Systematic Review and Meta-Analysis

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Therapeutic effect of Chinese herbal medicines for post-stroke depression

A meta-analysis of randomized controlled trials

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Abstract

Background: Whether the addition of Chinese herbal medicine (CHM) in routine western medicines for post-stroke depression yields additional therapeutic effects still remains to be controversial. This study aimed to assess the efficacy and safety of combination of CHM with routine western medicines versus routine western medicines alone in patients with post-stroke depression (PSD).

Methods: Electronic databases such as PubMed, EmBase, Cochrane library, and China National Knowledge Infrastructure were systematically searched from inception till October 2019. Studies designed as randomized controlled trials (RCTs) and that investigated the therapeutic effects of CHM plus routine western medicines (CHM group) versus routine western medicines alone (control group) in PSD patients were eligible. The relative risk (RR) and weighted mean difference (WMD) with 95% confidence interval (CI) were used to assess the categories and continuous data using random-effects model. Software STATA was applied to perform statistical analysis (Version 10.0; StataCorp, TX,).

Results: A total of 18 RCTs involving a total of 1,367 PSD patients were selected for final analysis. The effective rate in CHM group was significantly higher than that in control group (RR: 1.18; 95%CI: 1.12–1.24; $P < .001$). Moreover, patients in CHM group showed association with lower Hamilton Depression Rating Scale (WMD: -3.17; 95%CI: -4.12 to -2.22; $P < .001$) and Scandinavian Stroke Scale (WMD: -3.84; 95%CI: -5.73 to -1.96; $P < .001$) than those in control group. Furthermore, patients in CHM were associated with high level of Barthel Index than those in control group (WMD: 11.06; 95%CI: 4.01 to 18.10; $P = .002$). Finally, patients in CHM group had lower risk of gastrointestinal (RR: 0.49; 95%CI: 0.31–0.77; $P = .002$) and neurological (RR: 0.50; 95%CI: 0.33–0.75; $P = .001$) adverse events than those in control group.

Conclusions: The study findings revealed that addition of CHM to routine therapies could improve the therapeutic effects and reduce gastrointestinal or neurological adverse events.

Abbreviations: CHM = Chinese herbal medicine, PSD = post-stroke depression, RR = relative risk, SSS = Scandinavian Stroke Scale, WMD = weighted mean difference.

Keywords: Chinese herbal medicine, meta-analysis, post-stroke depression, therapeutic effect

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The authors have no conflicts of interest to disclose.

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1. Introduction

Stroke is a thromboinflammatory disease that is associated with high mortality, causing cognitive, physical and psychiatric disabilities.[1–3] Post-stroke depression (PSD) is the most common neuropsychiatric sequela following acute stroke, and its prevalence ranges from 29% to 35% during the first 5 years.[4] Patients diagnosed with PSD are characterized by sustained depressed mood, decreasing interest, physical fatigue, causing functional impairment, poor daily living activities, cognitive functioning, and social functioning.[5,6]

Pharmacological, non-pharmacological, or their combinations are widely used for the treatment of PSD.[7] Nowadays, selective serotonin reuptake inhibitors (e.g., fluoxetine) and serotonin and norepinephrine reuptake inhibitors are widely used antidepressants, while they are associated with several adverse events, including blurry vision, urinary retention, sexual dysfunction, tremors, hypotension, and severe insomnia.[8] Moreover, the potential risk of drug-drug interactions could restrict the uses of these antidepressants.[9] Therefore, additional effective therapeutic strategies should be identified to treat patients with PSD.

Currently, the risk factors associated with PSD have already been identified, which included mental illness history or family history, female, aging, neuroticism, stroke severity, and degree of disability.[10] Chinese herbal medicine (CHM) for the treatment of PSD has been introduced long before, and it could adjust the

potentially modifiable risk factors. Moreover, the multi-target regulation of CHM is consistent with that of the complex mechanism of PSD, and it cooperates with routine western medicines, yielding better therapeutic effects and avoiding potential adverse events. However, there is no systematic review and meta-analysis that investigated the therapeutic effects of the combination of CHM and routine western medicines in patients with PSD. Therefore, this current meta-analysis was conducted based on randomized controlled trials (RCTs) to assess the efficacy and safety of CHM plus routine western medicines (CHM group) versus routine western medicines alone (control group) for treating PSD in patients.

2. Methods

2.1. Ethical statement

This is a meta-analysis study conducted based on the previous literature. The consent of ethics committee and patients are not applicable for this study.

2.2. Data sources, search strategy, and selection criteria

This meta-analysis was reported and conducted according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis and the Cochrane Handbook for Systematic Reviews of Interventions.[11,12] This study compared the efficacy of CHM and control groups in PSD patients that are designed as RCTs eligible for inclusion in this study, and there was no restriction to the published language. The electronic databases such as PubMed, EmBase, Cochrane library, and China National Knowledge Infrastructure were searched using the key terms "post-stroke depression" AND "Chinese herbal medicine" AND "randomized controlled trials" from inception till October 2019. The details regarding the search strategy in PubMed were listed in Supplemental Digital Content 1, http://links.lww.com/MD/F537. After this, the reference lists of retrieved studies were reviewed manually to identify any other potential studies.

The literature search was carried out by 2 authors independently, and conflicts between them were resolved by discussion by reaching a consensus. The inclusion criteria were as follows:

(1) Study design: RCT;
(2) Patients: all patients diagnosed with PSD according to the Diagnostic and Statistical Manual of Mental Disorders or Chinese Classification of Mental Disorders;
(3) Intervention: CHM combined with routine western medicines;
(4) Control: routine western medicines alone;
(5) Outcomes: the study should report at least 1 of the following outcomes: effective rate, Hamilton Depression Rating Scale (HAMD), Scandinavian Stroke Scale (SSS), Barthel Index (BI), and potential gastrointestinal and neurological adverse events.

Effective rate was defined as the reduction rate of HAMD, in which HAMD of ≥75% represents disappearance of the psychiatric symptoms completely; the reduction rate of HAMD ranging from 50% to 75% represents disappearance of most of the psychiatric symptoms; and the reduction rate of HAMD ranging from 25% to 50% represents improvement in the psychiatric symptoms. Moreover, the SSS was applied to assess the severity of nerve function defect,[13] and the BI was used to evaluate the activities of daily living.[14] These 2 outcomes were considered as continuous variables, and the extent of improvement for SSS and BI was also assessed.

2.3. Data collection and quality assessment

The data items including the first authors' surname, publication year, inclusion period, sample size, age, percent male, intervention, control, treatment duration, assessed tool, and investigated outcomes were abstracted from each study. Study quality was assessed using the Jadad scale, which was based on randomization, blinding, allocation concealment, withdrawals and dropouts, and the use of intention-to-treat analysis.[15] Moreover, the scoring system of each trial ranged from 0 to 5, and each item was given response of yes, no, or not mentioned. Studies with a score of 3 or more were considered of high quality. The data collection and quality assessment was carried out by 2 authors, and any disagreement between them was settled by an additional author by referring to the original article.

2.4. Statistical analysis

Pooled analysis was divided into categories and continuous data, and the relative risk (RR) and weighted mean difference (WMD) with 95% confidence intervals (CIs) were used as an effect estimate, respectively. The analyses for investigating the outcomes were pooled using random-effects model.[16,17] The heterogeneity across the included trials were assessed using I^2 and Q statistic, and significant heterogeneity was found if $I^2 > 50.0\%$ or $P < .10$.[18,19] The robustness of pooled conclusion was assessed using sensitivity analysis.[20] Subgroup analyses for efficacy outcomes were conducted based on control drugs and treatment duration, and P value between the subgroups was assessed using P test interaction.[21] Publication bias was also tested through funnel plot, Egger and Begg tests.[22,23] The trim and fill method was applied if significant publication bias was detected.[24] The inspection level was 2-sided, and $P < .05$ was considered as

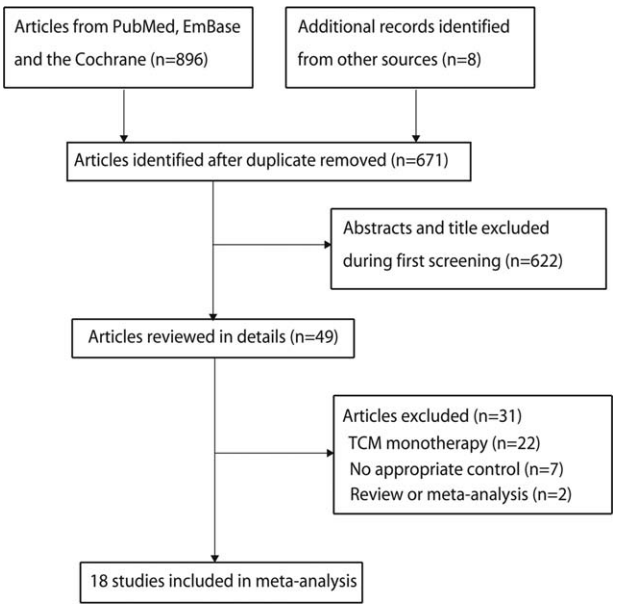

Figure 1. PRISMA flowchart for study selection process.

Table 1

The summary of baseline characteristics of included studies and patients.

Study	Inclusion period	Sample size (intervention/ control)	Age (yrs)	Percent male (%)	Intervention	Control	Treatment duration	Assessed tool	Outcomes	Study quality
Zhang 2006	2001–2005	108 (54/54)	62.5	63.0	Expectorant enlightening method plus fluoxetine (Fabanxia [10 g], Chenpi [10 g], Zhuru [10 g], Fuling [10 g], Zhishi [10 g], Calamus [10 g], Yujin [10 g], Danxing [10 g], Wushaoshe [10 g], Gancao [10 g], Danshen [20 g])	Fluoxetine (20–40 mg)	4.0 wks	SSS, BI	SSS: −8.73 (2.9) vs −5.35 (2.14); BI: 25 (3.48) vs 15 (4.68)	2
Zheng 2006	2004–2005	120 (60/60)	65.5/66.5	65.0	Huanglian wendan soup plus fluoxetine (Huanglian [10 g], chaihu [10 g], shuizhi [10 g], Chenpi [12 g], Banxia [12 g], Zhishi [12 g], Xiangfu [12 g], Yujin [15 g], Hehuanpi [15 g], Fuling [15 g], Zhuru [15 g], Dilong [15 g], Yuanzhi [15 g], Danshen [30 g], Shichangpu [30 g], Shenglongmu [30 g], Gancao [6 g])	Fluoxetine (20–40 mg)	8.0 wks	HAMD	Effective rate: 55 vs 48; HAMD: −15.1 (2.07) vs −11.3 (2.59)	3
Li 2006	NA	85 (43/42)	69.5/68.2	52.9	Xiaoyao san plus fluoxetine (Chaihu [10 g], Baishao [10 g], Danggui [10 g], Baishu [10 g], Fuling [10 g], Zhigancao [5 g], Bohe [3 g], Shengjiang [5 g])	Fluoxetine (20 mg)	4.0 wks	SSS, BI, HAMD	Effective rate: 41 vs 31; HAMD: −10.16 (3.34) vs −9.46 (3.33); SSS: −10.71 (6.61) vs −6.03 (7.02); BI: 18.78 (17.99) vs 12.18 (15.48); Gastrointestinal AEs: 2 vs 3; neurological AEs: 2 vs 2	3
Ye 2006	2001–2004	60 (30/30)	66.1	51.7	Jieyu anshen soup plus fluoxetine (Chaihu [10 g], Yujin [10 g], Shengbaishao [15 g], Shipuchang [10 g], Fuling [15 g], Baiziren [15 g], Yuanzhi [10 g], Danggui [10 g], Chaosuanzaoren [15 g], Taoren [10 g], Honghua [10 g], Zhishi [6 g])	Fluoxetine (20 mg)	8.0 wks	HAMD, SSS	Effective rate: 27 vs 24; HAMD: −15.91 (3.73) vs −11.78 (4.25); SSS: −12.56 (3.1) vs −7.14 (3.17); Gastrointestinal AEs: 9 vs 13; neurological AEs: 8 vs 15	1
Chen 2006	2002–2004	78 (46/32)	NA	NA	Ginkgo leaf tablets plus fluoxetine (Ginkgo biloba Tablet [240 mg])	Fluoxetine (20 mg)	6.0 wks	HAMD, SSS	HAMD: −18.9 (3.65) vs −14.7 (2.71); SSS: −17.3 (4.19) vs −13.3 (4.91); Gastrointestinal AEs: 26 vs 22; neurological AEs: 26 vs 24	1
Song 2008	2004–2008	72 (36/36)	61.1/63.4	54.2	Dan zhi xiaoyao powder plus fluoxetine (Mudanpi [15 g], Zhizi [15 g], Chaihu [15 g], Baishao [15 g], Danggui [15 g], Baishu [15 g], Dannanxing [12 g], Shichangpu [30 g], Fuling [30 g], Chuanqiong [30 g], Bohe [6 g], Gancao [6 g])	Fluoxetine (20 mg)	4.0 wks	SSS, BI, HAMD	Effective rate: 34 vs 33; HAMD: −14.67 (7.00) vs −11.09 (6.14); SSS: −3.09 (1.84) vs −6.3 (4.39); BI: 21.05 (6.94) vs 16.62 (6.49);	3
Li 2008	2005–2007	60 (30/30)	NA	NA	Yu xing chang zhi soup plus fluoxetine (Yujin [10 g], Dannanxing [10 g], Yuanzhi [10 g], Shichangpu [15 g], Baiziren [15 g], Fushen [12 g], Hehuanhua [12 g], Longchi [30 g])	Fluoxetine (20 mg)	6.0 weeks	HAMD, SSS	Effective rate: 25 vs 22; HAMD: −17.63 (3.89) vs −16.17 (4.39); SSS: −8.2 (2.78) vs −4.53 (2.83); Gastrointestinal AEs: 11 vs 15; neurological AEs: 2 vs 2	2

(*continued*)

Table 1

(continued).

Study	Inclusion period	Sample size (intervention/ control)	Age (yrs)	Percent male (%)	Intervention	Control	Treatment duration	Assessed tool	Outcomes	Study quality
Li 2008	2004–2006	72 (37/35)	57.0/58.0	65.3	Water-Nourishing Liver- Clearing plus fluoxetine (Shengdi [30 g], Shanzhuyu [6 g], Fushen [15 g], Danggui [6 g], Shanyao [12 g], Danpi [9 g], Chaihu [15 g], Shanzhi [9 g], Suanzaoren [20 g], Hehuanhua [30 g], Yujin [9 g], Shichangpu [9 g], Dannanxing [9 g])	Fluoxetine (20 mg)	4.0 wks	SSS, BI, HAMD	Effective rate: 35 vs 25; HAMD: −18.1 (2.15) vs −13 (2.23); SSS: −12 (5.82) vs −2.4 (6.35); BI: 32.3 (7.6) vs 2.8 (6.91)	1
Yang 2009	2005–2008	60 (30/30)	62.0/61.2	60.0	Jiawei Xiaoyao powder plus fluoxetine (Chaihu [10 g], Danggui [10 g], Baishao [10 g], Hehuanpi [15 g], Danshen [15 g], Zhike [9 g], Baishu [12 g], Fuling [12 g], Chuanqiong [12 g], Bohe [6 g], Gancao [6 g], Shengjiang [3 pieces])	Fluoxetine (20–40 mg)	4.0 and 8.0 wks	SSS	SSS: −9.9 (4.91) vs −4.9 (3.95) after 4 weeks, −12.9 (5.06) vs −9.5 (4.0) after 8 weeks; Gastrointestinal AEs: 3 vs 19; neurological AEs: 2 vs 5	2
Sun 2010	2006–2008	90 (60/30)	56.2/54.6	66.7	Dredge the method of smoothing, strengthening the spleen and nourishing the heart plus fluoxetine (Chaihu [10 g], Banxia [10 g], Dangshen [15 g], Zhigancao [10 g], Rougui [6 g], Huanglian [10 g], Yujin [10 g], Shenglong [30 g], Mu [30 g], Lianzixin [3 g], Zaoren [15 g], Baishao [10 g], Fuxiaomai [30 g], Zhenzhumu [30 g], Hehuanpi [10 g], Baihe [30 g])	Fluoxetine (20 mg)	4.0 wks	HAMD, SSS	Effective rate: 56 vs 23; HAMD: 6.12 (2.53) vs 12.1 (1.2); SSS: 11.52 (3.05) vs 18.12 (3.92); Gastrointestinal AEs: 6 vs 14; neurological AEs: 7 vs 16	1
Liu 2010	2010–2011	62 (31/31)	58.6/58.8	56.5	Tiaogan Huayu Tongluo method plus fluoxetine (Danggui [10 g], Baishao [10 g], Chaihu [10 g], Hehuanpi [15 g], Zhike [9 g], Baishu [12 g], Danshen [15 g], Fuling [12 g], Chuanqiong [12 g], Bohe [6 g], Gancao [6 g])	Fluoxetine (20 mg)	6.0 wks	HAMD	HAMD: −8.48 (2.47) vs −6.7 (1.67); Gastrointestinal AEs: 1 vs 2	3
Li 2011	2008–2009	84 (42/42)	58.4/59.6	40.5	Bupleurum and keel oyster soup plus fluoxetine (Huangling [12 g], Chaihu [12 g], Faxia [12 g], Guizhi [10 g], Dangshen [15 g], Fuling [15 g], Shengmuli [30 g], Dazao [10 g], Shenglonggu [30 g], Shengjiang [3 pieces], Dahuang [9 g], Shichangpu [15 g], Danshen [20 g])	Fluoxetine (20 mg)	8.0 wks	HAMD	Effective rate: 37 vs 28; HAMD: 0.40 (3.20) vs 2 (2.59); neurological AEs: 3 vs 6	2
Yang 2011	2007–2009	60 (30/30)	67.7/69.2	56.7	Naomaitai Capsule plus fluoxetine (1.0 g 3 times per day)	Fluoxetine (20 mg)	6.0 wks	SSS, BI, HAMD	Effective rate: 22 vs 13; HAMD: −10 (3.82) vs −7.3 (4.71); SSS: −3.1 (4.29) vs −3.1 (4.54); BI: 8 (14.12) vs 8.67 (15.25)	3

(*continued*)

Table 1

(continued).

Study	Inclusion period	Sample size (intervention/ control)	Age (yrs)	Percent male (%)	Intervention	Control	Treatment duration	Assessed tool	Outcomes	Study quality
Gan 2012	2011–2012	91 (45/46)	47.9/47.8	57.1	Shugan Jieyu decoction plus fluoxetine (Xiangfu [15g], Chaihu [15 g], Yujin [12 g], Danggui [12 g], Fushen [10 g], Chenpi [10 g], Suanzaoren [10 g], Zhigancao [6 g])	Fluoxetine (20 mg)	4.0 wks	HAMD, BI	Effective rate: 43 vs 35; HAMD: −9.2 (4.78) vs −3.9 (4.95); BI: 35.1 (6.32) vs 20.7 (6.24); Gastrointestinal AEs: 0 vs 2; neurological AEs: 1 vs 3	1
Xu 2014	2009–2011	50 (25/25)	51.0/50.4	77.1	Decoction for soothing liver, invigorating qi, activating blood circulation and clearing collaterals plus paroxetine (Huangqi [50 g], Chuanqiong [15 g], Chaihu [10 g], Baishao [10 g], Yujin [20 g], Hehuanpi [20 g], Danggui [15 g], Taoren [10 g], Honghua [10 g], Quanchong [9 g], Gancao [10 g])	Paroxetine (20 mg)	12.0 wks	HAMD	Effective rate: 23 vs 20	3
Zhou 2014	2012–2013	68 (34/34)	59.6/60.9	60.3	Traditional Chinese medicine decoction plus paroxetine (Chaihu [15 g], Xianggu [12 g], Chishao [12 g], Chenpi [12 g], Sangbaipi [12 g], Taoren [10 g], Danggui [10 g], Shichangpu [15 g], Chaozaoren [10 g], Banxia [6 g], Gancao [6 g])	Paroxetine (20 mg)	8.0 wks	HAMD, SSS	Effective rate: 32 vs 26; HAMD: −15.47 (5.17) vs -13.05 (5.32); SSS: −14.22 (5.78) vs −8.67 (6.04); Gastrointestinal AEs: 2 vs 2	3
Liu 2017	2015–2016	75 (37/38)	67.3/67.4	51.3	Bupleurum root and oyster keel plus citalopram (Chaihu, Huangling, Banxia, Dangshen, Guizhi, Chishao, Shenglong, Muli, Dahuang, Jianghuang, Fuling)	Citalopram (20 mg)	6.0 wks	HAMD	Effective rate: 32 vs 27; HAMD: −17.21 (2.06) vs −15.16 (2.04); Gastrointestinal AEs: 0 vs 3; neurological AEs: 1 vs 4	3
Zhou 2018	2013–2017	72 (36/36)	NA	57.4	The prescription of soothing liver and relieving depression plus deanxit (Tianma [10 g], Gouteng [10 g], Chaihu [10 g], Yujin [15 g], Chuanqiong [15 g], Danshen [20 g], Shichangpu [10 g], Yuanzhi [6 g])	Deanxit (1 piece)	8.0 wks	HAMD	Effective rate: 33 vs 30; HAMD: −14.09 (3.70) vs −11.72 (4.89); Gastrointestinal AEs: 1 vs 4; neurological AEs: 0 vs 3	1

*AEs = Adverse events, BI = Barthel Index, HAMD = Hamilton Depression Rating Scale, SSS = Scandinavian Stroke Scale.

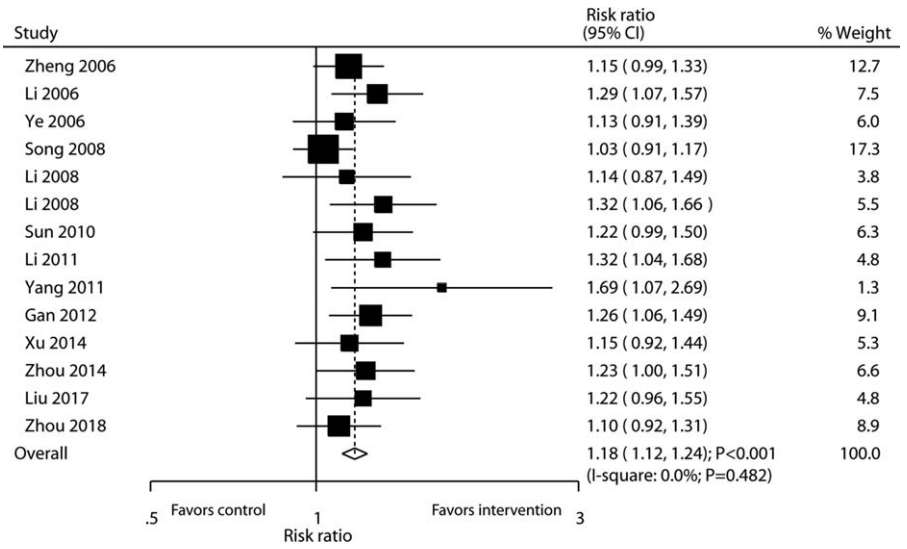

Figure 2. Therapeutic effect of CHM versus control groups for the incidence of effective rate.

statistically significant. STATA software (Version 10.0; StataCorp, TX) was used to conduct statistical analyses in this study.

3. Results

3.1. Literature search

The electronic search yielded a total of 896 articles, wherein 225 were excluded due to duplications. Next, a total of 622 studies were excluded after reading the titles and abstracts owing to irrelevant topics. The full-texts of the remaining 49 studies were retrieved, and 31 of these were excluded because of CHM monotherapy (n = 22), no appropriate control (n = 7), and review or meta-analysis (n = 2). After this, a total of 18 RCTs were considered eligible and satisfied the inclusion criteria.[25–42] Reviewing of the reference lists of these articles found 8 potentially relevant articles, but all these studies were obtained through initial electronic searches (Fig. 1).

3.2. Study characteristics

The baseline characteristics of studies and patients are summarized in Table 1. Studies included were published from 2006 to 2018, and included 50 to 120 patients in each individual trial. The mean age of included patients ranged from 47.8 to 69.5 years, and the percentage of males ranged from 40.5% to 77.1%. A total of 14 studies used CHM combined with fluoxetine, and the remaining 4 studies used CHM combined with other drugs (paroxetine, citalopram, and deanxit). The duration of treatment ranged from 4.0 to 12.0 weeks. Study quality was assessed using the Jadad scale, in which 8 studies scored 3, 4 studies scored 2, and the remaining 6 studies scored 1.

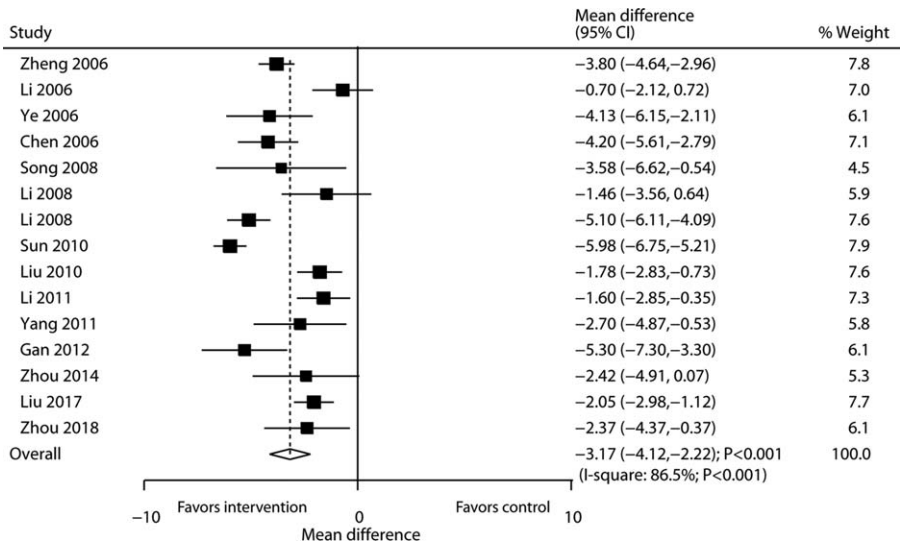

Figure 3. Therapeutic effect of CHM versus control groups for HAMD.

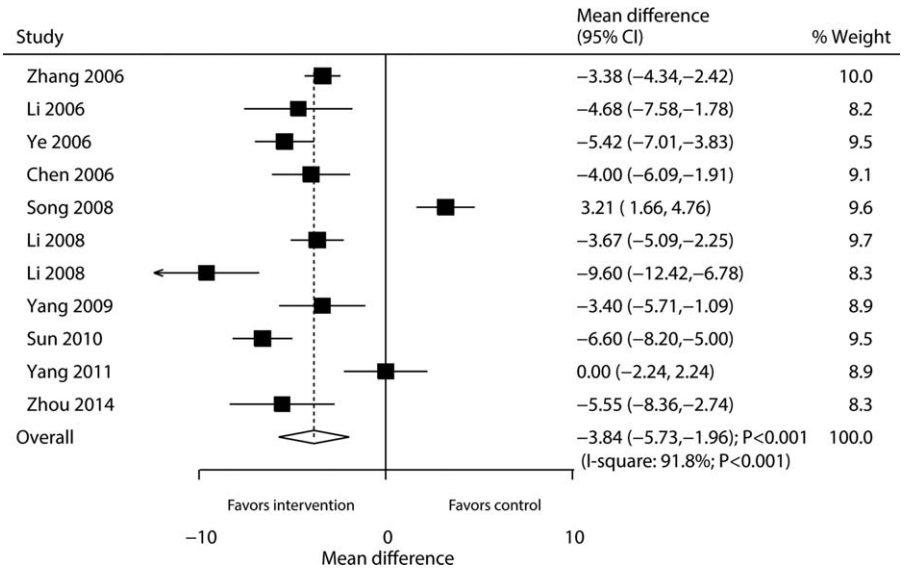

Figure 4. Therapeutic effect of CHM versus control groups for SSS.

3.3. Effective rate

A total of 14 studies reported the effective rate of PSD patients in CHM group versus control group. The pooled RR indicated that patients in CHM group were associated with high effective rate than those in the control group (RR: 1.18; 95%CI: 1.12–1.24; $P < .001$; Fig. 2), and there was no evidence of heterogeneity across the included studies ($I^2 = 0.0\%$; $P = .482$). The pooled conclusion was stable and unaltered by sequential exclusion of individual study (Supplemental Digital Content 2, http://links.lww.com/MD/F538).

3.4. HAMD

A total of 15 studies reported the change of HAMD for PSD patients in CHM group versus control group. Patients in CHM group showed association with lower HAMD than those in control group (WMD: −3.17; 95%CI: −4.12 to −2.22; $P < .001$; Fig. 3), and a significant heterogeneity was detected among the included studies ($I^2 = 86.5\%$; $P < .001$). Sensitivity analysis indicated that the conclusion was unaltered by sequential exclusion of each study (Supplemental Digital Content 2, http://links.lww.com/MD/F538).

3.5. SSS

A total of 11 studies reported the change of SSS in PSD patients in CHM group versus control group. We noted that patients in CHM group showed association with lower SSS than those in control group (WMD: −3.84; 95%CI: −5.73 to −1.96; $P < .001$; Fig. 4), and a significant heterogeneity was observed among the included studies ($I^2 = 91.8\%$; $P < .001$). The pooled conclusion remained stable and unchanged by excluding any particular

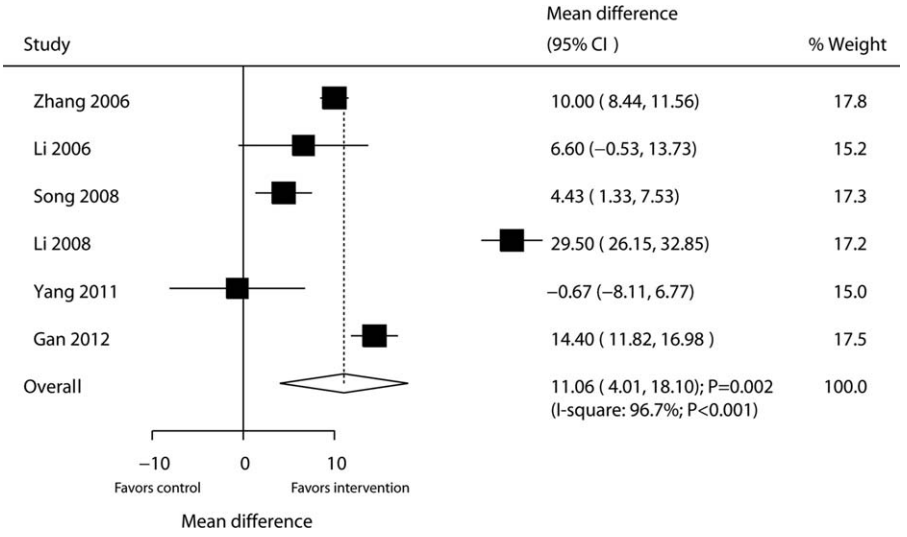

Figure 5. Therapeutic effect of CHM versus control groups for BI.

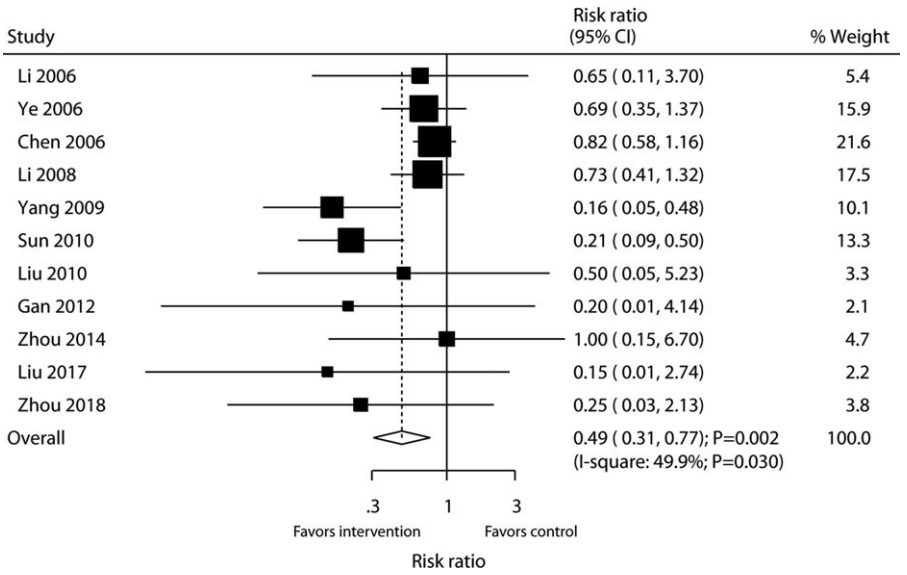

Figure 6. Therapeutic effect of CHM versus control groups for the risk of gastrointestinal adverse events.

study (Supplemental Digital Content 2, http://links.lww.com/MD/F538).

3.6. BI

A total of 6 studies reported the change of BI in PSD patients in CHM group versus control group. Patients in CHM group showed association with higher BI than those in control group (WMD: 11.06; 95%CI: 4.01 – 18.10; $P = .002$; Fig. 5), and a significant heterogeneity was detected across the included studies ($I^2 = 96.7\%$; $P < .001$). The conclusion was robust and unaltered by sequential exclusion of individual study (Supplemental Digital Content 2, http://links.lww.com/MD/F538).

3.7. Adverse events

The breakdown of the number of studies that reported the therapeutic effects of CHM versus control groups on the risk of gastrointestinal and neurological adverse events were 11 and 10, respectively. The pooled RR suggested that patients in CHM group were associated with lower risk of gastrointestinal (RR: 0.49; 95%CI: 0.31–0.77; $P = .002$; Fig. 6) and neurological (RR: 0.50; 95%CI: 0.33–0.75; $P = .001$; Fig. 7) adverse events when compared to those in control group. These conclusions were stable and unaltered by exclusion of any particular study (Supplemental Digital Content 2, http://links.lww.com/MD/F538).

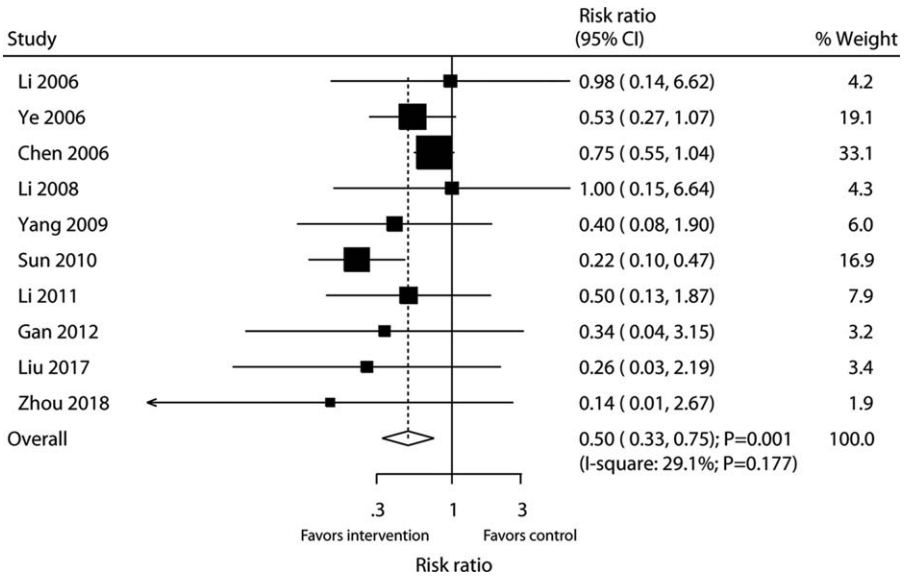

Figure 7. Therapeutic effect of CHM versus control groups for the risk of neurological adverse events.

Table 2

Subgroup analyses of investigated outcomes.

Outcomes	Variables	Subgroup	Number of studies	RR or WMD and 95%CI	*P* value	Heterogeneity (I^2)	*P* value for I^2	*P* value between subgroups
Effective rate	Control	Fluoxetine	12	1.19 (1.12–1.26)	<.001	8.0	.367	.715
		Other	2	1.14 (0.99–1.31)	.071	0.0	.489	
	Treatment duration	4.0 wks	5	1.20 (1.07–1.34)	.001	48.7	.100	1.000
		> 4.0 wks	9	1.18 (1.10–1.26)	<.001	0.0	.768	
HAMD	Control	Fluoxetine	13	−3.33 (−4.38 to −2.27)	<.001	86.8	<.001	<.001
		Other	2	−2.11 (−2.95 to −1.26)	<.001	0.0	.776	
	Treatment duration	4.0 wks	6	−3.72 (−5.64 to −1.80)	<.001	92.3	<.001	<.001
		> 4.0 wks	9	−2.80 (−3.55 to −2.05)	<.001	57.6	.016	
SSS	Control	Fluoxetine	11	−3.98 (−5.88 to −2.09)	<.001	91.9	<.001	–
		Other	0	–	–	–	–	
	Treatment duration	4.0 wks	6	−4.25 (−7.56 to −0.95)	.012	95.3	<.001	.319
		> 4.0 wks	6	−3.69 (−5.17 to −2.20)	<.001	70.2	.005	
BI	Control	Fluoxetine	6	11.06 (4.01 to 18.10)	.002	96.7	<.001	–
		Other	0	–	–	–	–	
	Treatment duration	4.0 wks	5	13.12 (5.58 to 20.66)	.001	97.1	<.001	.001
		> 4.0 wks	1	−0.67 (−8.11 to 6.77)	.860	–	–	

*BI = Barthel Index, CI = confidence interval, HAMD = Hamilton Depression Rating Scale, RR = relative risk, SSS = Scandinavian Stroke Scale, WMD = weighted mean difference.

3.8. Subgroup analysis

Subgroup analyses for efficacy outcomes were also investigated (Table 2). Firstly, although the effective rate between CHM and control groups were associated with statistically significance in most of the groups, but CHM combined with other drugs did not yield any significant effect on the effective rate than those treated with other drugs alone. Secondly, significant difference between CHM and control groups for HAMD in each subgroup was observed. Thirdly, CHM showed association with lower SSS than in control group in all other subsets. Finally, CHM showed significant association with higher BI than control in most of the subgroups, while no significant difference between groups was observed if the treatment duration was >4.0 weeks.

3.9. Publication bias

Publication bias for efficacy outcomes was assessed and presented in Supplemental Digital Content 3, http://links.lww.com/MD/F539. No evidence of publication bias was observed for HAMD (*P* value for Egger: .267; *P* value for Begg: .621), SSS (*P* value for Egger: .508; *P* value for Begg: .161), and BI (*P* value for Egger: .992; *P* value for Begg: 1.000). Although the Begg test suggested no publication bias for effective rate ($P = .155$), the result of Egger test showed significant publication bias ($P = .004$). The pooled conclusion for effective rate was unaltered after adjusting the publication bias (RR: 1.10; 95%CI: 1.05–1.08; $P < .001$).

4. Discussion

This study included 18 RCTs with 1,367 PSD patients according to strict inclusion and exclusion criteria. This meta-analysis suggested that patients in CHM group were associated with increased incidence of effective rate than those in the control group. Moreover, the HAMD, SSS, and BI in CHM group were significantly improved when compared with those in the control group. The findings of sensitivity analyses suggested stable and robust pooled conclusions. Subgroup analyses suggested significant improvement in the effective rate, HAMD, SSS, and BI between groups in most of the subgroups. Moreover, publication bias was observed for effective rate, and the conclusion was observed after adjusting for potential publication bias.

The therapeutic effects of electroacupuncture in PSD patients have already been illustrated, and the results revealed no significant difference between electroacupuncture and antidepressants on HAMD. Moreover, they also pointed out that PSD patients treated with electroacupuncture were associated with fewer adverse events.[43] Sun et al have conducted a meta-analysis of 42 RCTs and investigated the therapeutic effects of Chai Hu Shu Gan San on depression based on the types of depression. They pointed out better effects of Chai Hu Shu Gan San in PSD patients than fluoxetine based on 7 studies. Moreover, a fewer adverse events in patients treated with Chai Hu Shu Gan San were observed.[44] A meta-analysis of Ren et al compared the therapeutic effects of CHM and fluoxetine for depression and found no significant difference between CHM and fluoxetine for HAMD, and CHM showed association with reduced risk of adverse events.[45] However, no study investigated whether addition of CHM into routine western medicines yielded additional therapeutic effects for PSD. Therefore, the current meta-analysis was carried out to assess the efficacy and safety of combination of CHM with routine western medicines versus routine western medicines alone for PSD patients.

The summary results indicated that patients in CHM group showed significant improvement in the effective rate and HAMD when compared to those in control group. Subgroup analysis found no significant difference between groups for HAMD when combined with other drugs (paroxetine, citalopram, and deanxit). Moreover, this conclusion was robust after sequential exclusion of individual study and adjusting for potential publication bias. The potential reason for this could be that addition of CHM for PSD patients based on the location of syndrome differentiation, and significant association of different symptoms of specific organ with varied clinical symptoms of PSD. Moreover, no significant difference between groups for effective rate was observed in subgroup analyses, which might be due to smaller number of included studies.

This study found that patients in CHM group showed association with reduced SSS than those in control group. This effect was retained through sensitivity and subgroup analyses. Moreover, BI in CHM group was significantly improved than those in control group. Subgroup analysis found that BI showed no significant improvement if the treatment duration was greater than 4.0 weeks, which could be explained by only 1 study including in such subgroup, and the conclusion varied. PSD could affect the quality of life of patients, including did not cooperate with clinician, and delayed rehabilitation exercise. Moreover, depression could affect the pathological and biochemical function of the body, slowing the recovery of nerve function defects. Previous meta-analyses have revealed that patients treated with CHM could promote the recovery of stroke, and the potential mechanisms included activation of blood circulation and dissipation of blood stasis by CHM.[46,47] Finally, patients in CHM group showed association with lower risk of gastrointestinal and neurological adverse events. The potential reason for this could be due to acceleration of blood circulation by using CHM, and subsequent reduction of the risk of adverse events.[48]

However, there are several limitations in this study that should be acknowledged:

(1) several studies that were included had low quality, which in turn could affect the recommendation of our conclusions;
(2) the characteristics of disease status were not reported by most of the included studies, restricting us to conduct a more detailed analyses;
(3) although sensitivity and subgroup analyses were performed, the heterogeneity across the included studies could not be fully explained, which could be interpreted by varying disease status, background therapies, dose and type of CHM;
(4) the prognosis of PSD could be affected by the prescription of CHM, which differ across the included studies;
(5) inherent limitations of meta-analysis based on published articles, including publication bias and the analysis based on pooled data were not included.

In conclusion, this study suggested that the use of CHM could significantly improve the effective rate, HAMD, SSS, BI, and potential gastrointestinal and neurological adverse events in patients with PSD. Further large-scale RCTs verifying and assessing the therapeutic effects of CHM in patients with specific characteristics are warranted in the future.

Author contributions

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