening adverse effects were noted in all these SRs.

3.5. Other outcomes

3.5.1. Post-stroke cognitive impairment

One SR⁴² reviewed acupuncture plus cognitive rehabilitation demonstrated significant benefit in improving cognitive functions measured by increase Neurobehavior Cognitive State Examination Total Score after 3–4 weeks of treatment with low heterogeneity (Pooled OR=5.63, 95% CI=3.95 to 7.31, 2 RCTs, $I^2=0\%$). One

SR⁶³ showed that acupuncture or moxibustion plus cognitive rehabilitation versus cognitive rehabilitation has significant benefit in improving functional disability measured by ADL after 4 weeks to 3 months treatment with medium heterogeneity (Pooled WMD = 0.52, 95% CI = 0.31 to 0.73, 6 RCTs, $I^2 = 46\%$).

3.5.2. Post stroke depression

Three SRs^{66,67,69} reviewed acupuncture or Electro-acupuncture versus antidepressants for improvement of depression measure by HAMD (24 items) reduction rate. Acupuncture versus antidepressants demonstrated statistically significant improvement in HAMD reduction rate after 1–8 weeks treatment with low heterogeneity (Pooled OR = 1.15, 95% CI = 1.07 to 1.24, 5 RCTs, $I^2 = 24\%$).⁶⁷ This result was consistent another SR⁶⁶ which acupuncture versus Fluoxetine showed statistically significant improvement in HAMD reduction rate after 4 weeks treatment with low heterogeneity (Pooled OR = 1.11, 95% CI = 1.03 to 1.21, 8 RCTs, $I^2 = 0\%$). Electro-acupuncture versus Fluoxetine demonstrated statistically

Table 2
Methodological Quality of Included Meta-analyses on Acupuncture in the Treatment of Cognitive Impairment and Post Stroke Depression Management

First author and year of publication	AMSTAR 2 item															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Treatment of cognitive impairment																
Liu, 2014 ⁴²	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Partial Yes	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes
Liu, 2015 ⁶²	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	Yes	Yes	Yes	No	No	No	No
Xiong, 2016 ⁶⁴	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	No	Yes	No	No
Zhang, 2015 ⁶³	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
# of Yes	4	0	4	1	4	4	0	2	1	4	4	4	1	3	0	1
Treatment of depression																
Li, 2012 ⁷¹	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Li, 2018 ⁷⁴	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No
Niu, 2014 ⁶⁹	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	No
Que, 2018 ⁷⁰	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Wu, 2015 ⁷³	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	No	Yes	No	No
Xiong, 2010 ⁶⁷	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Xu, 2014 ⁶⁸	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	No	Yes	No	No
Zhang, 2014 ⁶⁵	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	Yes	Yes	Yes	No
Zhang, 2014 ⁹⁶	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Zhan, 2016 ⁷²	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	No	Partial Yes	No	No	Yes	No	No	Yes	Yes	Yes
# of Yes	10	1	10	1	10	10	0	3	5	3	10	5	5	8	3	2
(%) in total	100	7	100	14	100	100	0	36	43	50	100	64	43	79	21	21

AMSTAR 2 check list:

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

significant improvement in HAMD reduction rate after 4–8 weeks treatment with low heterogeneity (Pooled OR = 1.61, 95% CI = 1.09 to 2.38, 12 RCTs, $I^2 = 0\%$).⁶⁹

4. Discussion

To the best of our knowledge, this review is the first overview of systematic reviews to explore the efficacy and safety of acupuncture for the management of cognitive impairment and depression after stroke. The evidence compiled by this overview indicated that acupuncture in addition to conventional intervention could improve cognitive function. Furthermore, acupuncture can be more effective and safe than antidepressants in the treatment of post stroke depression.

4.1. Implication of practice

Our main aim in this study was to address the research evidence on acupuncture in post-stroke cognitive impairment and depression. We have conducted comprehensive searches of published reviews and electronic databases from both Chinese and English languages to minimize the potential publication bias and executed rigorous procedures for study selection, quality assessment and data extraction. The major practical contribution of our

research is that it provides evidence for clinicians and policy makers to identify treatment alternatives with acupuncture in managing post-stroke cognitive impairment and depression. In the management of post-stroke cognitive impairment, it is been suggested that cognitive rehabilitation could be a treatment of choice. However, Cochrane Systematic Reviews have showed that cognitive rehabilitation can only demonstrate the treatment benefits in independent living,⁷⁵ and improving memory deficits.⁷⁶ Thus, acupuncture is demonstrated as a potential alternative intervention for treating post-stroke patient with cognitive impairment.

A second important implication of our study derives from our finding on the depression management by acupuncture. Antidepressants have been used for treating post stroke depression more than 30 years. Nortriptyline was the first antidepressants studied in patients with post stroke depression and showed significant clinical benefit in comparing to placebo for reducing HAMD scores over 6 weeks in 1984.⁷⁷ Ten years later, Citalopram, the first SSRI, was also demonstrated the clinical benefit of reducing HAMD scores over 6 weeks in patients with post stroke depression.⁷⁸ Have not said that, treatment with antidepressants is not without risk. Side effects associated with antidepressants can leads to premature drug discontinuation. For example, patients who take TCA could experience peripheral anticholinergic side effects, which are dry mouth, constipation, and urinary hesitancy.⁷⁹ Furthermore, SSRI

Table 3
Acupuncture in the Treatment of Cognitive Impairment and Depression After Stroke: Overview of Meta-Analyses Results

First author and year of publication	Comparison	Time of assessment	No. of studies (no. of patients)	Pooled results (95%CI)	Heterogeneity I^2 (%)
The overview of meta-analysis result of acupuncture in the treatment of cognitive impairment after stroke					
<i>Change of Mini-mental state examination (MMSE) total scores</i>					
Liu, 2014 ⁴²	Acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 4 weeks treatment	4 (232)	Pooled WMD: 3.14 (2.06, 4.21)	36
Liu, 2014 ⁴²	Acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 8 weeks treatment	3 (128)	Pooled WMD: 2.03 (0.26, 3.80)	72
Liu, 2015 ⁶²	Electro-acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 4–8 weeks treatment	8 (NA)	Pooled WMD: 2.12 (0.16, 4.08)	95
Xiong, 2016 ⁶⁴	Scalp acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 8–12 weeks treatment	10 (732)	Pooled WMD: 2.22 (1.38, 3.07)	76
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. cognitive rehabilitation	After 4 weeks treatment	3 (208)	Pooled WMD: 3.22 (2.09, 4.34)	0
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. Nimodipin	After 4–8 weeks treatment	2 (175)	Pooled WMD: 1.84 (0.51, 3.16)	0
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. cognitive rehabilitation/Nimodipin	After 4–8 weeks treatment	5 (383)	Pooled WMD: 2.64 (1.78, 3.50)	0
<i>Change of Activities of Daily Living (ADL) scales</i>					
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. cognitive rehabilitation	After 4 weeks to 3 months treatment	4 (249)	Pooled WMD: 0.62 (0.36, 0.88)	46
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. cognitive rehabilitation/conventional intervention	After 4 weeks to 3 months treatment	6 (364)	Pooled WMD: 0.52 (0.31, 0.73)	46
The overview of meta-analysis result of acupuncture in the treatment of post stroke depression					
<i>Change of Hamilton Rating Scale for Depression (HAM-D) (17 items)</i>					
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	4 (270)	Pooled WMD: -3.29 (-6.87, 0.29)	95
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4–6 weeks treatment	5 (313)	Pooled WMD: -2.84 (-6.04, 0.36)	93
Zhang, 2014 ⁶⁶	Acupuncture vs. antidepressants (Fluoxetine)	After 2 weeks treatment	4 (192)	Pooled WMD: -2.34 (-3.46, -1.22)	5
<i>Change of HAM-D (24 items)</i>					
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 8 weeks treatment	2 (531)	Pooled WMD: -3.17 (-6.16, -0.18)	96
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	4 (268)	Pooled WMD: -1.42 (-3.45, 0.61)	79
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4–8 weeks treatment	7 (919)	Pooled WMD: -2.58 (-4.06, -1.09)	90
Xiong, 2010 ⁶⁷	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	7 (458)	Pooled WMD: -1.34 (-2.67, -0.02)	69
Zhang, 2014 ⁶⁶	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	7 (382)	Pooled WMD: -0.49 (-1.72, 0.74)	52
<i>HAM-D (24 items) reduction rate</i>					
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	6 (358)	Pooled OR: 1.57 (0.78, 3.16)	0
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 8 weeks treatment	5 (527)	Pooled OR: 1.72 (1.05, 2.28)	0
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 4–8 weeks treatment	12 (946)	Pooled OR: 1.61 (1.09, 2.38)	0
Xiong, 2010 ⁶⁷	Acupuncture vs. antidepressants	After 1–8 weeks treatment	5 (595)	Pooled RR: 1.15 (1.07, 1.24)	24
Zhang, 2014 ⁶⁶	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	8 (422)	Pooled RR: 1.11 (1.03, 1.21)	0
Zhang, 2014 ⁶⁶	Acupuncture vs. antidepressants	After 6 weeks treatment	3 (183)	Pooled RR: 1.10 (0.94, 1.28)	40
<i>Incidence of adverse event</i>					
Li, 2018 ⁷⁴	Electro-acupuncture vs. antidepressants	After 4–8 weeks treatment	8 (798)	Pooled RR: 0.21 (0.14, 0.33)	0
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4–8 weeks treatment	9 (628)	Pooled OR: 0.10 (0.05, 0.19)	42
Zhang, 2014 ⁶⁵	Acupuncture vs. antidepressants	After 4 weeks treatment	8 (502)	Pooled RR: 0.32 (0.19, 0.53)	0

use is associated with increased risk of hemorrhagic complications in elderly,^{80,81} and stroke, myocardial infarction, and all-cause mortality in postmenopausal women.⁸² The potential common adverse events associated with acupuncture is transient which included fainting during treatment, nausea and vomiting, increased pain, diarrhea, local skin irritation, headaches, sweating, and dizziness. Using unused sterile needle could further prevent the transmission of infectious diseases. Acupuncture is potentially effective and safe monotherapy for post stroke depression.

4.2. Implication of research

4.2.1. Study design

It has been found that cognitive performance was associated with symptoms of depression and with self-reported cognitive function on patient after stroke⁸³ and there is strong association existing between depression and the presence of cognitive deficits.⁸⁴ However, none of the included SRs studied the treatment benefits of acupuncture in post-stroke patients with both cognitive impairment and depression. Researcher should explore the potential treatment benefits in acupuncture for post-stroke patients with both cognitive impairment and depression. Furthermore, the treatment duration of all included SRs were below 24 weeks. The treatment benefits of acupuncture in post-stroke cognitive impairment and depression cannot be concluded in long-term treatment. In the future research, a consensus on study design and relevant outcome measures in conducting appropriate RCTs should be establishing in post-stroke cognitive impairment and depression management trials.

4.2.2. Study methodology

We did not cover Korean and Japanese database in our study. We are limited by our own language skills or ability to cover multi-countries' database and to access potentially relevant studies in other language. It is advisable to form an international review teams to enhance the diversity of language resources and publication channels than a local teamwork.

There is room for improvement in methodological quality of the SRs. None of SR provided the protocol and list out all excluded and included studies. The included systematic reviews were not reported optimally. The outcome measures were generally poorly elaborated. Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement was not fully executed in the SRs; for instance, study characteristics, reporting risk of bias of individual studies and how it could affect publication and selection bias, and funding sources should be reported. Researchers should implement the reporting of RCTs following to the Consolidated Standards of Reporting Trials (CONSORT) statement to facilitate reliable, transparent and complete reporting of trials.

From the available evidence, acupuncture may be beneficial for improving cognitive function and depressive disorder without obvious serious adverse events for post-stroke patients in the convalescent stage. However, various limitations of the original studies, lack of methodological details, and insufficient reporting of trials hinder the strength of this recommendation and argue for further research to support this claim and implement changes to clinical practice.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

No ethical approval was required for this manuscript as this study did not involve human subjects or laboratory animals.

Data availability

All data related to this study are within this article (Refer to Appendix).

Appendix I, II. Search strategies and results for overview review on systematic review with meta-analysis on acupuncture in the treatment of cognitive impairment and post stroke depression management all appendix.

1. Cochrane database of systematic reviews (CDSR) from inception to 5 April 2019

No.	Searches	Results
1	(cerebrovascular disorders)	565
2	(basal ganglia cerebrovascular disease)	119
3	(brain ischemia)	352
4	(carotid artery disease)	217
5	(intracranial arterial diseases)	214
6	(intracranial arteriovenous malformations)	43
7	(intracranial embolism and thrombosis)	163
8	(intracranial haemorrhages)	244
9	(brain infarction)	388
10	(vasospasm, intracranial)	81
11	(vertebral artery dissection)	77
12	(stroke, lacunar)	73
13	(cerebrovascular trauma)	186
14	(hypoxia-ischemia, brain)	44
15	(stroke)	1261
16	(poststroke)	138
17	(post-stroke)	133
18	(cerebrovasc\$)	139
19	(brain vascu\$)	1
20	(cerebral vascs)	110
21	(cva\$)	165
22	(apoplex\$)	105
23	(SAH)	97
24	(brain\$)	1870
25	(cerebr\$)	654
26	(intracran\$)	135
27	(intracerebral)	228
28	(isch\$emi\$)	144
29	(infarct\$)	293
30	(thrombo\$)	247
31	(emboli\$)	340
32	(occlus\$)	164
33	(intracranial)	554
34	(subarachnoid)	205
35	(haemorrhage\$)	1480
36	(hemorrhage\$)	1481
37	(haematoma\$)	518
38	(hematoma\$)	531
39	(bleed\$)	365
40	(hemiplegia)	95
41	(paresis)	122
42	(hemipleg\$)	65
43	(hemipar\$)	62
44	(paretic)	58
45	(cerebrovascular accident)	689

No.	Searches	Results
46	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45	3788
47	(acupuncture*)	384
48	(electroacupuncture*)	86
49	(electro-acupuncture*)	86
50	(acupoint*)	66
51	(Transcutaneous Electric Nerve Stimulat*)	87
52	(percutaneous electrical nerve stimulat*)	30
53	(TENS)	176
54	#47 or #48 or #49 or #50 or #51 or #52 or #53	494
55	#46 and #54	260

2. Database of abstracts of reviews of effects (DARE) from inception to 5 April 2019

No.	Searches	Results
1	cerebrovascular disorders	94
2	brain ischemia	123
3	carotid artery disease	12
4	intracranial arteriovenous malformations	7
5	intracranial embolism and thrombosis	1
6	intracranial haemorrhages	8
7	brain infarction	7
8	vasospasm	37
9	vertebral artery dissection	5
10	cerebrovascular trauma	1
11	hypoxia-ischemia	19
12	stroke	1968
13	poststroke	22
14	post-stroke	116
15	cerebrovasc*	348
16	cerebral vasc*	8
17	cva*	14
18	apoplex*	2
19	SAH	19
20	brain*	1018
21	cerebr*	1012
22	intracran*	338
23	intracerebral*	87
24	isch*emi*	1103
25	infarct*	1613
26	thrombo*	1645
27	emboli*	574
28	occlus*	454
29	intracranial	338
30	subarachnoid	110
31	haemorrhage*	581
32	hemorrhage*	878
33	haematoma*	154
34	hematoma*	48
35	bleed*	1289
36	hemiplegia	40
37	paresis	37
38	hemipleg*	53
39	hemipar*	22
40	paretic	16
41	cerebrovascular accident	45

42	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	7025
43	acupuncture*	605
44	electroacupuncture*	67
45	electro-acupuncture*	33
46	acupoint*	54
47	Transcutaneous Electric Nerve Stimulat*	55
48	percutaneous electrical nerve stimulat*	1
49	TENS	85
50	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	689
51	#42 AND #50	102

3. MEDLINE from inception to 5 April 2019

No.	Searches	Results
1	exp brain disease/or exp cerebrovascular disorders/or exp carotid artery diseases/or exp cerebrovascular trauma/or exp intracranial arterial diseases/or exp intracranial arteriovenous malformations/or exp *intracranial embolism and thrombosis*/or exp intracranial haemorrhages/or exp stroke/or exp vasospasm, intracranial/or exp vertebral artery dissection/	124,290
2	(stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.	238,828
3	((brain\$ or cerebr\$ or cerebell\$ or intracerebral) adj5 (inch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.	49,851
4	((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.	53,880
5	hemiplegia/or exp paresis/	18,761
6	(hemipleg\$ or hemipar\$ or paresis or paretic).tw.	29,846
7	1 or 2 or 3 or 4 or 5 or 6	347,012
8	Search:.tw.	334,997
9	meta analysis.mp.pt.	134,794
10	review.pt.	2,334,147
11	di.xs.	3,343,294
12	associated.tw.	2,927,523
13	8 or 9 or 10 or 11 or 12	7,576,754
14	exp acupuncture/	1596
15	acupuncture*.mp.	23,544
16	exp acupuncture points/	6044
17	exp acupuncture therapy/	22,520
18	exp acupuncture analgesia/	1181
19	exp electroacupuncture/	3565
20	electroacupuncture*.mp.	4285
21	electro-acupuncture*.mp.	706
22	acupoint*.mp.	3963
23	exp Transcutaneous Electric Nerve Stimulation/	7857
24	Transcutaneous Electric Nerve Stimulat*.mp.	4424
25	percutaneous electrical nerve stimulat*.mp.	43
26	TENS.mp.	9583
27	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	37,765
28	7 and 13 and 27	419

4. Excerpta Medica dataBASE (EMABSE) from inception to 5 April 2019

No.	Searches	Results
1	exp cerebrovascular accident/or exp cerebrovascular disease/or exp brain disease/or exp brain disease/or exp basal ganglion haemorrhage/or exp brain hemangioma/or exp brain hepatoma/or exp brain haemorrhage/or exp brain infarction/or exp brain schema/or exp carotid artery disease/or exp cerebral artery disease/or exp cerebrovascular malformation/or exp hypophysis apoplexy/or exp intracranial aneurysm/	1,849,939
2	exp basal ganglion hemorrhage/	683
3	exp brain arteriovenous malformation/or exp brain malformation/	72,315
4	(intracranial embolism and thrombosis).mp.	55
5	exp brain hematoma/or exp brain hemorrhage/	140,960
6	exp cerebrovascular accident/or exp lacunar stroke/	183,717
7	exp brain vasospasm/	7546
8	exp artery dissection/	8688
9	(stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasoc\$ or cerebral vasoc\$ or cerebral vasoc\$ or cva or apoplex\$ or SAH).tw.	419,240
10	((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$)).tw.	137,390
11	((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.	86,174
12	hemiparesis/or hemiplegia/or paresis/	43,704
13	(hemipeg\$ or hemipar\$ or paresis or paretic).tw.	33,205
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	2,027,351
15	meta-analys:.mp.	253,701
16	search:.tw.	508,699
17	review.pt.	2,420,973
18	15 or 16 or 17	2,896,149
19	exp acupuncture/	43,178
20	acupuncture*.mp.	42,646
21	exp acupuncture analgesia/	1568
22	exp acupuncture needle/	997
23	exp electroacupuncture/	6009
24	electroacupunctur*.mp.	6838
25	electro-acupunctur*.mp.	1175
26	acupoint*.mp.	5806
27	exp transcutaneous nerve stimulation/	1278
28	Transcutaneous Electric Nerve Stimulat*.mp.	369
29	percutaneous electrical nerve stimulat*.mp.	82
30	TENS.mp.	14,500
31	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	60,647
32	14 and 18 and 31	1204

5. Wan Fang from inception to 5 April 2019

cql://(("META") AND ("acupuncture" OR "electroacupuncture" OR "Auricular acupuncture" OR "scalp acupuncture" OR "aqua acupuncture") AND ("Stroke" OR "Cerebral infarction" OR "Cerebral hemorrhage" OR "Cerebral embolism" OR "Cerebrovascular disease" OR "Cerebrovascular disease" OR "Cerebrovascular accident" OR "Acute" OR "Integrated stroke unit" OR "Stroke unit"))

Search result = 166

6. Chinese Biomedical Database (CBM) from inception to 5 April 2019

("System Review" [full field] OR "meta-analysis" [full field] OR "META" [full field]) AND ("Acupuncture" [full field] OR "Acupuncture" [full field] OR "Electroacupuncture" [full field] OR "Auricular acupuncture" [full field] OR "scalp acupuncture" [full field] OR "aqua acupuncture" [full field]) AND ("stroke" [full field] OR "stroke" [full field] OR "cerebral infarction" [full field] OR "brain hemorrhage" [full field] OR "brain embolism" [full field] OR "cerebrovascular disease" [full field] OR "cerebrovascular accident" [full field] OR "acute phase" [full field] OR "Chinese and Western medicine combined stroke unit" [full field] OR "Chinese medicine stroke unit" [full field])

Search result = 142

7. Taiwan Periodical literature databases from inception to 5 April 2019

(TX=System Review OR Meta-analysis OR META) [AND] (TX=Acupuncture OR Acupuncture OR Electroacupuncture OR Auricular acupuncture OR scalp acupuncture OR aqua acupuncture) [AND] (TX=Stroke OR Stroke OR Cerebral Infarction OR Cerebral Hemorrhage OR Cerebral embolism OR cerebrovascular disease OR cerebrovascular accident OR acute phase OR TCM combined stroke unit OR TCM stroke unit)

Search result = 12

Appendix II. Acupuncture in the treatment of cognitive impairment and depression after stroke: Overview of Meta-Analyses Results (Other reported outcomes)

First author and year of publication	Comparison	Time of assessment	No. of studies (no. of patients)	Pooled results (95%CI)	Heterogeneity I^2 (%)
The overview of meta-analysis result of acupuncture in the treatment of cognitive impairment after stroke					
<i>Change of P300 amplitude</i>					
Liu, 2014 ⁴²	Acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 8 weeks to 3 months treatment	4 (194)	Pooled WMD: 1.38 (0.93, 1.82)	0
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. cognitive rehabilitation/conventional intervention	After 4 weeks to 3 months treatment	4 (243)	Pooled WMD: 1.23 (0.82, 1.63)	17
<i>Change of P300 latency</i>					
Liu, 2014 ⁴²	Acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 8 weeks to 3 months treatment	4 (194)	Pooled WMD: -12.80 (-21.08, -4.51)	93
Xiong, 2016 ⁶⁴	Scalp acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 8 weeks to 3 months treatment	3 (180)	Pooled WMD: -1.85 (-3.04, -0.66)	91
Zhang, 2015 ⁶³	Acupuncture/moxibustion + cognitive rehabilitation vs. cognitive rehabilitation	After 4 weeks to 3 months treatment	4 (243)	Pooled WMD: -18.46 (-30.51, -6.41)	91
<i>Change of Neurobehavioral cognitive state examination total score</i>					
Liu, 2014 ⁴²	Acupuncture + cognitive rehabilitation/conventional intervention vs. cognitive rehabilitation/conventional intervention	After 3–4 weeks treatment	2 (121)	Pooled OR: 5.63 (3.95, 7.31)	0
Li, 2018 ⁷⁴	Electro-acupuncture vs. antidepressants	After 4 weeks treatment	7 (503)	Pooled WMD: -0.04 (-0.18, 0.10)	23
Li, 2018 ⁷⁴	Electro-acupuncture vs. antidepressants	After 6 weeks treatment	3 (186)	Pooled WMD: 0.04 (-0.43, 0.51)	62
Li, 2018 ⁷⁴	Electro-acupuncture vs. antidepressants	After 8 weeks treatment	5 (542)	Pooled WMD: -0.01 (-0.23, 0.22)	28
Wu, 2015 ⁷³	Xingnao KaiQiao acupuncture vs. antidepressants (Fluoxetine)	Not reported	5 (728)	Pooled WMD: -3.07 (-6.10, -0.05)	98
Xu, 2014 ⁶⁸	Acupuncture vs. antidepressants	Not reported	18 (NR)	Pooled WMD: -0.42 (-0.52, -0.32)	90
Zhang, 2014 ⁶⁵	Acupuncture vs. antidepressants	Not reported	12 (731)	Pooled WMD: 0.26 (0.11, 0.40)	29
Zhan, 2016 ⁷²	Electro-acupuncture vs antidepressants	Not reported	12 (1040)	Pooled WMD: -0.77 (-1.47, -0.07)	85
Zhang, 2014 ⁶⁶	Acupuncture vs. antidepressants	Not reported	3 (163)	Pooled WMD: -0.06 (-0.37, 0.25)	8
The overview of meta-analysis result of acupuncture in the treatment of post stroke depression					
<i>HAMD (17 or 24 items) reduction rate</i>					
Wu, 2015 ⁷³	Xingnao KaiQiao acupuncture vs. antidepressants	Not reported	5 (728)	Pooled RR: 1.06 (0.93, 1.22)	72
<i>Change of Self-rating Depression Scale</i>					
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	Not reported	3 (247)	Pooled WMD: -1.40 (-3.10, 0.30)	77
Xiong, 2010 ⁶⁷	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	3 (194)	Pooled WMD: -6.02 (-8.73, -3.30)	90
<i>Change of Barthel index</i>					
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	4 (242)	Pooled WMD: -0.07 (-2.78, 2.64)	57
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants	After 8 weeks treatment	2 (100)	Pooled WMD: 6.67 (-8.01, 21.35)	91
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 4–8 weeks treatment	6 (342)	Pooled WMD: 1.38 (-1.88, 4.65)	75
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	Not reported	3 (180)	Pooled WMD: 16.32 (13.92, 18.71)	16
<i>Change of Modified Edinburgh-Scandinavian Stroke Scale (MESSS) reduction scores</i>					
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	2 (130)	Pooled WMD: -1.89 (-4.77, -0.99)	70
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4–8 weeks treatment	3 (351)	Pooled WMD: -5.23 (-10.57, 0.11)	92
Que, 2018 ⁷⁰	Acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	2 (120)	Pooled WMD: -7.46 (-12.2, -2.72)	71
<i>Modified Edinburgh-Scandinavian Stroke Scale (MESSS) reduction rate</i>					
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants (Fluoxetine)	After 4 weeks treatment	2 (130)	Pooled OR: 1.80 (0.61, 5.31)	0
<i>Change of Fugl-Meyer scales (FMS)</i>					
Niu, 2014 ⁶⁹	Electro-acupuncture vs. antidepressants	After 4 weeks treatment	2 (152)	Pooled WMD: 3.50 (0.14, 6.86)	86

Appendix III. Study protocol

Protocol Title: Overview of systematic reviews with meta-analyses on acupuncture in post-stroke cognitive impairment and depression management

Protocol Version: 1

Protocol Date: 5 August 2016

Principal Investigator: Caroline, yik-fong, Hung

Research Team: Xin-yin Wu, Vincent Chi-ho Chung, Endy Chun-hung Tang, Justin Che-yuen Wu, Alexander Yuk-lun Lau

I Abstract

Incident stroke could lead to emotional changes and an acute decline in cognitive function [1,2]. The emotional changes after stroke is thought to result from disruption of prefrontal system and lesions damaging the striato-pallido-thalamo-cortical pathways [3–5] while the decline in cognitive function after stroke is due to the reduction of regional blood flow blocked by recurrent and multiple infarctions [6]. It has been found that cognitive performance was associated with symptoms of depression and with self-reported cognitive function on patient after stroke [7]. Although it has been suggested that Selective Serotonin Reuptake Inhibitors (SSRIs) is the first line treatment for post stroke depression [8], there is still insufficient evidence and unclear effectiveness of cognitive rehabilitation for improving individuals cognitive function [9,10].

II Background and significance/preliminary studies

Systematic reviews (SRs) with meta-analysis have also been conducted to examine the relative benefits or harms of acupuncture together with conventional medicine intervention in the treatment of cognitive impairment and depression. An overview of SRs with meta-analyses on acupuncture in post-stroke cognitive impairment and depression management can provide a concise summary of results from SRs, and is essential for overcoming the knowledge gaps by composing, appraising, and summarizing all critical information from individual SRs.

III Study aim

This study aims to provide an overview of the effectiveness and safety of different CHM for post-stroke management. With a comprehensive synthesis of clinical evidence on the add-on effect of CHM in routine stroke care, this study will provide support to evaluate the effectiveness of CHM in combination with conventional medicine intervention in stroke management.

IV Administrative organization

- Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong; 9/F, Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T., Hong Kong
- Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong; 4/F, School of Public Health, Prince of Wales Hospital, Shatin, N.T., Hong Kong
- The Hong Kong Institute of Integrative Medicine, The Chinese University of Hong Kong, Hong Kong; 4L, 4/F, Day Treatment Block, Prince of Wales Hospital, 30–32 Ngan Shing Street, Shatin, New Territories, Hong Kong

V Study design

This is an overview of the effectiveness and safety of acupuncture for post-stroke cognitive impairment and post stroke depression.

VI Study procedures

a. Eligibility criteria

1. Types of studies

- We include SRs with meta-analysis of randomized controlled trials (RCTs) and quasi-randomized controlled trials in this overview.
- We exclude SRs with meta-analysis of observational studies, which include case-control studies, cross-sectional studies, longitudinal studies, and cohort studies.
- We use the Cochrane Collaboration definition for systematic review.

2. Subjects

- We include patients diagnosed with any type of stroke by World Health Organization stroke criteria [11] (ischemic stroke, acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, acute stroke, progressive cerebral infarction, acute cerebral infarction, cerebral hemorrhage, and cerebral ischemic stroke), or American Stroke Association criteria [12] (ischemic, hemorrhagic, transient ischemic) and received acupuncture along with conventional intervention (cognitive rehabilitation and conventional therapy) in post-stroke management.
- The subjects in the included reviews are not limited by gender, age, course of the disease, and treatment duration.

3. Intervention and control

- We include peer-reviewed full articles published in English and Chinese language.
- Subjects are using were using acupuncture and conventional intervention.
- Acupuncture included (needle) acupuncture, electro-acupuncture, and moxibustion therapy. The specific types of (needle) acupuncture and moxibustion referred to 'Acupuncture and moxibustion law, 7th edition' as the selection criteria [13].
- We include acupuncture interventions regardless of needle material, treatment points (e.g., single head acupuncture treatment or scalp), the implementation of techniques, selected points to implement the hands of time, leaving the needle time and treatment is not limited.
- Conventional medicine intervention is defined by American Stroke Association and European Stroke Organization [14,15].
- Conventional therapy include the use of drugs, such as antiplatelet agents, anticoagulants, fibrinogen-depleting agents, and volume expansion and vasodilators, and neuroprotective agents; but not including thrombolytic agents.

b. Information sources

- We perform a literature search of online databases [MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effect (DARE)] and Chinese databases [Chinese Biomedical Databases (CBM), Wan Fang Digital journals and Taiwan Periodical Literature Databases] from inception to August 2017.

c. Data management

- We extract the following data from full-text articles: (i) basic characteristics of the SRs, searching date of the study, number of included studies, total number of patients and bibliographic information; (ii) detail information on study

design and patient, intervention, control and outcomes; (iii) meta-analysis results of the including pooled effects of each comparison for each outcome; and (iv) results of methodological quality assessment.

d. Selection process

1. Methodological quality of SRs is assessed using Assessing the Methodological Quality of Systematic Review (AMSTAR). The judgments are given in 11 items as “yes”, “no”, “cannot answer” or “not applicable” based on the information provided.

e. Data collection process

1. Two researchers (CYFH and XYW) conduct literature selection, data extraction and methodological quality assessment independently. Any disagreement will be discussed with consensus. A third reviewer (VCHC) will assess unresolved discrepancy when necessary.

f. Data items and synthesis

1. The acupuncture treatments are assessed at SRs level.
 2. The pool effect estimates are extracted from each meta-analyses.
 3. We extract pooled relative risk (RR) or pooled odds ratio (OR) for dichotomous outcomes, and pooled weighted mean difference (WMD) for continuous outcomes with 95% confidence interval (CI). Heterogeneity across RCTs is reported by describing I^2 values reported in included meta-analysis; I^2 values of 0–25%, 26–50%, and above 50% represented low, medium and high heterogeneity, respectively [16].

4.3. Outcomes and prioritization

- The primary clinical outcomes are cognitive function improvement and depression symptoms improvement.
- Cognitive function is assessed at the end of treatment course by MMSE [17]. Depression were assessed at the end of treatment course by Hamilton Rating Scale for Depression (HAM-D) [18].
- All adverse events will be reported.
- We also report on other outcomes, including activity of daily living, change of Barthel index, Change of Mini-mental state examination, change of Fugl-Meyer scales in this paper.

VII Literature cited

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Appendix IV. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

		Treatment of post-stroke cognitive impairment				Treatment of post stroke depression									
		Liu, 2014 ⁴²	Liu, 2015 ⁶²	Xiong, 2016 ⁶⁴	Zhang, 2015 ⁶³	Li, 2012 ⁷¹	Li, 2018 ⁷⁴	Niu, 2014 ⁶⁹	Que, 2018 ⁷⁰	Wu, 2015 ⁷³	Xiong, 2010 ⁶⁷	Xu, 2014 ⁶⁸	Zhang, 2014 ⁶⁵	Zhang, 2014 ⁶⁶	Zhan, 2016 ⁷²
1	Title	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Abstract	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Introduction	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Methods	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
6	Eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Information sources	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Search	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Study selection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Data collection process	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Data items	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Risk of bias in individual studies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
13	Summary measures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Synthesis of results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
15	Risk of bias across studies	No	No	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No	Yes
16	Additional analyses	Yes	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No
17	Results	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
18	Study characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Risk of bias within studies	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
20	Results of individual studies	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21	Synthesis of results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22	Risk of bias across studies	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
23	Additional analysis	Yes	No	No	Yes	No	Yes	No	No	No	No	No	Yes	No	No
24	Discussion	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
25	Limitations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
26	Conclusions	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
27	Funding	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	Yes	Yes	No

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