Original Article

Moxibustion for treating patients with post-stroke depression: a systematic review and meta-analysis

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Background: To assess the effectiveness and safety of moxibustion for post-stroke depression (PSD).

Methods: A search was conducted in the following English and Chinese databases: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature (CBM), VIP and Wanfang. The outcomes included Hamilton Depression Rating Scale (HAMD), effective rate, and Modified Edinburgh-Scandinavian Stroke Scale (MESSS) scale. The formulation of search strategy, data extraction, and quality evaluation of involved studies was performed according to Cochrane handbook guidelines. The software RevMan 5.4 and Stata 16 were used for data analysis. The evidence quality of each outcome was evaluated by GRADEpro guideline development tool (GDT).

Results: A total of 14 trials with 863 participants were included. A certain risk of bias of unclear or high was detected in the included studies. Compared with the control group, adding moxibustion could change the value of HAMD [standardized mean difference (SMD) =−1.17; 95% confidence interval (CI): −1.55 to −0.79; I^2=85.5%; P<0.01] and the effective rate [risk ratio (RR) =1.22; 95% CI: 1.13 to 1.32; I^2=0.0%; P=0.56], and the differences in the MESSS scale (SMD =−0.72; 95% CI: −1.06 to −0.38; I^2=0.0%; P=0.80) had statistical differences. The certainty was low in effective rate, and very low in HAMD and MESSS. Besides, moxibustion was shown to be generally safe.

Discussion: This review found that moxibustion may be an effective intervention for PSD. However, the results of this study have a certain limitation. The benefits of moxibustion for PSD need to be confirmed in the future by more high-quality randomized controlled trials (RCTs).

Keywords: Moxibustion; post-stroke depression (PSD); efficacy; meta-analysis; effectiveness

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Introduction

Post-stroke depression (PSD) is a common and serious complication after stroke, with an estimated prevalence ranging from 25% to as high as 79% (1). Additionally, PSD is the main limiting factor of recovery and rehabilitation in stroke patients (2). The interaction between depression and stroke may play an important role in the development of PSD (3), and it has been seen that PSD can increase mortality by up to 10 times (4). It is determined by biological and psychosocial factors, symptoms of which can be categorized into three dimensions: affective, somatic, and cognitive (5,6). Social activities and cognitive function are negatively affected by PSD, which is characterized by depression, dysphasia, functional impairment, living alone, and social isolation (7,8). In addition, emotional injury, phlegm and blood stasis and Qi deficiency were the main causes leading to PSD, based on Chinese traditional medicine. Depression after stroking can increase morbidity, mortality, and worsened functional recovery (9,10). Concurrently, additional stress can be caused by the burden of medical costs and social pressures. Thus, it is very important to treat PSD patients.

The are many methods of treating PSD, including both pharmacological and non-pharmacological therapies (11). However, antidepressant drugs can have serious side effects. For example, selective serotonin reuptake inhibitors (SSRIs) may cause bleeding and intracerebral hemorrhage (12). The tolerability of antidepressants by patients at a late stage of PSD is also a shortcoming of pharmacological therapies (13). Due to the prevalence of the neuropsychiatric disorder that is PSD, finding an effective, safe, and convenient method is necessary (14).

As a traditional Chinese external therapy, moxibustion involves burning mugwort, called ai-ye in China, to produce a warm effect on the meridians, acupoints, and surface areas of the body (15,16). Moxibustion plays a key role in regulating the innate yin and yang in the body, therefore its application is very common in many disorders, such as knee osteoarthritis, irritable bowel syndrome, cancer-related fatigue, coronavirus disease 2019, and alleviating side effects of chemotherapy or radiotherapy in cancer patients (17-22). Nevertheless, as an important part of acupuncture, up to nowadays, moxibustion therapy has not been widely promoted worldwide.

The therapy of moxibustion includes moxa-stick moxibustion and moxa-cone moxibustion. Moxa-cone moxibustion includes direct moxibustion and indirect moxibustion. The materials of indirect moxibustion such as salt, ginger slice, garlic slice, and monkshood, can be placed between skin and moxa to produce a desired effect (23). The recognized effective moxibustion pathways can be divided into four aspects: warming effect, infrared radiation, medicinal penetration, and aromatherapy (24). Several studies have supported the anti-depression effect of moxibustion. Even more importantly, prolonged treatment of moxibustion could promote the brain uptake of L-tryptophan (Trp), shifting the Trp metabolism to 5-hydroxytryptamine (5-HT) (25-27).

There were two similar meta-analyses about the acupuncture and herbal medicine for treating patients with PSD. One evaluated the effectiveness and safety of Chinese herbal medicine (CHM) versus fluoxetine on depression. Although the results were weak evidence, the study showed CHM had similar effect to fluoxetine on depression (28). In addition, the other meta-analysis showed that acupuncture or moxibustion plus cognitive rehabilitation, versus cognitive rehabilitation; meanwhile, acupuncture versus antidepressant demonstrated statistically significantly alleviated depression in comparing to cognitive rehabilitation (29). In our review, subgroup analysis was performed on moxibustion alone and moxibustion combined with other therapies. We comprehensively evaluated the clinical efficacy of moxibustion on PSD.

Dozens of clinical studies relevant to moxibustion have been conducted, with results supporting that moxibustion is an effective alternative therapy for depression. Moxibustion has been applied widely in PSD treatment (30), and several clinical trials have shown that moxibustion is an effective method for treatment of PSD (31-44). However, there has no high-quality systematic review conducted to evaluate the efficacy and safety of moxibustion for PSD. Our research conducted a search for both Chinese and English literature. After screening, the remaining 14 articles were all in Chinese. We speculated the reason was that moxibustion therapy had not been popularized around the world, so the majority of clinical trials were conducted in China. In this systematic review, the aim was to provide some desirable propositions and assess whether it is an effective therapeutic supplement for patients with PSD. We present the following article in accordance with PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3421/rc) (45).

Methods

The protocol has been registered on the PROSPERO

platform (CRD42020178218).

Data sources and search strategy

The following English and Chinese databases were searched: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature (CBM), VIP, and Wanfang. The search was conducted independently by two reviewers on 15 August 2021. The search strategy was formulated according to the Cochrane handbook guidelines (46). The PubMed search strategy is shown in Table S1. The two authors independently conducted a preliminary screening based on the title and abstracts of the searched articles. If the studies met the inclusion criteria, they were re-screened based on the full text, to obtain the finally included studies. Excluded studies during re-screening had their exclusion explanations recorded. In addition, the references of the included studies were read to identify additional relevant studies.

Inclusion criteria

(I) Participants: patients with ischemic or hemorrhagic stroke and stroke mortality, whom were subsequently experiencing depression (47). (II) Interventions: all kinds of moxibustion therapies alone or those combined with conventional treatment were included. Moxibustion therapies included moxa-stick moxibustion, incorporating mild moxibustion, pecking moxibustion, cyclomoxibustion (in a circular motion), and moxa-cone moxibustion, which consisted of direct moxibustion and indirect moxibustion. (III) Comparisons: the patients were given conventional treatment, including fluoxetine, psychology, CHM, or acupuncture. (IV) Outcomes: the primary outcome was the score from the Hamilton Depression Rating Scale (HAMD), and secondary outcomes were the effective rate and the score from the Modified Edinburgh-Scandinavian Stroke Scale (MESSS). (V) Study types: randomized controlled trials (RCTs).

Exclusion criteria

(I) Moxa needle therapy was excluded, which consists of a needle inserted into a point with a moxa attached to and ignited at the handle of the needle. (II) Full text unavailable.

Data extraction

The data was extracted from each document by two reviewers independently. The information extracted included author name, published year, sample size, gender, age, interventions and control characteristics (e.g., specific intervention, frequency, duration), and outcomes (primary and secondary outcomes specifically mentioned above). Any disagreements between reviewers were resolved by consultation with a third reviewer.

Quality assessment

The risk of bias was assessed by two reviewers with the Cochrane Collaboration's tool for risk of bias assessment. The Cochrane risk of bias tool (ROB) by RevMan 5.4 (Computer program; The Cochrane Collaboration, Copenhagen, Denmark, 2020) was used to evaluate the quality of the included studies from seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (48). Each aspect could be divided into three levels: low risk, high risk, and unclear risk.

Data synthesis and Statistical analysis

Data synthesis was carried out using the risk ratio (RR) and standardized mean difference (SMD) with 95% confidence interval (CI) to analyze the outcomes. Heterogeneity analysis included of all kinds of variations among the trials.

Chi-square-based Q-test will be used to check heterogeneity. When $I^2 \leq 50\%$, the study was not considered to have significant heterogeneity. When $I^2 > 50\%$, a possible significant heterogeneity was considered. Moreover, if there was no significant heterogeneity, the fixed-effects model was applied to data synthesis (49). Otherwise, the random-effects model was used for data synthesis. Any comparison with high heterogeneity will be explored by subgroup analyses or sensitivity analysis. In addition, the study design and characteristics in the included studies will be analyzed.

The funnel plot, Begg's test, and Egger's test were used to assess the publication bias if more than 10 RCTs were included for primary outcome. Statistical analysis was performed using the software Stata 16 (StataCorp., LLC, College Station, TX, USA) and RevMan 5.4.

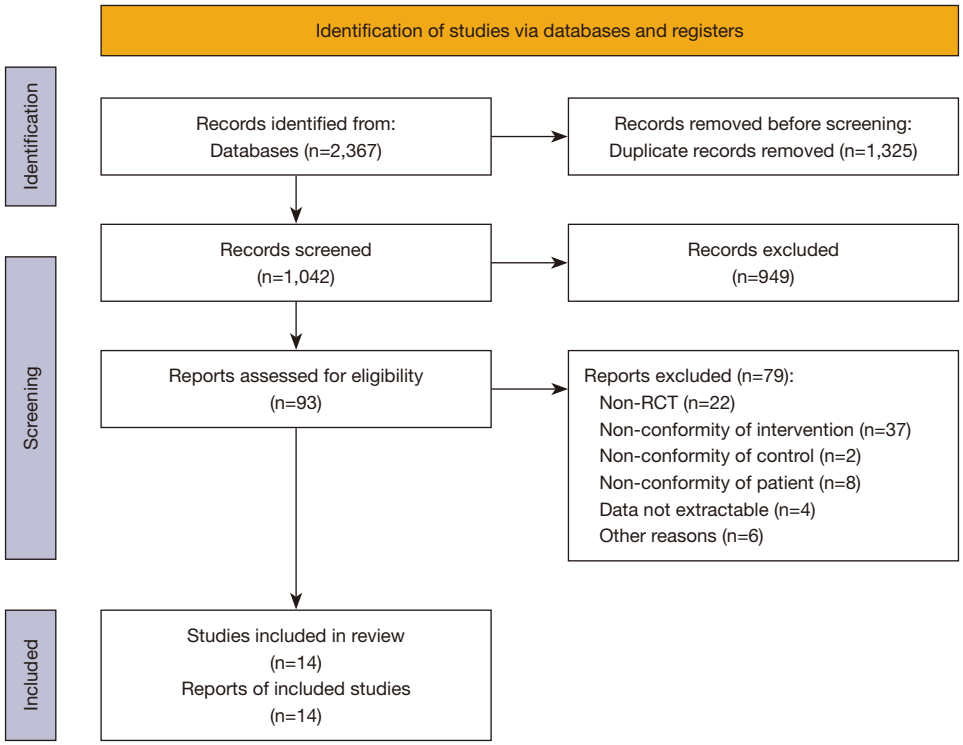

Figure 1 Flow diagram of literature search and trial selection. RCT, randomized controlled trial.

Assessment of evidence quality

The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to rate the quality of evidence for each outcome. According to the GRADE guideline, the quality of evidence was divided into levels of high, moderate, low, and very low quality. The GRADEpro guideline development tool (GDT; https://gradepro.org/) was applied to create the summary of evidence table (50-53).

Subgroup analysis

Subgroup analysis was performed based on the difference in interventions, which was categorized as moxibustion alone, or moxibustion combined with other different therapies.

Assessment of outcome

We assessed the outcomes of moxibustion for PSD by the score of HAMD reducing, effective rate and MESSS scale scores. Since several studies (54-56) had used the HAMD as an outcome, we used the score of HAMD reducing as primary outcome in our review.

Results

Description of studies

The study selection processes were conducted according to the PRISMA flowchart and are shown in *Figure 1*. A total of 2,367 articles were identified initially from the seven databases, and 1,042 studies remained after deduplication. After a preliminary screening, 949 irrelevant articles were removed. The remaining 93 articles were re-screened, among which 14 RCTs met the inclusion criteria and were included in this study.

The characteristics of the included trials are shown in *Table 1*. These 14 studies were all conducted in China, involving a total of 863 PSD patients. The sample size of included trials ranged from 32 to 120. The duration of treatments ranged from 3 to 12 weeks, with an average of 6.57 weeks. The age range of participants ranged from 23 to 90 years. Only 1 trial used moxibustion alone and compared it to fluoxetine in the control arms (39), to explore the effects of moxibustion used alone. In the other 13 trials, the intervention group involved moxibustion combined with conventional therapies, such as fluoxetine (35,37,40), acupuncture (36,41,43), CHM (31,34,44), psychology

Table 1 Characteristics of the included trials

Study ID	Total/treatment/control	Age range/mean ± SD (years)	Treatment	Control	Frequency	Duration	Outcome indicators
Cai 2020 (31)	88/44/44	T: 23–49/32±4.52; C: 23–50/29±4.36	Moxibustion + CHM	CHM	1 time/d	8 weeks	(I) HAMD; (II) MESSS; (III) effective rate
Deng 2014 (32)	80/40/40	T: 63.60±7.80; C: 64.55±8.60	Moxibustion + psychotherapy	Fluoxetine + psychotherapy	1 time/d	4 weeks	(I) HAMD; (II) effective rate; (III) MESSS
Deng 2019 (33)	64/32/32	T: 24–90/7±16.31; C: 35–85/8.88±14.10	Moxibustion + basic treatment + psychotherapy	Basic treatment + psychotherapy	NR	8 weeks	(I) HAMD; (II) effective rate
Gan 2021 (34)	82/41/41	T: 52.20±4.51; C: 51.98±4.67	Moxibustion + CHM	CHM	1 time/d	12 weeks	(I) HAMD
Jiang 2013 (35)	60/30/30	T: 40–75/1.45±5.32; C: 40–75/0.37±7.13	Moxibustion + fluoxetine	Fluoxetine	1 time/d	6 weeks	(I) HAMD; (II) effective rate
Luo 2017 (36)	64/32/32	T: 60.29±8.35; C: 61.27±9.85	Moxibustion + acupuncture	Acupuncture	1 time/d	4 weeks	(I) HAMD; (II) effective rate
Miao 2018 (37)	32/16/16	T: 40–79/4.97±9.45; C: 39–78/4.13±9.26	Moxibustion + fluoxetine	Fluoxetine	1 time/d	8 weeks	(I) HAMD; (II) effective rate
Niu 2015 (38)	120/60/60	T: 48–75/8.64±8.92; C: 48–75/60.23±10.51	Moxibustion + fluoxetine + acupuncture	Fluoxetine + acupuncture treatment	1 time/d	6 weeks	(I) HAMD
Shan 2017 (39)	60/30/30	T: 44–64/5.45±3.16; C: 46–65/6.49±3.19	Moxibustion	Fluoxetine	1 time/d	8 weeks	(I) HAMD; (II) effective rate
Wan 2011 (40)	60/30/30	T: 53.6±5.2; C: 52.4±5.3	Moxibustion + basic treatment	Fluoxetine + basic treatment	5 times/w	4 weeks	(I) HAMD; (II) MESSS; (III) effective rate
Wang 2015 (41)	45/23/22	T: 32–78/5±55; C: 30–75/1±50	Moxibustion + acupuncture	Acupuncture	1 time/d	3 weeks	(I) HAMD; (II) effective rate
Wang 2021 (42)	60/30/30	T: 63.23±7.24; C: 64.03±8.46	Moxibustion + fluoxetine	Fluoxetine	1 time/w	12 weeks	(I) HAMD; (II) effective rate
Zhai 2021 (43)	48/24/24	T: 56.27±7.59; C: 57.01±6.72	Moxibustion + acupuncture	Acupuncture	1 time/d	6 weeks	(I) HAMD
Zou 2014 (44)	54/27/27	T: 61.43±9.62; C: 59.36±10.23	Moxibustion + CHM	CHM	1 time/d	3 weeks	(I) HAMD

T, treatment group; C, control group; CHM, Chinese herbal medicine; HAMD, Hamilton Depression Rating Scale; MESSS, Modified Edinburgh-Scandinavian Stroke Scale.

guidance (32,33), and combination of acupuncture and fluoxetine (38).

Quality assessment

The judgment regarding each risk of bias item is shown in *Figure 2*. A total of 10 trials reported the method of random sequence generation, among which 3 (38,41,44) were high risk and 7 trials (32,34-36,39,40,43) reported "randomly allocating", which was classified as low risk. For allocation concealment, 2 RCTs (35,36) were assessed as low risk and 9 (31,34,38-44) were high risk. Meanwhile, due to

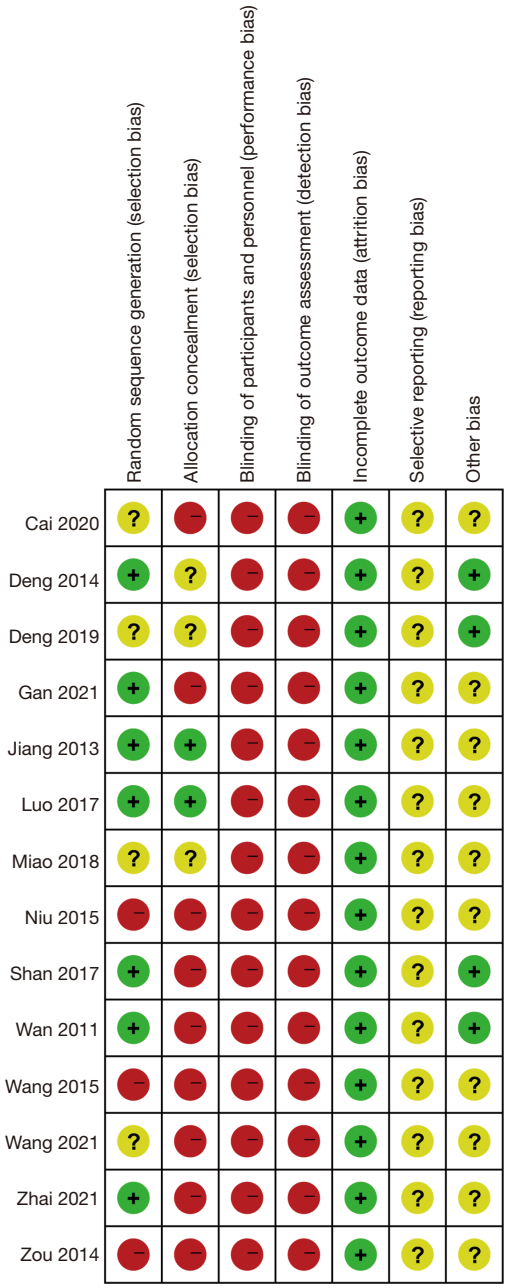

Figure 2 Risk of bias for included studies.

inability to implement blinding, all the bias risk of blinding were assessed as high risk. All the included trials provided complete outcome data, and without attrition bias. Selective reporting bias of all the trials was unclear due to their protocols being unavailable. The bias of the other 4 trials (32,33,39,40) were low risk due to providing clear conflict of interest, and the other 10 trials (31,34-38,41-44) were judged as "unclear".

Outcomes

Primary outcomes

HAMD

The comparison of HAMD scale scores is shown in *Figure 3*. All studies, which included a total of 914 patients, reported HAMD scale scores. Due to significant heterogeneity, a random-effects model was used for statistical analysis. Results showed that when compared with the control group, the change in value of the treatment group was statistically significant (SMD =−1.17; 95% CI: −1.55 to −0.79; I^2=85.5%; P<0.01).

Subgroup analysis was used according to the variation of different interventions. The result of each subgroup showed that compared with the other treatments, moxibustion combined with CHM (SMD =−2.42; 95% CI: −3.80 to −1.03; I^2=93.6%; P<0.01) (31,34,44), fluoxetine (SMD =−1.08; 95% CI: −1.69 to −0.47; I^2=66.1%; P=0.05) (35,37,42), acupuncture (SMD =−0.64; 95% CI: −0.96 to −0.31; I^2=0.0%; P=0.99) (36,41,43), fluoxetine and acupuncture together (SMD =−1.73; 95% CI: −2.15 to −1.31) (38), and moxibustion alone (SMD =−0.92; 95% CI: −1.30 to −0.55; I^2=0.0%; P=0.38) (39,40), respectively, had a statistically significant ability to decrease HAMD scores. However, there was no statistically significant difference between moxibustion plus psychology therapies group and conventional treatment group (SMD =−0.46; 95% CI: −1.03 to 0.11, I^2=65.6%, P=0.09) (32,33).

Secondary outcomes

Effective rate

The comparison of effective rate is shown in *Figure 4*. A total of 10 studies (31-37,39-41), which included a cumulative 632 participants, reported the outcome of effective rate. Due to insignificant heterogeneity, the fixed-effects model was used for statistical analysis. The results showed that compared to the control group, the effective rate in the treatment group was better, and the difference was statistically significant (RR =1.22; 95% CI: 1.13 to 1.32; I^2=0.0%; P=0.56).

Subgroup analysis indicated that CHM (RR =1.18; 95% CI: 1.04 to 1.33; I^2=66.9%, P=0.08) (31,34), psychology (RR =1.28; 95% CI: 1.06 to 1.54; I^2=0.0%; P=0.48) (32,33), fluoxetine (RR =1.32; 95% CI: 1.06 to 1.66; I^2=0.0%; P=0.84) (35,37), and acupuncture (RR =1.21; 95% CI: 1.01 to 1.44; I^2=10.9%; P=0.29) (36,41),

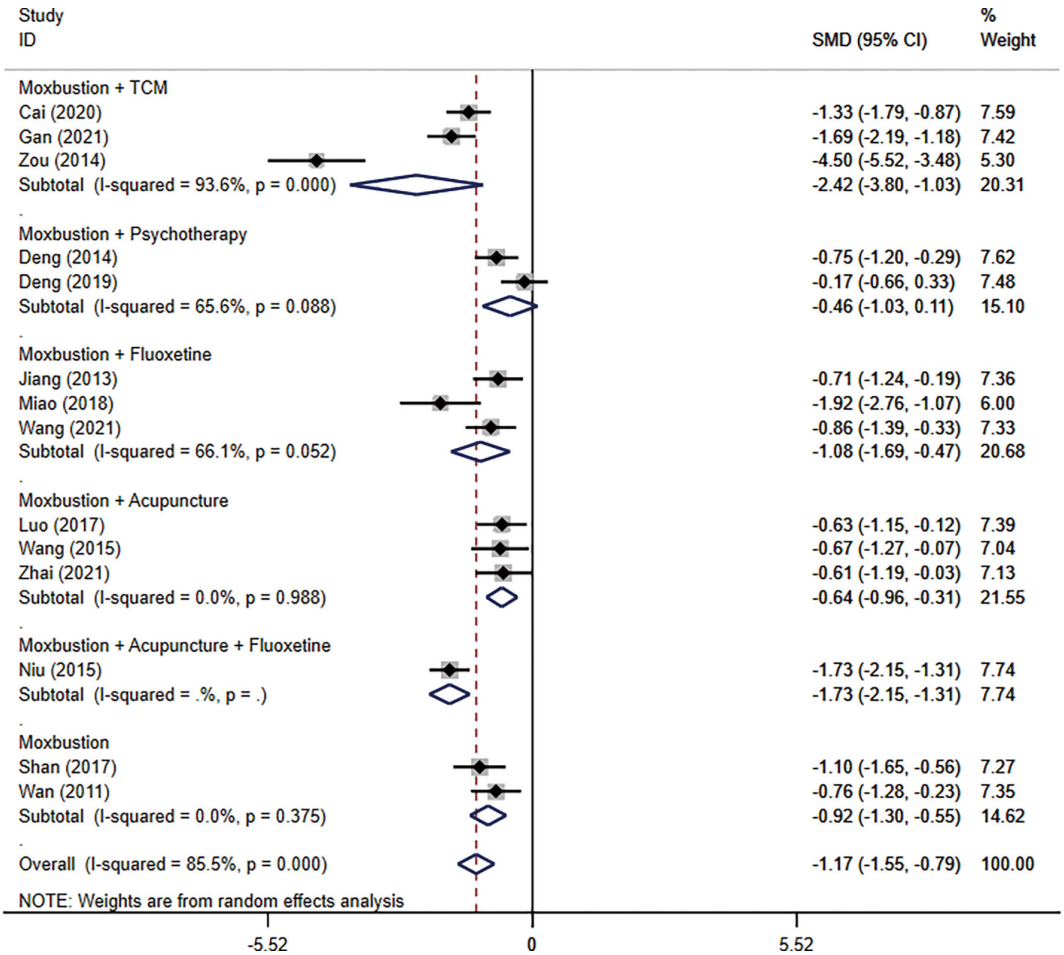

Figure 3 Comparison of the outcome of HAMD. HAMD, Hamilton Depression Rating Scale; SMD, standardized mean difference; CI, confidence interval; TCM, traditional Chinese medicine.

respectively, plus moxibustion have statistically significant impact on modifying effective rate. The other 2 trials used moxibustion alone compared to fluoxetine (39,40) for which the difference in effective rate was not statistically significant (RR =1.18; 95% CI: 0.99 to 1.42; I^2=0.0%; P=0.68).

MESSS

The comparison of results from the MESSS scale is shown in *Figure 5*. A total of 2 studies (32,40), which included a cumulative 140 patients, reported the outcome of the MESSS scale scores. Due to insignificant heterogeneity, the fixed-effects model was used for statistical analysis. Our results showed that compared with the control groups, the MESSS scale results were improved in the treatment group, and the difference was statistically significant (SMD=−0.72; 95% CI: −1.06 to −0.38; I^2=0.0%; P=0.80).

Publication bias

Publication bias regarding the HAMD scale was assessed using funnel plots (*Figure 6*). The Begg's test and Egger's test of HAMD demonstrated that the P values were all greater than 0.05 (Begg's test, P=0.443; Egger's test, P=0.097), which showed no significant symmetry, indicating no publication bias of the primary outcome.

Summary of evidence

The evidence quality of moxibustion for PSD is shown in *Table 2*. Generally, the quality was not high. The outcome of HAMD and MESSS had very low certainty, and the outcome of effective rate had low certainty.

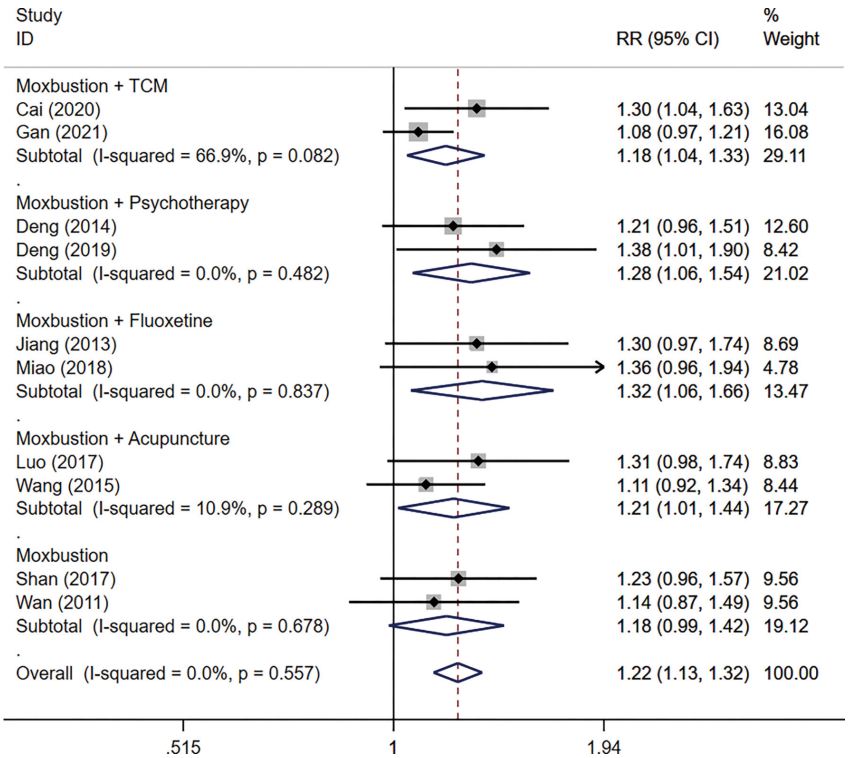

Figure 4 Comparison of effective rate. RR, risk ratio; CI, confidence interval; TCM, traditional Chinese medicine.

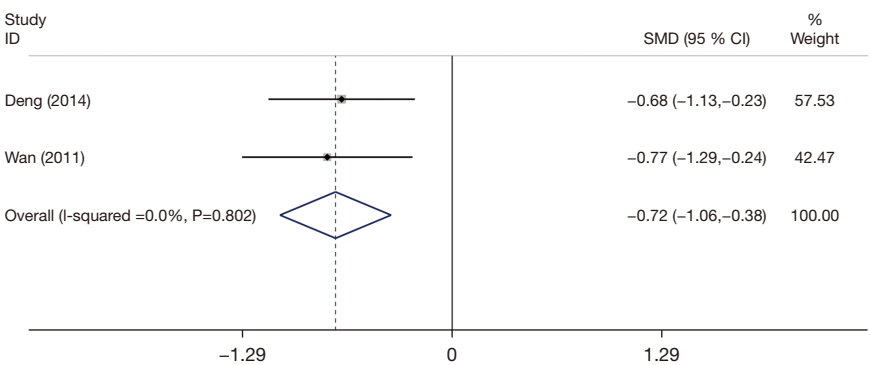

Figure 5 Comparison of MESSS scale. MESSS, Modified Edinburgh-Scandinavian Stroke Scale; SMD, standardized mean difference; CI, confidence interval.

Discussion

Summary of main results

A total of 14 RCTs were included and systematically evaluated the effectiveness and safety of moxibustion for PSD. Overall, on the basis of conventional treatment, adding moxibustion reduced the score of HAMD by 1.17 (0.79 to 1.55) scores, effective rate, and MESSS. However, subgroup analysis showed that compared with conventional treatment, although the effect of moxibustion combined with psychotherapy on HAMD, and the effect of moxibustion alone on the effective effect had a favorable trend, the difference was not statistically significant.

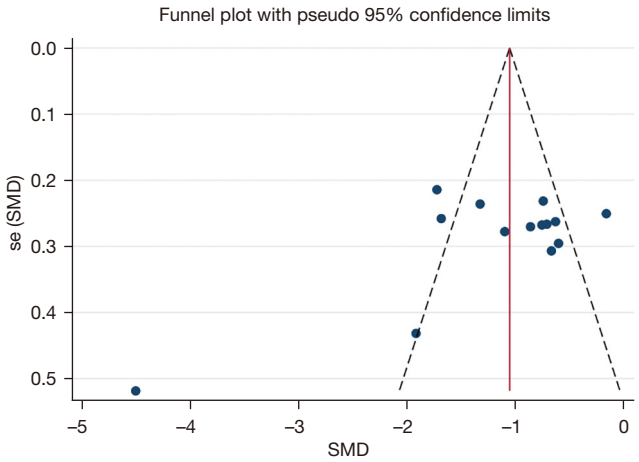

Figure 6 Publication bias regarding the scale of HAMD. HAMD, Hamilton Depression Rating Scale; SMD, standardized mean difference.

Strengths and limitations of this systematic review

The HAMD and MESSS scales are the currently recognized tools for evaluating the severity of PSD patients. Therefore, to strengthen the reliability of the efficacy of PSD patients, the above two outcomes and the effective rate were used to evaluate the efficacy of moxibustion on PSD patients. In addition, to explore the difference in the efficacy of moxibustion combined with other interventions for PSD patients, we also conducted a subgroup analysis according to the specific intervention methods.

There were some limitations in this study. Firstly, all the eligible trials were available from China, which may limit the application of the results. Secondly, there was a certain clinical heterogeneity in the interventions of the included studies. Although subgroup analysis of different interventions was performed, it made the sample size in the subgroup smaller and reduced the efficacy of the test. Thirdly, most of the included studies had flaws in methodological design, such as unclear allocation concealment or clinical trial registration. Last, all the included 14 articles were in Chinese. Our guess was that moxibustion therapy has not been popularized around the world, therefore, most of trials were conducted in China.

Relation with previous works

Previously, researchers systematically reviewed the efficacy of moxibustion in the treatment of PSD (57), but only 5 articles were included at that time, and meta-analysis was not conducted. This study finally included 14 studies on moxibustion treatment of PSD. As the interventions were not completely the same in the included studies, we divided the study into five subgroups according to the specific intervention methods and performed meta-analysis of the overall efficacy and the efficacy of the subgroups. Also, previous studies have shown that moxibustion works by promoting the absorption of Trp in the brain and transferring the metabolism of Trp to serotonin, which can increase the production of serotonin and exert an antidepressant effect (25). In addition, compared to Western drugs for PSD, the advantages of traditional Chinese medicine (TCM) were safety and low side effects. Meanwhile, the external treatment of Chinese medicine had less damage to the gastrointestinal tract and little irritation to the liver and kidney. Meanwhile, the operation was simple and easy to learn.

Implications for further studies

Further research should be aimed at evaluating the curative effect of moxibustion, such as using moxibustion alone versus fluoxetine alone. In addition, it is recommended to use the HAMD scale as the main outcome evaluating the efficacy of PSD patients. At the same time, the safety of moxibustion needs to be evaluated and analyzed in detail.

Conclusions

This systematic review and meta-analysis provide a detailed summary of the efficacy of moxibustion in treating patients with PSD. Based on 14 trials with a certain content of methodological quality defects, moxibustion seemed to be safe and effective for reducing the HAMD scale score, MESSS scale score, and improving the effective rate in PSD patients. However, due to the limitations around the quality of evidence, we suggest a large scale multi-centered RCT

Table 2 The evidence quality of moxibustion for PSD

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moxibustion	Fluoxetine	Relative (95% CI)	Absolute (95% CI)		
HAMD												
14	Randomized trials	Serious[a]	Serious[b]	Serious[c]	Not serious	None	458	45	–	SMD 1.15 SD lower (1.53 lower to 0.78 lower)	⊕◯◯◯, very low	Critical
Effective rate												
10	Randomized trials	Serious[a]	Not serious	Serious[c]	Not serious	None	282/316 (89.2%)	230/316 (72.8%)	RR 1.22 (1.13 to 1.32)	175 more per 1,000 (from 105 more to 260 more)	⊕⊕◯◯, low	Important
MESSS												
2	Randomized trials	Serious[a]	Not serious	Serious[c]	Serious[d]	None	70	70	–	MD 4.71 lower (6.89 lower to 2.54 lower)	⊕◯◯◯, very low	Important

[a], the risk of bias is decreased by one level: there are some high risks and unclear risk bias; [b], inconsistency is reduced by one level: I^2 value is large, with significant statistical heterogeneity over 70%; [c], indirectness is decreased by one level: there is a certain difference between the included intervention; [d], inaccuracy is decreased by one level: fewer patients were included. PSD, post-stroke depression; HAMD, Hamilton Depression Rating Scale; MESSS, Modified Edinburgh-Scandinavian Stroke Scale; CI, confidence interval; RR, risk ratio; SMD, standardized mean difference; MD, mean difference.

trial for moxibustion use as a PSD treatment be conducted in future.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3421/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3421/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Search strategy of PubMed

No.	Search query
#1	Randomized controlled trial [pt]
#2	Controlled clinical trial [pt]
#3	Randomized [tiab]
#4	placebo [tiab]
#5	drug therapy [sh]
#6	randomly [tiab]
#7	trial [tiab]
#8	groups [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	animals [mh] NOT humans [mh]
#11	#9 NOT #10
#12	“Stroke”[Mesh]
#13	Stroke or Strokes or Cerebrovascular Accident or Cerebrovascular Accidents or CVA or CVAs or Cerebrovascular Apoplexy or Brain Vascular Accident or Brain Vascular Accidents or Apoplexy or Acute Cerebrovascular Accident or Acute Cerebrovascular Accidents
#14	#12 or #13
#15	“Depressive Disorder”[Mesh]
#16	Depressive Disorders or Depressive Neuroses or Depressive Neurosis or Endogenous Depression or Endogenous Depressions or Depressive Syndrome or Depressive Syndromes or Neurotic Depression or Neurotic Depressions or Melancholia or Melancholias or Unipolar Depression or Unipolar Depressions
#17	#15 or #16
#18	#14 and #17
#19	“Moxibustion”[Mesh]
#20	Moxibustion therapy or Heat-sensitive moxibustion or Partition moxibustion or Spreading moxibustion or Thunder-fire moxibustion
#21	#19 or #20
#22	#11 and #18 and #21

CVA, cerebrovascular accident.

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