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The efficacy and safety of Chai Hu Shu Gan San as an adjuvant drug for selective serotonin reuptake inhibitors in the treatment of post-stroke depression: A meta-analysis

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Abstract

Post-stroke depression often seriously affects the prognosis and quality of life of patients and many clinical trials had shown that Chai Hu Shu Gan San (柴胡疏肝散) combined with selective serotonin reuptake inhibitors (SSRIs) had good efficacy and minor side effects. We aimed to conduct this meta-analysis to evaluate the efficacy and safety of Chai Hu Shu Gan San as an adjuvant drug for SSRI in treating post-stroke depression. We searched PubMed, EMBASE, Cochrane Library, Wanfang, China Biology Medicine disc (CBM), Chongqing VIP, and CNKI (China National Knowledge Infrastructure) from their date of foundation to December 15, 2018. Literature screening, data extraction and quality assessment were conducted by two authors independently. The data synthesis and analysis were performed by using Review Manager (RevMan) 5.3 software and sensitivity analysis was conducted to assess the robustness of the results. Finally, a total of 22 articles were included. The meta-analysis confirmed the advantages of the combination of SSRI and Chai Hu Shu Gan San, mainly from four aspects: the Hamilton Depression (HAMD) scale score (MD=3.66; 95% DI=2.33-4.98; p<0.001), the Modified Edinburgh Scandinavian Stroke Scale (MESSS) score (MD=4.87; 95% CI=2.32-7.43; p<0.001), the efficacy rate (OR=3.50; 95% CI =2.61-4.69; p<0.001) and the incidence of adverse reactions (OR=0.28; 95% CI=0.17-0.46; p<0.001). No significant publication bias was observed, and sensitivity analysis suggested a good stability of the results. According to the present evidence, we concluded that Chai Hu Shu Gan San in combination with SSRI may be effective and safe in the treatment of post-stroke depression.

Keywords: Chai Hu Shu Gan San, selective serotonin reuptake inhibitors, post-stroke depression, meta-analysis

INTRODUCTION

Post-stroke depression (PSD) is considered the most frequent and important neuropsychiatric consequence of stroke[1], affecting around 33% of stroke survivors.[2] PSD has a negative impact on the rehabilitation, recuperation of motor and cognitive deficits following stroke and significantly increases the chances of relapsing neurovascular events.[2] The highest rates of incident depression are reported early in the first month after stroke and, although the incidence may decline over time and there may be a general trend toward improvement of symptoms, post-stroke depression may persist in a significant proportion of individuals.[3]

A better management of PSD is critical to reduce morbidity and mortality.[4]Among the different modalities for treating this population, the use of antidepressants is supported by adequate evidence from multiple studies.[4-7] To date, antidepressants such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs) have been used to treat PSD.[4] Among them, SSRI is a commonly used first-

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line antidepressant at present and it may be preferred in clinical practice due to relatively few adverse reactions. Therefore, we decide to conduct a meta-analysis on SSRI rather than other antidepressants. Conventional antidepressants also can improve depressive symptoms, and some new evidences that antidepressants, and SSRIs in particular, can make a substantial contribution to stroke recovery is explored[8], but they can have some relatively frequent side effects, such as gastrointestinal symptoms, headache, sexual dysfunction, and insomnia.[9] There are also some studies that suggest they may increase the risk of fractures[10-12], acute myocardial infarction[13,14] and upper gastrointestinal bleeding.[15,16]

Traditional Chinese medicine has also been used alone for mild depression or combined with antidepressants for moderate and severe depression in clinical studies.[17] Chai Hu Shu Gan San (柴胡疏肝散) is described in the Chinese ancient book Jing Yue Quan Shu by Jingyue Zhang of the Ming dynasty.[18] It has been proved to be an effective traditional Chinese medicine formula for treatment of depression and is featured as multi-ingredients preparation and multi-targets intervention on the systemic level.[19] But the number of studies about Chai Hu Shu Gan San as monotherapy in post-stroke depression is too few to conduct a meta-analysis after a comprehensive literature search.

Nowadays, it is a common practice in the Chinese Medicine to combine Chai Hu Shu Gan San and SSRIs. There have been a number of clinical studies on the two drugs in China. Many clinical trial studies have shown that the combination of Chai Hu Shu Gan San and SSRIs may be more effective and safe than SSRIs alone in the treatment of PSD, however, due to the small sample size, there is insufficient evidence about the efficacy and adverse reactions of the combination drugs. This meta-analysis may provide high-quality evidence and help us optimize treatment for patients with PSD. We believe it may be of help to the daily clinical practice.

METHODS

Search strategy

The following work was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[20] Literatures were searched in PubMed, EMBASE, the Cochrane Library, Wanfang, China Biology Medicine disc(CBM), Chongqing VIP, and CNKI (China National Knowledge Infrastructure), without language or publication status restrictions. The search terms were:" chai hu shu gan", "stroke", "depression" and "depressive disorder". Medical Subject Headings (MESH) words need to be retrieved together with text words if they exist. It is also necessary to use homophones and synonyms when searching Chinese databases. See Appendix1 for details of the search strategy. The literatures applying both SSRIs and Chai Hu Shu Gan San were screened. In order not to omit the literatures, we also need to search their references. The search period was from their inception to December 15, 2018.

Inclusion and exclusion criteria

The criteria for inclusion were as follows: (1) Participants: patients with definite diagnosis of post-stroke depression; stroke meets the standardized diagnostic criteria and is confirmed by CT or MRI; the depression is in line with the International Classification of Disease (ICD-9, ICD-10), Chinese Classification of Mental Disorders (CCMD-2, CCMD-3) or Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IIIR,DSM-IV, DSM-V) criteria.[21] (2) Intervention and comparison: intervention groups were treated with Chai Hu Shu Gan San and SSRIs, regardless of the dose and duration of medication, and control groups were treated with the same SSRIs alone; (3) Outcome index: the Hamilton Depression Scale (HAMD) scores, the Modified Edinburgh Scandinavian Stroke Scale (MESSS) score ,the efficacy rate and the adverse events of medicines; (4) Study types: randomized control trials (RCT).

The criteria for exclusion were as follows: (1) Acupuncture and moxibustion, other traditional Chinese medicine, psychological treatment, were used; (2) Unable to obtain valid information.

Literature screening

After the repeated studies were removed, the articles that did not meet the inclusion criteria were excluded by reading the titles and abstracts. Then, the full text of the identified studies was examined to determine the included and excluded studies and clarify the reasons for exclusion. This was carried out by two of the authors (CL Wang and JG Gao) individually and any disagreements was resolved via discussion with a third review author (BL Zhang).

Quality assessment

Two of the authors (CL Wang and JG Gao) evaluated the risk of bias. In case of disagreement, consensus decision was reached through consultation with another author (BL Zhang). The quality of the included studies was evaluated according to the Cochrane Collaboration evaluation standard items and tools[22] which include seven items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. When the article did not involve relevant information, it was considered "unclear".

Data extraction

Two of the authors (CL Wang and BL Zhang) independently extracted the data as follows: the first authors, publication year, number/age/gender of participants, number of patients in the intervention groups and the control groups, intervention and control measures, period of treatment, the baseline Hamilton Depression (HAMD) scale score and Modified Edinburgh Scandinavian Stroke Scale (MESSS) score, HAMD and MESSS score after treatment, follow-up, efficacy rate and the adverse events. When there was any disagreement, the consensus was reached after discussion with a third author (JG Gao).

Statistical analysis

The Review Manager (RevMan) 5.3 software, which was provided by the Cochrane Collaboration (www.cochrane.org/) and Stata version 15.0 were applied to our statistical analyses. Dichotomous data (efficacy rate and incidence of adverse reactions) was analyzed by using the Mantel-Haenszel (M-H) fixed-effect or random-effects models. And the continuous data (HAMD and MESSS score) was processed by applying the Inverse variance fixed-effect or random-effects models. The final results were represented by odds ratio (OR) or mean difference (MD), with a 95% confidence interval (CI) depending on the types of variables**.** Heterogeneity between the studies was assessed using the I^2 statistic: a value of 0% indicated no heterogeneity, 50% indicated moderate heterogeneity, and 75% indicated high heterogeneity and in general, heterogeneity was defined as $I^2 \geq 50\%$.[23] In the meta-analysis, a fixed-effect model was used if I^2 was less than 50%; otherwise, a random-effects model was used. [24] To assess the robustness of our results and to explore the contribution of each included trial, sensitivity analysis was used by omitting the studies one by one and recalculating the data. [25] The publication bias was represented by funnel plot. Finally, $P < 0.05$ was identified as statistically significant.

RESULTS

Study identification and selection

A total of 320 articles were obtained by searching 7 databases respectively. After removing the 180 duplicate articles, 109 articles that did not meet the inclusion criteria were removed after reading the titles and abstracts of the remaining 140 literatures. The final inclusion was determined by reading the full texts of the remaining 31 articles in detail. Nine articles were removed because they did not meet the inclusion criteria, the remaining 22 articles were included in the study. The flow diagram of study selection was as shown in Figure 1.

Risk of bias assessment

The quality of the included studies was evaluated using the Cochrane Collaboration evaluation standard items and tools.[22] The final evaluation results were displayed through RevMan5.3 and shown in Figures 2A and 2B.

Characteristics of the studies

Finally, a meta-analysis was performed on 22 articles, including a total of 1,946 patients. Among them, 991 were in the intervention groups and 955 in the control groups. All studies were conducted from 2005 to 2018.The intervention groups were treated with Chai Hu Shu Gan San and a SSRI. There were 16 articles about fluoxetine[26-41], 1 article about citalopram oxalate[42], 1 article about citalopram hydrobromide[43], 2 articles about paroxetine[44,45] and sertraline[46,47] respectively. The control groups were only given the same SSRI as the intervention groups. The efficacy rate was reported in 20 articles[26-28,30-39,41-47], HAMD scale score was shown in 19 articles[26,28-36,38-45,47], MESSS score was reported in 5 articles[33,35,36,38,41] and adverse reactions were described in 9 articles.[26,27,30,32,35,36,39,45,46] Two of the articles were excluded because we could not obtain valid data (one article[32] was excluded as the number of adverse events was not included in the study,

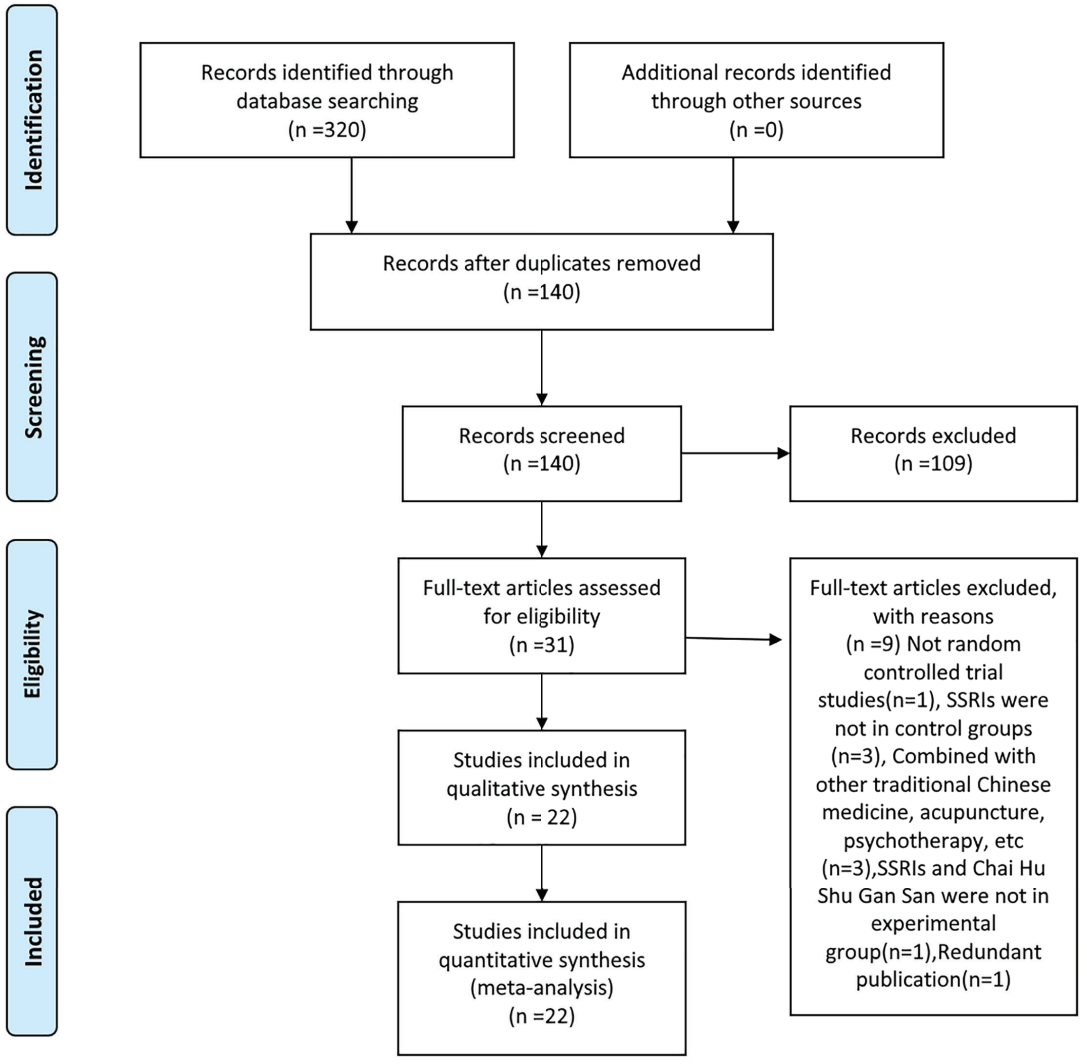

Figure 1. Flow diagram of study selection.

and the other study[36] was not included in order to improve the accuracy of data, that is to say, it was not clear whether there was a cross between the two adverse reactions). There were 4 studies which only mentioned there was no apparent adverse effects in both groups without description of other information, while the rest of the studies did not mention adverse reactions. Thus, a total of 7 articles were included regarding adverse events. Common adverse reactions were headache, dizzy, dry mouth, nausea, tiredness, and gastrointestinal reaction. The duration of medication varied from 4 weeks to 3 months. Only 3 studies[26,35,37] had information regarding follow-up and the longest follow-up time was 6 months.[18] The result showed that the long-term efficacy of the intervention groups was still better than the control groups and the recurrence rate was lower than the control groups. Details of the included literatures were shown in Table 1.

Outcomes

HAMD scale score

In most cases, we used HAMD to assess severity of depression and to observe if the disease has improved. We analyzed 19 literatures which reported HAMD data and the result showed the HAMD scale score had more significant decrease in intervention groups than control groups (MD=3.66; 95%CI=2.33-4.98; P<0.001; I^2=91%). Due to insufficient information, we were unable to conduct subgroup analysis and finally chose

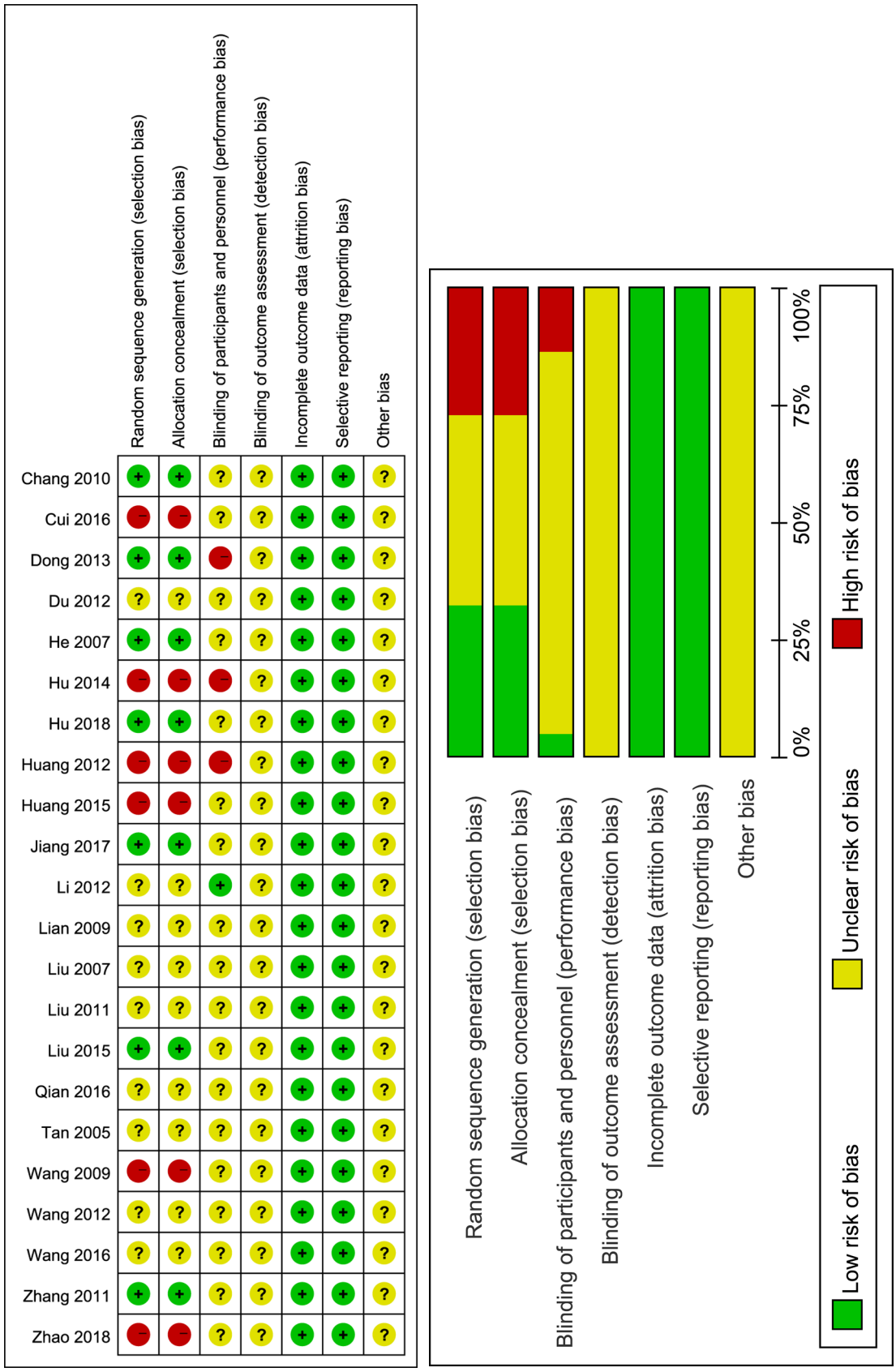

Figure 2. Assessment of the quality of included studies. (A) risk of bias summary. (B) risk of bias graph.

Table 1: Characteristics of the included studies

Author (year)	Sample size (I/C)	Gender (M/F)	Mean Age (±SD)(I/C)	Baseline HAMD scale score mean (±SD)(I/C)	HAMD scale score after treatment mean (±SD)((I/C)	Baseline MESSS score mean (±SD)(I/C)	MESSS score after treatment mean (±SD)(I/C)	Intervention Group	Control Group	Course of reatment	Following up	Efficacy Rate (events/total)	Adverse Events
Chang XH2010[38]	50/50	I:31/19 C:28/22	NR	23.73±6.2/ 22.63±6.7	10.24±3.4/ 14.20±2.7	23.8±7.1/ 26.2±6.8	11.9±3.5/ 17.9±3.3	CHSGS+fluoxetine	fluoxetine	28days	N	I:48/50C:42/50	NR
Cui Y 2016[42]	30/30	I:18/12 C:16/14	52.23±9.90/ 50.73±10.52	22.50±4.48/ 23.77±4.63	8.67±4.97/ 12.40±6.97	NR	NR	Citalopram oxalate+CHSGS	Citalopram oxalate	6weeks	N	I:28/30C:25/30	No apparent adverse effects in both groups
Dong N 2013[41]	30/30	I:16/14 C:19/11	52.73±6.22/ 54.77±7.14	21.23±3.22/ 20.53±3.17	7.20±2.14/ 8.80±2.28	25.17±5.24/ 26.40±6.19	16.20±2.96/ 17.83±3.20	CHSGS+fluoxetine	fluoxetine	6weeks	N	I:28/30C:25/30	No apparent adverse effects in both groups
Du LF 2012[37]	41/37	I:17/24 C:16/21	56/58	NR	NR	NR	NR	CHSGS+fluoxetine	fluoxetine	4weeks	half a year	I:38/41C:24/37	NR
He XM 2007[36]	36/18	I:21/15 C:11/7	53.24±6.31/ 54.36±4.42	40.22±3.31/ 40.44±3.43	16.41±2.56/ 22.06±3.35	22.34±2.52/ 22.12±3.05	13.12±2.45/ 20.24±2.21	CHSGS+fluoxetine	fluoxetine	60days	N	I:32/36C:11/18	gastrointestinal discomfort (I=8 vs C=10) Autonomic nerve dysfunction(I=10 vs C=9)
Hu JQ 2014[40]	52/41	I:37/15 C:27/14	59.05±9.45/ 58.12±10.25	25.91±1.11/ 26.88±2.43	14.51±0.96/ 18.57±1.26	NR	NR	CHSGS+fluoxetine	fluoxetine	4weeks	N	NR	NR
Hu D 2018[43]	32/32	I:17/15 C:18/14	67.41±6.98/ 68.06±7.21	15.59±4.96/ 15.41±4.78	5.78±1.98/ 7.75±3.14	NR	NR	Citalopram Hydrobromide+ CHSGS	Citalopram Hydro-bromide	8weeks	N	I:28/32C:24/32	NR
Huang YS 2012[39]	39/39	I:22/17 C:20/19	62.51±7.47/ 61.93±7.82	23.77±3.49/ 23.73±3.61	9.57±2.11/ 13.08±2.58	NR	NR	CHSGS+fluoxetine	fluoxetine	90days	N	I:35/39C:32/39	I:No adverse effect C:6cases with dry mouth, nausea, vomit, appetite reduced, insomnia, headache, tiredness
Huang WB 2015[35]	40/40	I:26/14 C:27/13	63.5±4.3/ 64.3±4.6	26.5±8.7/ 27.1±7.6	11.6±3.8/ 14.3±4.3	27.1±8.9/ 26.2±8.1	14.7±7.1/ 19.5±6.9	CHSGS+fluoxetine	fluoxetine	4weeks	3months	I:38/40C:32/40	headache(I=0 vsC=1), dizzy(I=4 vs C=3)-dry mouth(I=2 vsC=8), nausea(I=1vsC=1), tiredness(I=1vsC=1)
Jiang R 2017[47]	42/42	I:26/16 C:27/15	65.27±9.37/ 64.86±9.18	18.17±8.69/ 18.36±9.12	7.02±5.20/ 11.37±6.14	NR	NR	Sertraline+CHSGS	Sertraline	8weeks	NR	I:38/42C:30/42	No apparent adverse effect in both groups
Li FC 2012[34]	42/46	I:23/19 C:28/18	62/65	21.38±1.78/ 20.35±1.89	6.04±0.73/ 12.06±2.36	NR	NR	CHSGS+fluoxetine	fluoxetine	4weeks	N	I:39/42C:23/46	NR
Lian Z 2009[33]	30/30	I:17/13 C:16/14	56.20±18.6/ 54.6±17.5	23.91±4.52/ 22.81±3.74	6.12±2.53/ 12.10±1.25	26.13±4.25/ 25.96±3.36	11.52±3.05/ 18.12±3.92	CHSGS+fluoxetine	fluoxetine	4weeks	N	I:39/42C:23/46	NR
Liu N 2007[32]	60/60	I:27/33 C:29/31	66.5/66.8	27.42±3.76/ 26.95±3.28	7.55±2.05/ 11.12±2.11	NR	NR	CHSGS+fluoxetine	fluoxetine	8weeks	N	I:55/60C:48/60	headache, nausea, appetite descent(case unknown)

Author (year)	Sample size (I/C)	Gender (M/F)	Mean Age (±SD)(I/C)	Baseline HAMD scale score mean (±SD)(I/C)	HAMD scale score after treatment mean (±SD)((I/C)	Baseline MESSS score mean (±SD)(I/C)	MESSS score after treatment mean (±SD)(I/C)	Intervention Group	Control Group	Course of reatment	Following up	Efficacy Rate (events/total)	Adverse Events
Liu YJ 2011[31]	35/32	I:19/16 C:17/15	63.29±10.01/ 63.21±10.59	24.1±5.1/ 25.4±4.9	10.7±4.2/ 11.1±4.5	NR	NR	CHSGS+fluoxetine	fluoxetine	8weeks	N	I:31/35C:28/32	No apparent adverse effect in both groups
Liu ZB 2015[30]	65/64	I:21/44 C:22/42	53.6±5.6/ 53.4±5.5	23.73±6.81/ 23.66±6.78	7.92±8.21/ 11.9±9.12	NR	NR	CHSGS+fluoxetine	fluoxetine	6weeks	N	I:60/65C:50/64	gastrointestinal discomfort (I=1vsC=4), erythra(I=0vsC=1), tiredness(I=1vsC=2), headache(I=0 vs C=2)
Qian J 2016[45]	60/60	I:35/25 C:36/24	65.3±4.7/ 67.2±5.6	4.65±1.31/ 4.62±1.38	1.87±0.75/ 2.06±0.67	NR	NR	paroxetine+CHSGS	paroxetin	NR	N	I:54/60C:48/60	headache(I=1vs C=3),dry mouth(I=1vsC=3), tiredness (I=2 vs C=5)
Tan LR 2005[29]	50/30	I:32/18 C:16/14	61.3/NR	39.12±9.61/ 38.54±9.57	8.01±4.68/ 14.23±8.12	NR	NR	CHSGS+fluoxetine	fluoxetine	4weeks	N	NR	NR
Wang GL 2009[44]	66/66	I:22/44C:28/38	63.5±2.3/ 64.5±3.4	23.9±4.6/ 24.1±3.9	7.2±2.1/ 10.1±1.7	NR	NR	paroxetine+CHSGS	paroxetine	6weeks	N	I:62/66C:52/66	NR
Wang H 2012[46]	26/26	I:18/8C:19/7	68/66	NR	NR	NR	NR	Sertraline+CHSGS	Sertraline	90days	N	I:25/26C:20/26	gastrointestinal discomfort(I=4vsC=12), Autonomic nerve dysfunction(I=5vs C=14)
Wang WF 2016[28]	65/65	I:33/32C:32/33	41.5±2.5/ 41.6±2.4	26.5±8.7/ 27.1±7.6	12.6±3.4/ 15.5±3.2	NR	NR	CHSGS+fluoxetine	fluoxetine	4weeks	N	I:63/65C:55/65	NR
Zhang T 2011[27]	35/35	I:22/13C:20/15	50.08±7.26/ 49.68±8.15	NR	NR	NR	NR	CHSGS+fluoxetine	fluoxetine	4weeks	N	I:32/35C:25/35	I:5cases with epigastric discomfort, C:9cases with dry mouth, headache, tiredness, nausea, appetite descent
Zhao FC 2018[26]	65/62	I:36/29C:34/28	51.72±4.06/ 52.81±4.14	28.16±4.42/ 27.82±4.53	8.42±2.24/ 13.95±3.71	NR	NR	CHSGS+fluoxetine	fluoxetine	60days	3months	I:59/65C:50/62	Gastrointestinal reaction(I=2vsC=3), Liver function transient injury(I=1vsC=1), dizzy(I=2 vs C=2)

I/C, intervention group/control group; M/F, male/female.
HAMD, Hamilton Depression; SD, standard deviation.
MESSS, Modified Edinburgh Scandinavian Stroke Scale.
CHSGS, Chai Hu Shu Gan San.
NR, not reported; N, no; VS, versus.

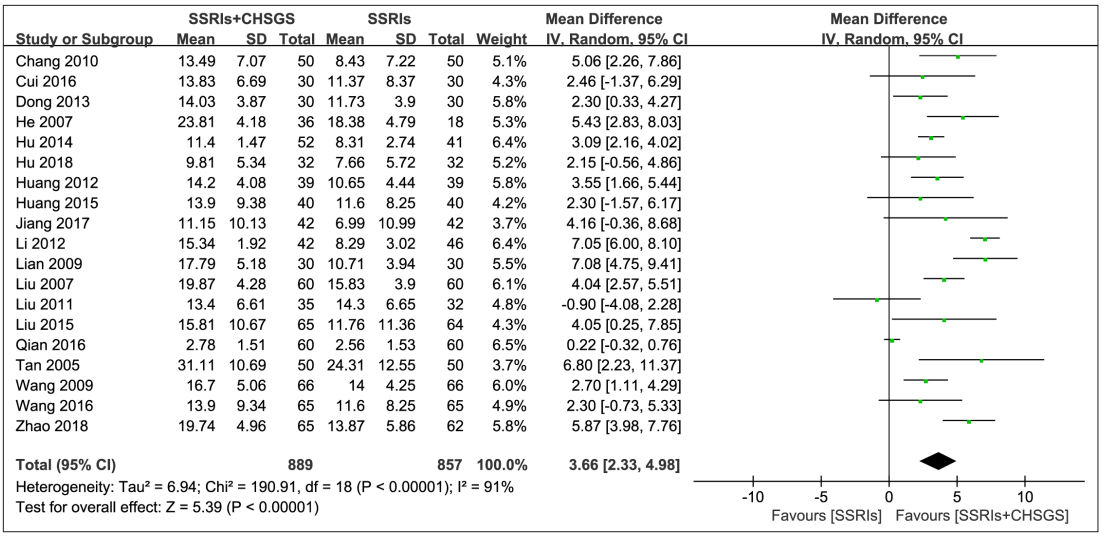

Figure 3. Forest plot of HAMD scale score.
CHSGS, Chai Hu Shu Gan San; SSRIs, selective serotonin reuptake inhibitors; CI, confidence interval; SD, standard deviation.

to use the random-effects model. Details were given in Figure 3.

MESSS score

The meta-analysis showed that the improvement of MESSS score in the intervention groups was better than that in the control groups (MD=4.87; 95%CI= 2.32-7.43; P=0.0002; I^2=73%). There was moderate heterogeneity, while only five studies mentioned MESSS score and therefore the sample size was too small to conduct further analysis. Similarly, it was treated as a random-effects model. Refer to Figure 4 to get more information.

Efficacy rate

We analyzed twenty articles with efficacy rate, and the final results showed that the efficacy rate of the intervention groups was higher than that of the control groups (OR=3.50; 95%CI=2.61-4.69; P<0.00001; I^2=0%), as detailed in Figure 5.

Adverse events

We analyzed seven articles with adverse reactions and the result showed that the incidence of adverse events in the intervention groups was lower than that in the control groups (OR=0.28; 95%CI=0.17-0.46; P<0.00001; I^2=43%), Figure 6 showed the details. However, due to the different evaluation scales of adverse reactions in different studies, the results were inevitably biased, thus we could not undertake further analysis.[18] Currently, there are few reports about adverse reactions, so it is necessary to expand the sample size for further in-depth study.

Sensitivity analysis

We applied the Stata version 15.0 for sensitivity analysis and the result showed that the meta-analysis was robust. More details about sensitivity analysis were given in Figure 7.

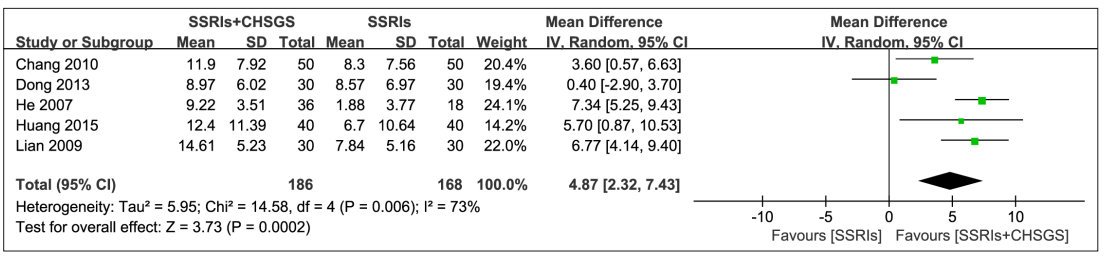

Figure 4. Forest plot of MESSS score.
CHSGS, Chai Hu Shu Gan San; SSRIs, selective serotonin reuptake inhibitors; CI, confidence interval; SD, standard deviation.

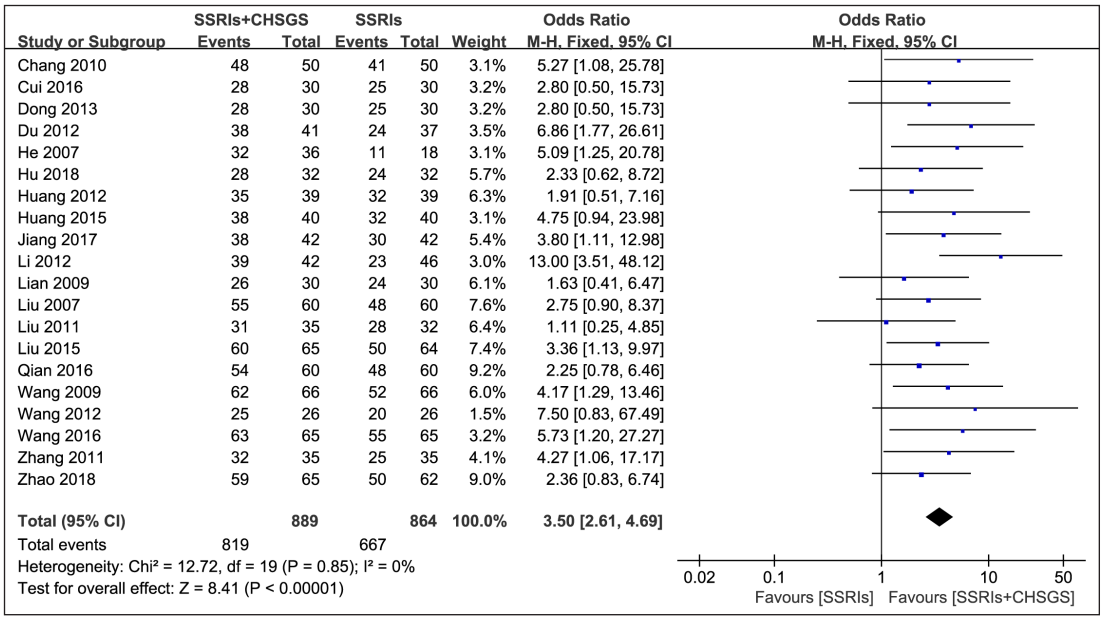

Figure 5. Forest plot of efficacy rate.
CHSGS, Chai Hu Shu Gan San; SSRIs, selective serotonin reuptake inhibitors; M-H, Mantel-Haenszel; CI, confidence interval.

Publication bias

There was no obvious publication bias in funnel plot, and the specific information was shown in Figure 8.

DISCUSSION

PSD is among the most frequent neuropsychiatric consequences of stroke, affecting approximately one third of stroke patients.[21] The pathogenesis of depression is complicated and mainly involves both neuroendocrine (eg, corticotropin-releasing hormone, corticosteroids) and central nervous system dysfunction, as well as the disturbance of neurotransmitters (eg, serotonin, norepinephrine, and dopamine agonists).[21,48,49] The mechanism by which antidepressants reduce the degree of PSD is dependent on increasing serotonin (5-HT) and norepinephrine (NE) release to produce an antidepressant response.[21,50,51]

Timely and reasonable antidepressant treatment is not only helpful for relieving depression, but also benefits neurological outcome and long-term prognosis.[17] Antidepressant treatment is required as soon as the patients are diagnosed with PSD, including medication, physical therapy, and psychological therapy.[17] Several meta-analyses have confirmed the efficacy of antidepressant

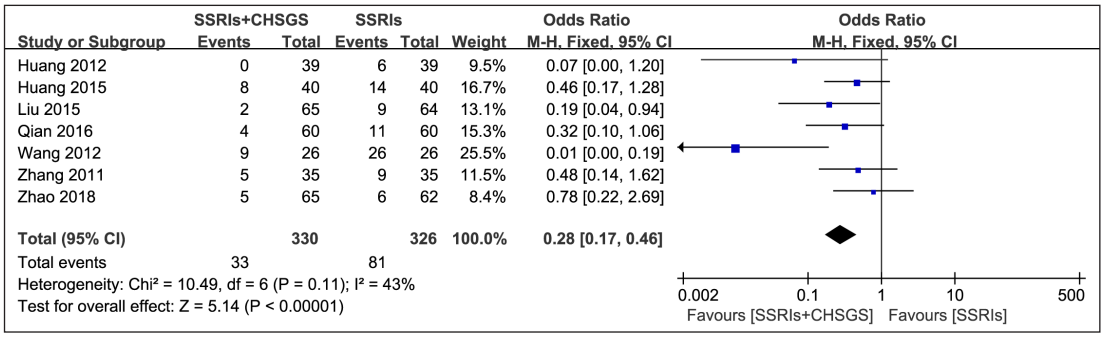

Figure 6. Forest plot of adverse events.
CHSGS, Chai Hu Shu Gan San; SSRIs, selective serotonin reuptake inhibitors; M-H, Mantel-Haenszel; CI, confidence interval.

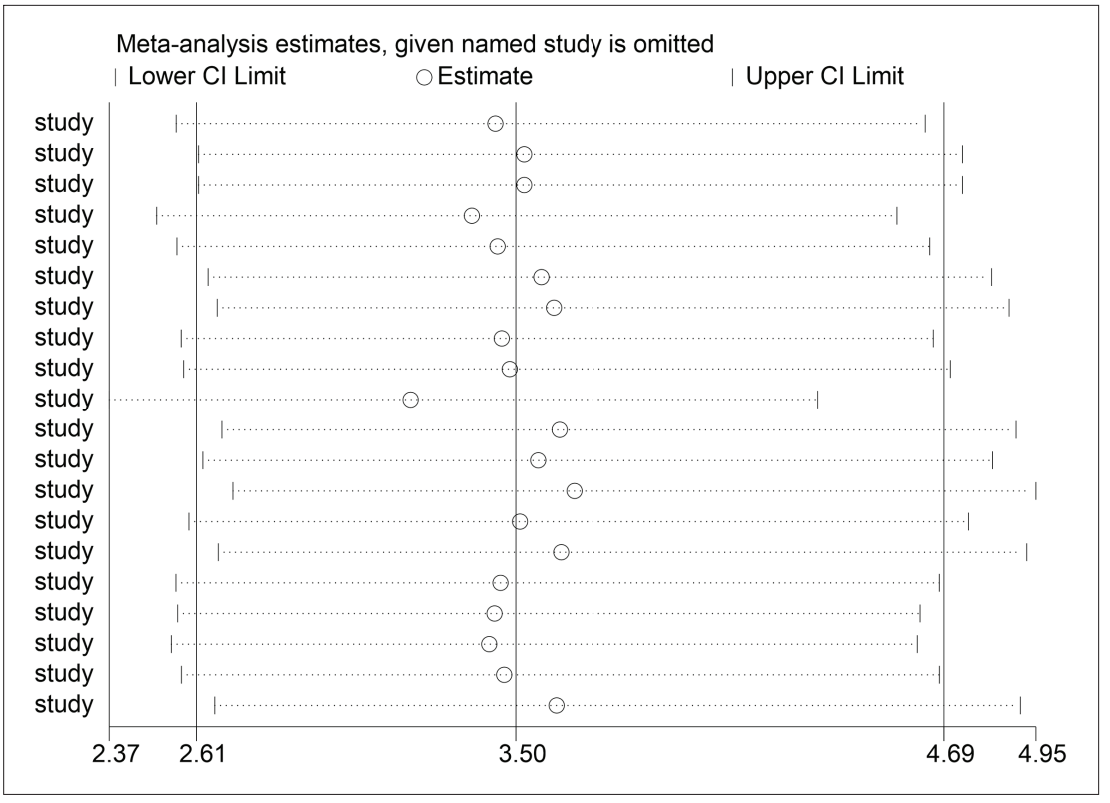

Figure 7. Sensitivity analysis of the outcome.

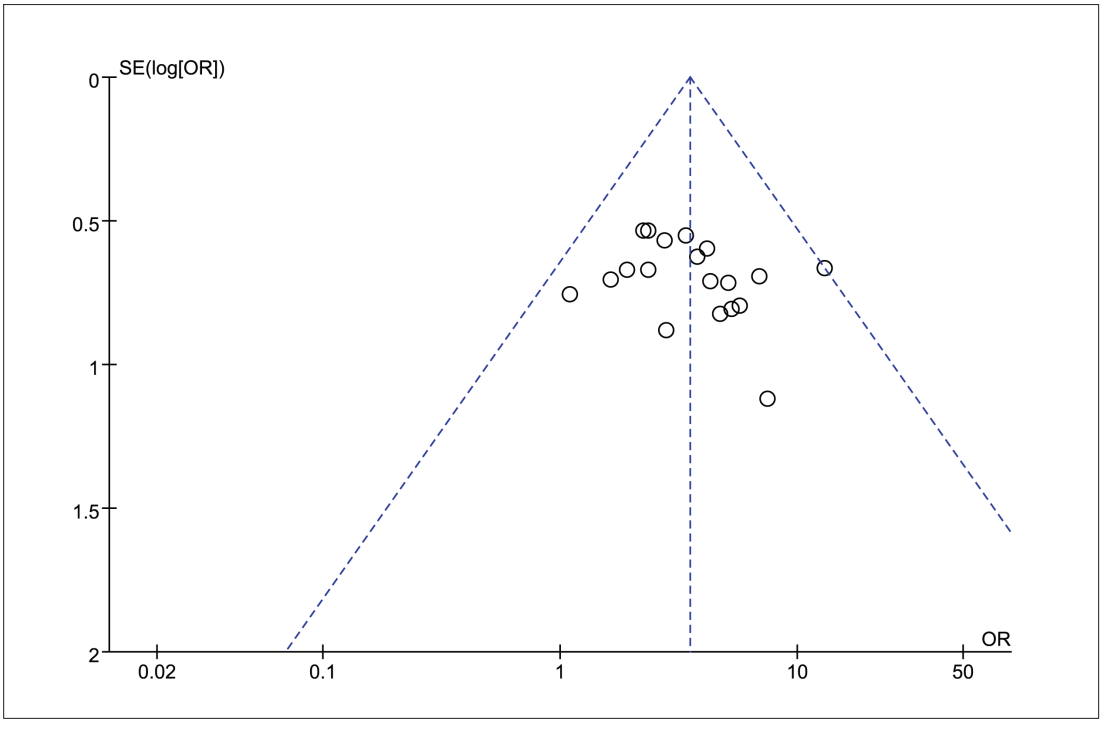

Figure 8. The funnel plot of publication bias.

treatment in PSD as compared to placebo in patients with stroke.[4,52,53] The assessment of the efficacy and safety of treatments of PSD are thus pivotal to reduce the burden of healthcare.[21] One previous meta-analysis supported the beneficial effects of Chai Hu Shu Gan San in patients with depression.[18] However, depression is not the same as post-stroke depression, and some studies have shown that Chai Hu Shu Gan San is also effective in the treatment of post-stroke depression. It has also been reported to be more effective and has fewer side effects when combined with SSRIs. So it is necessary to conduct a meta-analysis to further confirm this conclusion.

In our assessment of the included studies, PSD patients receiving Chai Hu Shu Gan San and SSRIs achieved higher efficacy rate and lower HAMD scores compared with those receiving SSRIs alone. Apart from improving depressive symptoms, Chai Hu Shu Gan San combined with SSRIs also improved the MESSS score compared with controls. The result also showed that the incidence of adverse reactions in the intervention groups was fewer than that in the control groups. We found that the kind of common adverse events between the two groups was similar, therefore, the treatment with Chai Hu Shu Gan San and SSRIs seemed to be safe and well tolerated.[54] Nevertheless, Chinese medicine in combination with Western medicine may exert adverse effect-neutralizing/synergistic potential; thus, closely monitoring the adverse effects is warranted during treatment period.[54]

Adjunctive treatment with medication of liver-soothing-oriented method (疏肝解郁法) (MLSM) is one of the most commonly used approaches for subjects with depression after cerebrovascular accident (DCVA) in China, the meta-analysis indicates that adjunctive treatment with MLSM could improve symptoms of depressive disorders, enhance immediate response and quality of life in subjects with DCVA.[55] The whole recipe is composed of Chai Hu(柴胡) (Radix Bupleuri), Chuanxiong(川芎) (Rhizoma ligustici wallichii), Xiangfu(香附) (Rhizoma Cyperi), Zhishi(枳实) (Fructus Aurantii Immaturus), Shaoyao(芍药) (Radix Paeoniae), Chenpi(陈皮) (Pericarpium Citri Reticulatae) and Gancao(甘草) (Radix Glycyrrhizae).[56] Among them, Radix Bupleuri is the main drug. It is also an example of a medicinal plant for Liver-Qi regulation(肝气调节) (MPLR) in the treatment of PSD.[57] Rhizoma ligustici wallichii can relieve depression in the treatment of PSD.[58] Rhizoma may play an antidepressant role by regulating the content of 5-HT and DA in the brain.[59] The Fructus Aurantii Immaturus play an anti-depression effect mainly through the regulation of hypothalamic-pituitary-adrenal (HPA) axis and monoamine transmitter system.[60] One study has shown that Paeoniflorin significantly inhibited KCL-induced increases in intracellular Ca^{2+} concentration and the voltage-gated calcium channel (Ca_v)1.2 current density, it may function via the calmodulin/calmodulin-dependent protein kinase II pathway and its downstream signaling molecules by regulating Ca_v1.2, thus playing an important role in the treatment and alleviation of affective disorders.[61] These studies confirmed that Radix Glycyrrhizae and its active components have definite antidepressant effect and the mechanisms may include anti-oxidative, anti-apoptotic injury, anti-monoamine oxidase, regulating monoamine neurotransmitter,etc.[62-64] Finally, Pericarpium Citri Reticulatae can enhance the efficacy of antidepressant drugs.[65]

There were some limitations in the analysis. First of all, the quantity of literatures we found through searching multiple databases was low and most included studies did not mention adequate information about random sequence generation and allocation concealment. Besides, different designs and participants' baseline characteristics of the included studies would lead to high heterogeneity that may limit the quality of the evidence of this meta-analysis. Secondly, most of the literatures had no information about follow-up, so we were unable to analyze the recurrence rate and the long-term efficacy of the treatment. Thirdly, because of lack of data, it was difficult to get a definitive answer about the peak efficacy and the trough of the adverse event after treatment, so the relevant indicators need to be measured with the same scale after the same course of treatment. Finally, despite the funnel plot not exhibiting evidence of publication bias, it could not be ignored because all included trials were published in China.[54]

In conclusion, it could be concluded that Chai Hu Shu Gan San as an adjuvant drug for SSRIs is effective with fewer side effects in treating PSD. But there are still needs for high-quality RCT .

DISCLOSURE

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