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Efficacy of Shuganjieyu capsule for treatment of neurologic disorders combined with depression: A meta-analysis

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Abstract: Shuganjieyu capsule (SGJY) is the first Chinese herbal medicine approved for treatment of depression; however, the Shuganjieyu capsule efficacy in patients with neurologic disorders combined with depression remains to be determined. Embase, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI) and other electronic databases were searched to obtain relevant studies through May 2019. Newcastle-Ottawa and Jadad scales are used for the quality assessed. Sensitivity analysis, subgroup analysis and meta-regression were performed to evaluate sources of heterogeneity. Sixty-seven studies were selected for further analysis. Patients who had Shuganjieyu therapy had a higher effective rate and lower Hamilton Depression Rating Scale (HAM-D) score compared to patients who had non-shuganjieyu therapy. In addition, Shuganjieyu capsule improve symptoms of patients with stroke (National Institutes of Health Stroke Scale (NIHSS) score: Weighted mean difference (WMD)= -2.64; 95% CI: -3.95 to -1.33; P<0.001), Parkinson's disease score: WMD= -2.53; 95% CI: -3.92 to -1.14; P<0.001), and sleep disorders (Pittsburgh Sleep Quality Index (PSQI) score: WMD= -4.97; 95% CI: -7.56 to -2.38; P<0.001). Our results demonstrated that there were clinical benefits for patients with neurologic disorders after Shuganjieyu capsule therapy compared with non-shuganjieyu therapy with respect to effective rate and HAM-D, NIHSS, UPDRS and PSQI scores.

Keywords: Depression, neurologic disorders, Shuganjieyu capsule, stroke, Parkinson's disorder.

INTRODUCTION

Depression is a common mental disorder characterized by the presence of persistent sadness, decreased self-esteem, loss of interest, reduced energy, pain with no obvious cause, cognitive dysfunction and suicidal tendencies (Beck *et al*., 2009). Epidemiological investigations performed in the general population have demonstrated that the lifetime prevalence of depression is within the range of 10%-15% (Lepine *et al*., 2011). The prevalence of depression combined with neurologic disorders such as stroke or Parkinson's disease are significantly greater than that of the general population because of severe physical damage or dysfunction of the central or peripheral nervous systems. The mean frequency of major depression and minor depression among poststroke patients were 19.3% and 18.5%, respectively. The rate is about the same as patients with Parkinson's disease (21%) (Robinson *et al*., 2003). Therefore, effective therapy for these neurologic disorders in patients with co-morbid depression could improve physical function and increase their quality of life.

Many classes of antidepressants are available to alleviate the symptoms of depression, including selective serotonin reuptake inhibitors (SSRI) (sertraline and citalopram), serotonin-norepinephrine reuptake inhibitors (SNRI) (venlafaxine and duloxetine), monoamine oxidase inhibitors (tranylcypromine), tricyclic antidepressants (imipramine) and atypical antidepressants (such as mirtazapine) (Lepine *et al*., 2011). Shuganjieyu capsule (SGJY) is the first Chinese herbal medicine approved for treatment of depression by National Medical Products Administration (NMPA) in 2009, which soothes the liver, relieves depression, strengthens the spleen and calms the nerves (Xie *et al*., 2015). The major ingredients of Shuganjieyu capsule are*: Hypericum perforatum* Linn and Acanthopanax extract, which has similar to that of SSRIs in mechanism action (Alexopoulos *et al*., 2009). Therefore, these ingredients, are clinical treated the patients with Chinses medicine symptoms liver-chi stagnation and splenic deficiency, which is topical for used mild and moderate depression These symptoms manifest as failing interest and anxiety, low energy and fatigue, sleep disorders, indigestion and loss of appetite, slow movements, irritability, sweating, white or greasy appearance of the tongue, as well as wiry pulse, or low blood pressure (Feng *et al*., 2016).

Clinical studies show that Shuganjieyu capsule treatment group has lower Hamilton Depression Scale (HAM-D)

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score and higher total effective rate compared to the no Shuganjieyu capsule group for patients exhibiting mild or moderate depression, or patients with depression and co-morbid functional dyspepsia, myocardial infarction or stroke (Zhang *et al*., 2018; Yang *et al*., 2017; Liu ey al., 2016). Moreover, multiple meta-analyses of randomized controlled trials (RCTs) have investigated the safety and efficacy of Shuganjieyu capsule in mild-to-moderate depression (Zhang *et al*., 2014) However, there has not been a comprehensive meta-analysis investigating efficacy of Shuganjieyu capsule in patients with neurologic disorders including stroke, Parkinson's disease and sleep disorders. Here, we used meta-analysis s to systematically review the literature and analyze the efficacy of Shuganjieyu capsule in neurologic disorders.

MATERIALS AND METHODS

This study was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Moher *et al*., 2009).

Databases, search scheme and selection criteria

Studies comparing the effect of Shuganjieyu capsule with non-shuganjieyu therapy for neurologic disorders according to the inclusion criteria. We searched all studies published before May 2019 from the Embase, PubMed, Cochrane Library, WanFang, CNKI and Chongqing VIP Information (VIP) electronic databases. The search keywords and phrases comprised: "shuganjieyu", "neurologic disorders", "stroke", "Parkinson's disease", "sleep disorders" and "depression". Publication date and language were unrestricted. To identify the potentially relevant studies, we further searched the reference lists of eligible studies manually. Two authors worked on literature search independently and if there are any inconsistencies, it would be resolved by Group discussion .Inclusion criteria: (1) all included subjects suffered from neurologic disorders and depression; (2) Studies for the effect of "shuganjieyu capsule therapy" vs "without shuganjieyu capsule therapy" were investigated; (3) Studies have reported results on depression such as effective rate and HAM-D score and effects on neurologic disorders such as NIHSS score, Unified Parkinson's Disease Rating Scale (UPDRS) score and PSQI score.

Collection and quality assessment of eligible data

We have collected the following information: study design, first author, sample size, publication date, mean age, percentage of male patients, course of treatment, agents of control group and outcomes.

RCTs quality was evaluated using the Jadad scale according to the randomization, follow-up completeness, blinding, treatment allocation concealment and an intention to treat analysis. The quality of the non-randomized reports was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), with up to nine points awarded to each individual study: participant selection (four points), group comparability (two points), and outcome assessment (three points).

STATISTICAL ANALYSIS

The effective rate extracted prior to pooling the data was calculate the odds ratios (OR) with 95% confidence intervals (CI). A weighted mean difference (WMD) with 95% CI was used to compare HAM-D, NIHSS, UPDRS, and PSQI scores between the shuganjieyu group (SGJY group) and non-shuganjieyu group (non-SGJY group). To assessment the potential heterogeneity in studies, Cochran's Q-statistic and I^2 statistics were employed (Higgins *et al*., 2003). For a P-value for heterogeneity of <0.05 or I^2 $>50\%$, pool the study results used a random effects model in all other instances used a fixed effects model (Ades *et al*., 2005). To assess whether the likelihood that the effect size would change following the removal of each individual study, a sensitivity analysis was conducted. were We used outcomes based on diseases, course of treatment, comparison of treatment, and quality of studies in subgroup analyses. Visual examinations of the funnel plots were conducted and Egger's and Begg's tests were used as a quantitative evaluation of publication bias (Egger *et al*., 1997; Begg *et al*., 1994). All reported P-values were in two-sided and a threshold P-value <0.05 was considered to indicate significance. STATA software (Stata Corporation, College Station, TX, USA version 14.0) was used for all statistical analyses.

RESULTS

Characteristics of the included studies

Our searching strategy yielded a total of 206 studies. After the titles and abstracts were reviewing the, 104 studies were irrelevant to our aims (fig. 1). After detailed evaluations, 9 were reviews, 6 studies compared two groups receiving shuganjieyu treatment with no other comparator, 12 were lacking necessary data, 3 being different publications of the same trials for whose main results were already included and 5 did not have full-text versions available. Therefore, the current systematic review and meta-analysis included 67 studies (Zhang *et al*., 2018; Zhu *et al*., 2017; Zhong *et al*., 2016; Zheng *et al*., 2017; Zheng *et al*., 2014; Zhao *et al*., 2013; Zhang *et al*., 2017; Zhang *et al*., 2013; Yi *et al*., 2018; Ye *et al*., 2012; Xue *et al*., 2014; Xu *et al*., 2012; Xing *et al*., 2011; Xiao *et al*., 2015; Wu *et al*., 2015; Wang *et al*., 2017; Wang *et al*., 2013; Tan *et al*., 2018; Su *et al*., 2012; Shang *et al*., 2015; San *et al*., 2010; Pan *et al*., 2018; Na *et al*., 2012; Mao *et al*.,2016; Liu *et al*., 2018; Liu *et al*., 2018; Liao *et al*., 2016; Liang *et al*., 2013; Li *et al*., 2015; Li *et al*., 2015; Li *et al*., 2014; Li *et al*., 2011; Li *et al*., 2017; Li *et al*., 2013; Kang *et al*., 2015; Guo *et al*., 2017; Xie *et al*., 2016; Jia *et al*., 2017; Jia *et al*., 2017; Huang *et*

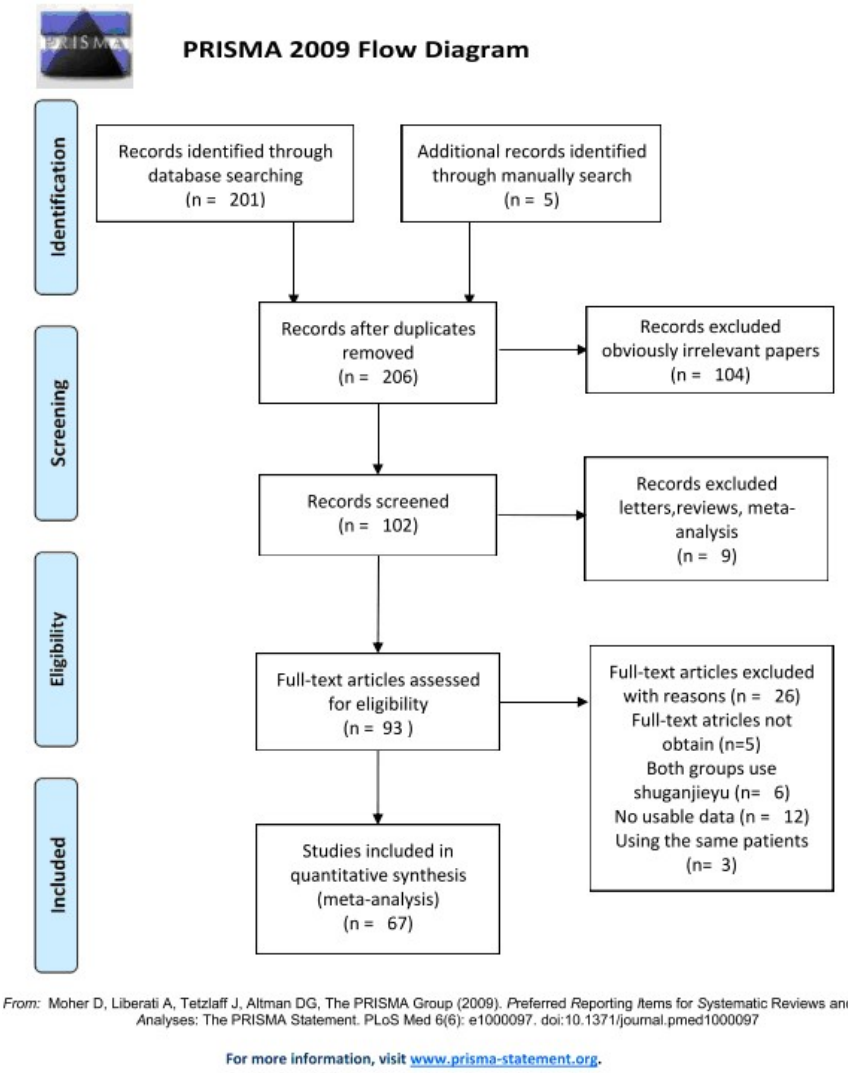

Fig. 1: Flow schematic showing the procedure of literature retrieval and selection of studies.

al., 2018; Hu *et al*., 2013; Hou *et al*., 2015; Hou *et al*., 2016; Guo *et al*., 2016; Gu *et al*., 2018; Reheman *et al*., 2013; Feng *et al*., 2017; Ding *et al*., 2014; Deng *et al*., 2016; Cheng *et al*., 2016; Chen *et al*., 2014; Chen *et al*., 2015; Chen *et al*., 2013; Zheng *et al*., 2014; Zhang *et al*., 2016; Yao *et al*., 2018; Yang *et al*., 2016; Xie *et al*., 2015; Liu *et al*., 2017; Liu *et al*., 2015; Hu *et al*., 2017; Zhang *et al*., 2016; Wang *et al*., 2018; Wang *et al*., 2015; Qin *et al*., 2017; Ding *et al*., 2013; Chen *et al*., 2013). There are total of 6,053 participants were included in here which 3,144 and 2,909 patients underwent shuganjieyu treatment and non-shuganjieyu treatment, respectively. There were 54 articles about post-stroke depression (PSD) (Zhang *et al*., 2018; Zhu *et al*., 2017; Zhong *et al*., 2016; Zheng *et al*., 2017; Zheng *et al*., 2014; Zhao *et al*., 2013; Zhang *et al*., 2017; Zhang *et al*., 2013; Yi *et al*., 2018; Ye *et al*., 2012; Xue *et al*., 2014; Xu *et al*.,2012; Xing *et al*., 2011; Xiao *et al*., 2015; Wu *et al*., 2015; Wang *et al*., 2017; Wang *et al*., 2013; Tan *et al*., 2018; Su *et al*., 2012; Shang *et al*., 2015; San *et al*., 2010; Pan *et al*., 2018; Na *et al*.,2012; Na *et al*., 2012; Liu *et al*., 2018; Liu *et al*., 2018; Liao *et al*., 2016; Liang *et al*., 2013), 7 for Parkinson's disease with depression (Zhang *et al*., 2016; Yao *et al*., 2018; Yang *et al*., 2016; Yang *et al*., 2016; Liu *et al*., 2017; Liu *et al*., 2015; Hu *et al*., 2017) and 6 for sleep disorders with depression (Zhang *et al*., 2016; Wang *et al*., 2018; Wang *et al*., 2015; Qin *et al*., 2017; Ding *et al*., 2013; Chen *et al*., 2013). The treatment group contained patients treated with shuganjieyu capsule with or without chemical antidepressants, while the control group consisted of patients treated with chemical antidepressants or placebo (table 1). The course of treatment ranged from 2 weeks to 12 weeks. All studies were conducted in China. None of the 67 studies included were completely randomized; 22 studies used random number tables but did not mention randomization concealment, 36 studies did not include a description of the randomization method and the remaining studies were not randomized or employed incorrect methods.

Table 1: Baseline characteristic of studies included in this meta-analysis

study	disease	intervention & comparision	number of patients	male percentage (%)	age	study design	NOS/Jadad score	course of treatment (week)	outcomes
Zhang J, 2018	PSD	SGJY+ Deanxit vs Deanxit	74 vs 65	27 vs 30.8	43.7±14.7 vs 43.4±14.6	cohort	8	8	HAM-D, NIHSS
Yi KC, 2018	PSD	SGJY+ Paroxetine vs Paroxetine	48 vs 48	45.8 vs 47.9	59.29±2.61 vs 59.24±2.13	RCT	3	8	HAM-D, Effective rate
Tan HY, 2018	PSD	SGJY+ Citalopram vs Citalopram	62 vs 62	51.6 vs 50	60.19±7.2 vs 59.6±2.1	cohort	7	6	HAM-D, NIHSS, Effective rate
Pan ZS, 2018	PSD	SGJY+ Mirtazapine vs Mirtazapine	42 vs 42	52.4 vs 54.8	65.12±8.35 vs 64.73±7.78	RCT	3	8	HAM-D, Effective rate
Liu W, 2018	PSD	SGJY+ Citalopram vs Citalopram	38 vs 38	44.7 vs 39.5	64.86±4.74 vs 65.38±5.25	RCT	4	8	HAM-D, Effective rate
Liu RX, 2018	PSD	SGJY+ Citalopram vs Citalopram	45 vs 45	60 vs 57.8	52.24±7.21 vs 52.32±7.15	RCT	4	8	HAM-D, NIHSS, Effective rate
Huang W, 2018	PSD	SGJY+ Estazolam vs Estazolam	43 vs 43	55.8 vs 51.2	62.13±10.68 vs 60.8±9.48	RCT	3	2	NIHSS
Gu DJ, 2018	PSD	SGJY+ Deanxit vs SGJY vs Deanxit	50 vs 50 vs 50	52 vs48 vs 50	67.4±5.1 vs 67.1±5.3 vs 66.9±4.9	cohort	8	4	HAM-D
Zhu NJ, 2017	PSD	SGJY vs Deanxit	30 vs 30	NA	67.1±5.1 vs 67.4±5.2	cohort	7	4	NIHSS, Effective rate
Zheng XD, 2017	PSD	SGJY vs Placebo	40 vs 40	57.5 vs 47.5	59.32±4.02 vs 60.24±3.58	RCT	3	6	HAM-D, Effective rate
Zhang J, 2017	PSD	SGJY+ Citalopram vs Citalopram	38 vs 37	50 vs 48.6	52.35±6.7 vs 52.1±4.61	RCT	3	6	HAM-D, Effective rate
Wang XJ, 2017	PSD	SGJY+ Citalopram vs Citalopram	32 vs 32	53.1 vs 56.3	61.37±6.26 vs 60.89±6.19	RCT	3	6	HAM-D, Effective rate
Li KJ, 2017	PSD	SGJY+ Citalopram vs Citalopram	59 vs 59	57.6 vs 62.7	69.1±8.4 vs 67.4±8.9	RCT	3	12	HAM-D
Jin H, 2017	PSD	SGJY+ Venlafaxine vs Venlafaxine	35 vs 35	45.7 vs 42.9	39.8±10.7 vs 40.1±11.3	RCT	3	12	HAM-D, Effective rate
Jia X, 2017	PSD	SGJY+ Citalopram vs Citalopram	35 vs 35	NA	58.67±3.64 vs 58.67±3.64	RCT	2	6	Effective rate
Jia K, 2017	PSD	SGJY+ Citalopram vs Citalopram	26 vs 26	57.7 vs 53.8	61.2±4.4 vs 60.7±5.2	RCT	4	8	HAM-D
Feng ZF, 2017	PSD	SGJY vs Sertraline	35 vs 35	40 vs 42.9	64±6.2 vs 63.6±6.3	cohort	8	8	HAM-D, Effective rate
Zhong H, 2016	PSD	SGJY+ Deanxit vs Deanxit	49 vs 49	NA	67.45	cohort	8	4	HAM-D
Zhong H-2, 2016	PSD	SGJY vs Deanxit	49 vs 49	NA	NA	cohort	8	4	HAM-D
Mao SL, 2016	PSD	SGJY vs Fluoxetine	60 vs 60	53.3 vs 48.3	62.5±3.8 vs 61.8±2.1	RCT	4	8	HAM-D, Effective rate
Liao SZ, 2016	PSD	SGJY+ Citalopram vs Citalopram	43 vs 43	39.5 vs 34.9	61.53±7.68 vs 60.84±7.45	RCT	4	6	PSQI, Effective rate
Xie K, 2016	PSD	SGJY+ Fluoxetine vs Fluoxetine	40 vs 40	55 vs 50	66±6.1 vs 64±5.6	RCT	3	6	HAM-D, NIHSS
Hou JX, 2016	PSD	SGJY vs Placebo	32 vs 32	NA	65.4	RCT	3	6	HAM-D, Effective rate
Guo JJ, 2016	PSD	SGJY vs Deanxit	34 vs 34	55.9 vs 52.9	65.7±5.4 vs 65.2±5.7	RCT	4	4	HAM-D
Deng XL, 2016	PSD	SGJY vs Sertraline	28 vs 27	57.1 vs 63	61±11.3 vs 62.4±10.6	RCT	4	12	HAM-D, Effective rate
Cheng Q, 2016	PSD	SGJY+ Citalopram vs Citalopram	42 vs 42	59.5 vs 57.1	53.7±3.6 vs 54.2±3.5	RCT	4	8	HAM-D, Effective rate

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Xiao ZC, 2015	PSD	SGJY vs Deanxit	48 vs 47	56.3 vs 59.6	65.84±10.27 vs 64.58±11.37	RCT	2	6	HAM-D, Effective rate
Wu HY, 2015	PSD	SGJY+ Deanxit vs Deanxit	40 vs 40	65 vs 57.5		RCT	3	4	HAM-D, Effective rate
Shang YL, 2015	PSD	SGJY+ Deanxit vs Deanxit	50 vs 50	NA	39-80	RCT	3	2	HAM-D, NIHSS
Li YX, 2015	PSD	SGJY vs Placebo	81 vs 76	NA	49.8 (32-52)	RCT	3	6	HAM-D, NIHSS
Li YT, 2015	PSD	SGJY+ Mirtazapine vs Mirtazapine	61 vs 58	45.9 vs 46.6	53.11±2.57 vs 52.27±3.09	RCT	4	8	HAM-D
Kang R, 2015	PSD	SGJY vs Citalopram	51 vs 51	47.1 vs 49	44.8±6.5 vs 45.6±5.4	RCT	3	8	HAM-D, Effective rate
Hou JH, 2015	PSD	SGJY+ Paroxetine vs Paroxetine	36 vs 36	58.3 vs 52.8	68.9±7.1 vs 69.3±7.5	RCT	4	8	HAM-D, Effective rate
Chen JB, 2015	PSD	SGJY vs Paroxetine	78 vs 78	52.6 vs 51.3	62.04±2.24 vs 63.21±2.3	RCT	3	6	HAM-D, Effective rate
Zheng AJ, 2014	PSD	SGJY vs Paroxetine	32 vs 32	NA	34-75	RCT	3	6	HAM-D, Effective rate
Xue XX, 2014	PSD	SGJY+ Paroxetine vs Paroxetine	40 vs 40	42.5 vs 45	62.83±10.79 vs 61.93±10.79	RCT	4	12	HAM-D
Li RX, 2014	PSD	SGJY+ Citalopram vs Citalopram	32 vs 32	78.1 vs 0	67.51±10.21 vs	RCT	3	6	HAM-D, NIHSS
Ding N, 2014	PSD	SGJY+ Paroxetine vs Paroxetine	40 vs 40	55 vs 52.5	56.42±5.18 vs 55.38±6.32	RCT	3	8	HAM-D, Effective rate
Chen W, 2014	PSD	SGJY+ Venlafaxine vs Venlafaxine	58 vs 57	48.3 vs 50.9	58.6±5.8 vs 58.5±5.7	RCT	4	6	Effective rate
Zeng XL, 2014	PSD	SGJY vs Paroxetine	41 vs 41	107.3 vs 0	62.3±9.2 vs	RCT	4	6	Effective rate
Zhao Z, 2014	PSD	SGJY+ Paroxetine vs Paroxetine	40 vs 40	52.5 vs 55	61.2±11.2 vs 62.3±10.1	RCT	4	6	HAM-D, Effective rate
Zhang RC, 2013	PSD	SGJY vs Placebo	40 vs 40	62.5 vs 60	49-71 vs 44-68	RCT	3	12	HAM-D, NIHSS
Wang S, 2013	PSD	SGJY vs Placebo	30 vs 30	70 vs 56.7	66.2±10.12 vs 65.35±11.2	RCT	3	4	HAM-D
Liang SP, 2013	PSD	SGJY vs Deanxit	75 vs 75	54.7 vs 53.3	59.6±7.7 vs 60±7.5	RCT	3	4	Effective rate
Li JL, 2013	PSD	SGJY vs Fluoxetine	27 vs 27	70.4 vs 74.1	57.9±8.1 vs 58.2±6.7	RCT	3	8	HAM-D, Effective rate
Hu J, 2013	PSD	SGJY+ Sertraline vs Sertraline	45 vs 44	66.7 vs 63.6	56.42±5.18 vs 55.38±6.32	RCT	2	6	HAM-D, Effective rate
GLNS, 2013	PSD	SGJY vs Doxepin	45 vs 35	31.1 vs 28.6	59.1±1.1 vs 55.4	RCT	3	6	HAM-D, Effective rate
Chen AJ, 2013	PSD	SGJY+ Paroxetine vs Paroxetine	39 vs 39	NA	NA	cohort	8	6	Effective rate
Ye QH, 2012	PSD	SGJY vs Deanxit	30 vs 30	46.7 vs 50	64.5±6.8 vs 63.8±7.1	RCT	2	6	HAM-D, NIHSS
Xu M, 2012	PSD	SGJY+ Venlafaxine vs Venlafaxine	60 vs 60	61.7 vs 66.7	52-76 vs 55-74	RCT	3	6	HAM-D, Effective rate
Su W, 2012	PSD	SGJY vs Citalopram	42 vs 42	42.9 vs 38.1	68.12±10.51 vs 71.44±14.26	RCT	4	6	HAM-D, Effective rate
Na WQ, 2012	PSD	SGJY+ Sertraline vs Sertraline	41 vs 39	43.9 vs 43.6	71.12±5.51 vs 72.54±7.16	RCT	4	8	HAM-D, Effective rate
Xing XR, 2011	PSD	SGJY+ Citalopram vs SGJY vs Citalopram	38 vs 39 vs 37	47.4 vs 53.8 vs 51.4	52.23±7.5	RCT	3	6	HAM-D, Effective rate
Li L, 2011	PSD	SGJY vs Deanxit	31 vs 31	58.1 vs 45.2	60.6±3.1 vs 61.2±4.4	RCT	3	12	Effective rate
San XZ, 2010	PSD	SGJY vs Amitriptyline	30 vs 30	56.7 vs 60	65.8±9.86 vs 66.2±10.36	RCT	3	6	HAM-D, Effective rate
Yao XD, 2018	Parkinson's disease	SGJY+ Duloxetine vs Duloxetine	37 vs 36	37.8 vs 44.4	66.59±8.32 vs 66.84±8.09	RCT	4	8	HAM-D, UPDRS, Effective rate

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Liu XB, 2017	Parkinson's disease	SGJY+ Paroxetine vs Paroxetine	40 vs 40	55 vs 60	64.37±7.05 vs 63.79±8.21	RCT	4	6	HAM-D, UPDRS, Effective rate
Hu J, 2017	Parkinson's disease	SGJY+ Sertraline vs Sertraline	45 vs 45	66.7 vs 68.9	65.1±5.24 vs 65.25±5.72	RCT	3	12	HAM-D, Effective rate
Zhang XD, 2016	Parkinson's disease	SGJY vs Paroxetine	25 vs 25	52 vs 56	NA	RCT	4	6	Effective rate
Yang QY, 2016	Parkinson's disease	SGJY vs Paroxetine	39 vs 39	NA	65.12±6.63	RCT	3	8	HAM-D, Effective rate
Xie N, 2015	Parkinson's disease	SGJY+ Venlafaxine vs Venlafaxine	30 vs 30	60 vs 53.3	62.5±6.1 vs 63.2±7.3	RCT	3	6	
Liu H, 2015	Parkinson's disease	SGJY vs Sertraline	36 vs 34	63.9 vs 61.8	62.3±7.4 vs 61.2±7.3	RCT	4	12	HAM-D, UPDRS, Effective rate
Wang Y, 2018	sleep disorders	SGJY vs Paroxetine	49 vs 49	46.9 vs 42.9	45.07±12.11 vs 46.52±13.49	RCT	4	8	HAM-D, PSQI
Qin AF, 2017	sleep disorders	SGJY+ Citalopram vs Citalopram	70 vs 70	NA	63.5±7.2 vs 61.4±5.9	RCT	4	12	HAM-D, PSQI, Effective rate
Zhang MX, 2016	sleep disorders	SGJY+ Fluoxetine vs Fluoxetine	29 vs 29	48.3 vs 44.8	33.2±11.8 vs 34.7±15.3	RCT	3	6	HAM-D, PSQI, Effective rate
Wang J, 2015	sleep disorders	SGJY+ Mirtazapine vs Mirtazapine	36 vs 36	58.3 vs 63.9	43.5±2.4 vs 44±2.2	RCT	3	6	HAM-D, Effective rate
Ding SS, 2013	sleep disorders	SGJY+ Fluvoxamine vs SGJY vs Fluvoxamine	40 vs 40 vs 23	22.5	39.5	RCT	3	4	Effective rate
Chen JY, 2013	sleep disorders	SGJY vs Estazolam	33 vs 31	45.5 vs 45.2	51.23±2.43 vs 52.56±2.76	RCT	3	6	Effective rate

NOS, Newcastle-Ottawa Quality Assessment Scale; PSD, post-stroke depression; SGJY, shuganjieyu capsule; vs, versus; RCT, randomized controlled trial; HAM-D, Hamilton Depression Scale; NIHSS, National Institute of Health stroke scale; UPDRS, Unified Parkinson's Disease Rating Scale; PSQI, Pittsburgh sleep quality index; NA, not available.

Effective rate

Fifty studies provided detailed data on effective rate with 2,157 subjects in the SGJY group and 2,103 in the non-SGJY group. The pooled analysis revealed that the subjects showed higher effective rate in the SGJY group v.s. the non-SGJY group (OR = 2.81, 95% CI: 2.37-3.34, P<0.001; fig. 2). Minor heterogeneity was observed within the groups (I^2 = 30.7%, P=0.023). In addition, the data were in line with the overall findings in subgroup analysis and no pre-defined factors impacted the therapeutic efficacy of Shuganjieyu capsule (table 2). A meta-regression analysis was conducted based on sample size and course of treatment. Overall, the effective rate of Shuganjieyu capsule was not significantly affected by the sample size (P=0.195) or course of treatment (P=0.856) (Supplemental fig. 1A and fig. 1B). In the sensitivity analysis showed that, the sequential removal of each study from the pooled analysis had no significant effect on the meta-analysis overall results.

HAM-D score

There were 57 studies that investigated the effect of Shuganjieyu capsule on HAM-D scores. The results indicated that Shuganjieyu capsule was associated with the lower HAM-D scores (WMD= -3.76; 95% CI: -4.70 to -2.83; P<0.001; fig. 3); however, these studies were also associated with significant heterogeneity (I^2 = 98.7%, P<0.001). Furthermore, SGJY capsule did not significantly reduce the HAM-D scores in Parkinson's disease in subgroup analysis (WMD= -3.24; 95% CI: -6.83 to 0.36; P=0.077; table 2). In addition, neither the sample size (P=0.127) nor the course of treatment (P=0.398) significantly affected the HAM-D scores (Supplemental fig. 2A and 2B). The sensitivity analysis revealed that exclusion of any specific trials for HAM-D scores did not impact the conclusions.

NIHSS score

To evaluate the effect of Shuganjieyu capsule on stroke symptom improvement, NIHSS scores were extracted and analyzed. Pooled analysis results indicated that a lower NIHSS score was observed in the shuganjieyu group (WMD= -2.64; 95% CI: -3.955 to -1.33; P<0.001; fig. 4). Furthermore, subgroup analysis suggested Shuganjieyu capsule significantly reduced NIHSS scores when combined with chemical antidepressants compared to chemical antidepressants without Shuganjieyu capsule (WMD= -3.20; 95% CI: -4.81 to -1.59; P<0.001; table 2). Sample size (P=0.535) and course of treatment (P=0.710) did not significantly affect the effective rate of Shuganjieyu capsule treatment (fig. 3). Despite the substantial heterogeneity observed regarding the magnitude of the effect across in all studies (I^2=97.2%; P<0.001), and sequential exclusion of any particular study from the pooled analyses were not affected the final conclusion.

Table 2: Subgroup analyses for investigated outcomes

Subgroup	N	OR/WMD (95%CI)	P	I^2	$P_{heterogeneity}$
Effective rate					
Overall	50	2.81(2.37, 3.34)	<0.001	30.7	0.023
Disease					
PSD	38	2.75(2.27, 3.33)	<0.001	31.5	0.035
Parkinson	6	2.47(1.46, 4.18)	0.001	54.5	0.051
Sleep disorder	6	4.20(2.26, 7.78)	<0.001	0	0.687
Course of treatment					
≤6 weeks	31	2.91(2.35, 3.60)	<0.001	33.2	0.039
>6 weeks	19	2.67(1.99, 3.54)	<0.001	30.1	0.105
Treatment					
SGJY+ chemical antidepressants vs chemical antidepressants	27	3.27(2.56, 4.20)	<0.001	0	0.605
SGJY vs chemical antidepressants	20	1.81(1.38, 2.37)	<0.001	13	0.292
SGJY vs placebo	3	7.84(4.40, 13.94)	<0.001	85.2	0.001
HAM-D score					
Overall	57	-3.76 (-4.70, -2.83)	<0.001	98.7	<0.001
Disease					
PSD	48	-3.74(-4.92, -2.55)	<0.001	98.7	<0.001
Parkinson	5	-3.24(-6.83, 0.36)	0.077	99.4	<0.001
Sleep disorder	4	-4.95(-6.21, -3.70)	<0.001	73.6	<0.001
Course of treatment					
≤6 weeks	31	-3.26(-4.65, -1.88)	<0.001	97.3	<0.001
>6 weeks	26	-3.99(-5.24, -2.7)	<0.001	99	<0.001
Treatment					
SGJY+ chemical antidepressants vs chemical antidepressants	33	-4.22(-5.18, -3.27)	<0.001	98.2	<0.001
SGJY vs chemical antidepressants	19	-1.66(-2.65, -0.66)	0.001	92.1	<0.001
SGJY vs placebo	5	-6.80(-4.56, -2.62)	0.038	99.5	<0.001
NIHSS score					
Overall	11	-2.64 (-3.95, -1.33)	<0.001	97.2	<0.001
Course of treatment					
≤6 weeks	8	-2.16(-3.74, -1.33)	0.008	94.5	<0.001
>6 weeks	3	-3.82(-6.20, -1.43)	0.002	98.7	<0.001
Treatment					
SGJY+ chemical antidepressants vs chemical antidepressants	6	-3.20(-4.87, -1.59)	<0.001	96.4	<0.001
SGJY vs chemical antidepressants	2	-3.16(-9.16, 2.83)	0.301	94.1	<0.001
SGJY vs placebo	3	-1.37(-4.51, 1.76)	0.391	98.1	<0.001

PSD, post-stroke depression; SGJY, Shuganjieyu capsule; vs, versus; OR, odds ratio; WMD, weighted mean difference; CI, confidence intervals; HAM-D, Hamilton Depression Scale; NIHSS, National Institute of Health Stroke Scale.

Table 3: P value of egger and Begg test

P value	Effective rate	HAM-D	NIHSS
Egger test	0.013	<0.001	0.842
Begg test	0.015	0.491	0.436

HAM-D, Hamilton Depression Scale; NIHSS, National Institute of Health stroke scale.

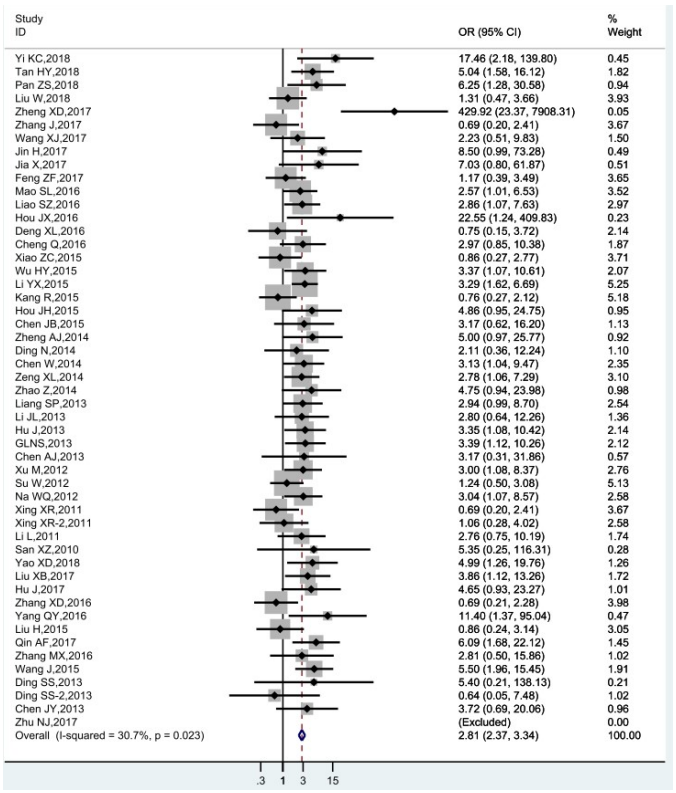

Fig. 2: Forest plot displaying the overall effect of Shuganjieyu capsule versus controls on the effective rate.

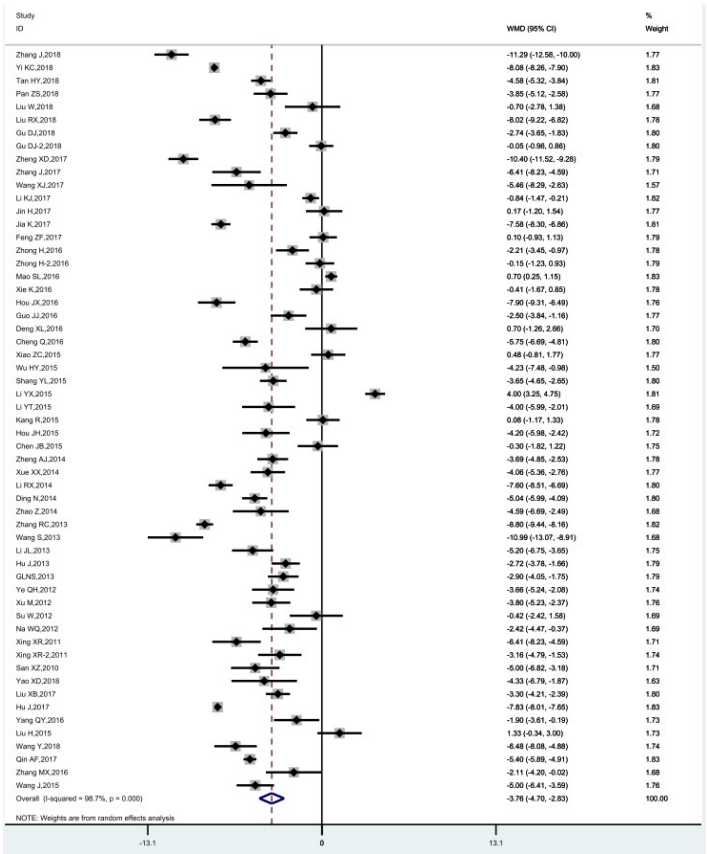

Fig. 3: Forest plot displaying the overall effect of Shuganjieyu capsule versus controls on the HAMD score.

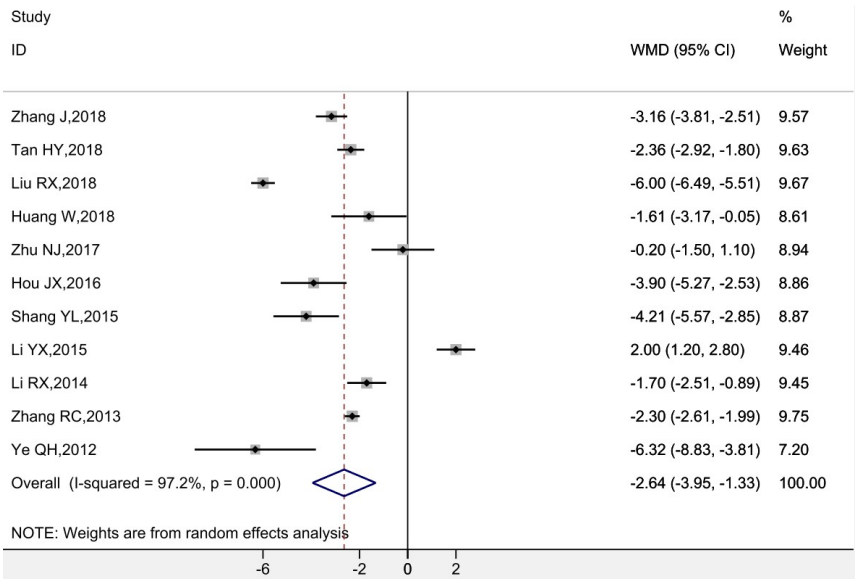

Fig. 4: Forest plot displaying the overall effect of Shuganjieyu capsule versus controls on the NHISS score.

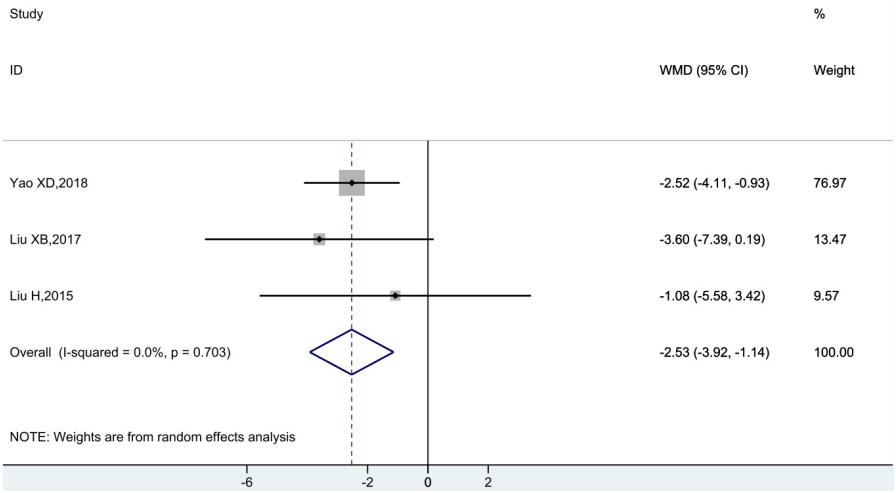

Fig. 5: Forest plot displaying the overall effect of Shuganjieyu capsule versus controls on the UPDRS score.

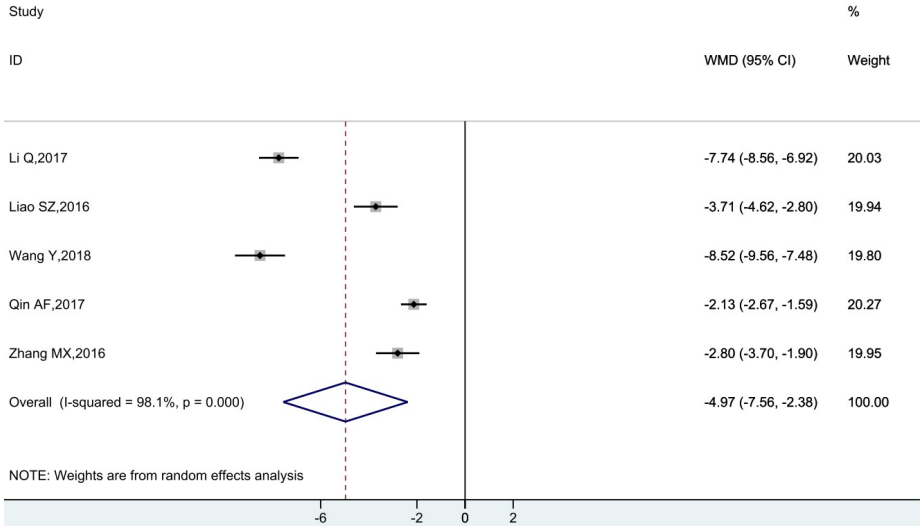

Fig. 6: Forest plot displaying the overall effect of Shuganjieyu capsule versus controls on the PSQI score.

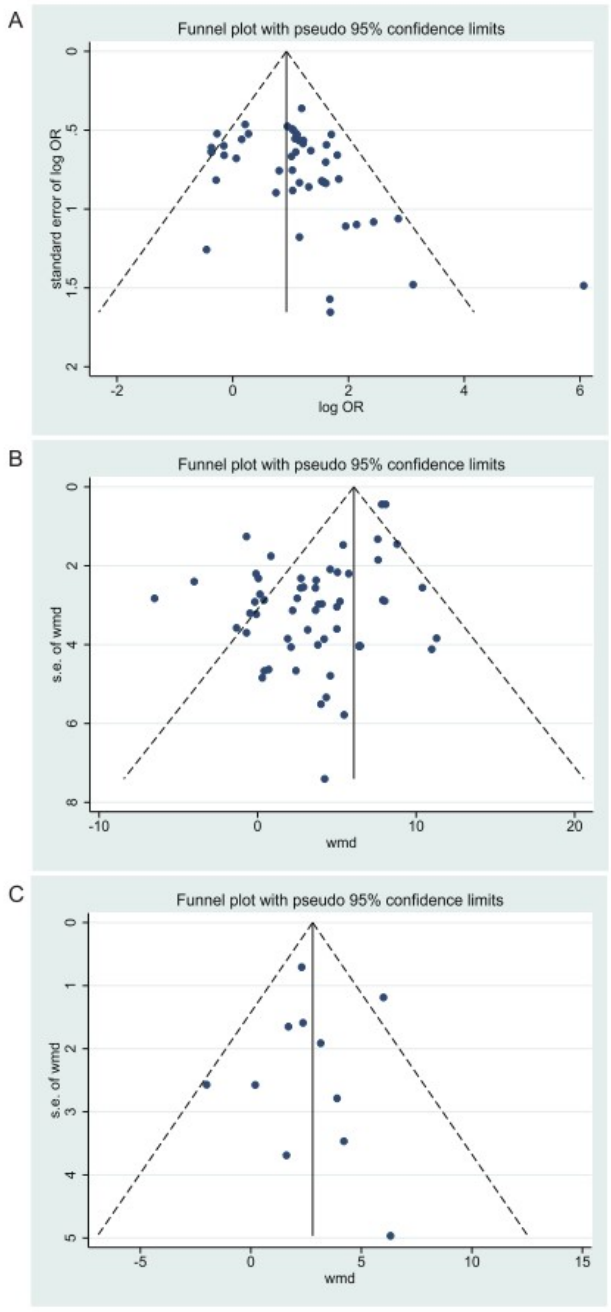

Fig. 7: Funnel plots for effective rate (A), HAMD score (B), NHISS score (C).

UPDRS score

To elucidate Shuganjieyu capsule effect on Parkinson's disease symptom improvement, UPDRS scores were extracted and analyzed. Pooled analysis of the results indicated that a lower UPDRS score was observed in SGJY group (WMD= -2.53; 95% CI: -3.92 to -1.14; P<0.001; fig. 5). And no heterogeneity was observed within the groups (I^2 = 0.0%, P=0.703).

PSQI score

To evaluate the effect of Shuganjieyu capsule on sleep disorders symptom improvement, PSQI scores were extracted and analyzed. Pooled analysis results indicated that a lower PSQI score was observed in the shuganjieyu group (WMD= -4.97; 95% CI: -7.56 to -2.38; P<0.001; fig. 6) with high heterogeneity (I^2 = 98.1%, P<0.001).

Evaluation of publication bias

There are funnel plot review, which was not able to rule out potential publication bias (fig. 7). While, Begg's test and Egger's test showed effective rate and HAM-D score had shown potential publication bias (table 3). The conclusions remained unchanged after publication bias was adjusted via all fill method and the trim..

DISCUSSION

The aim of this meta-analysis aimedis evaluate the Shuganjieyu capsule effect on neurologic disorder patients with concomitant depression. Sixty-seven studies with 6,153 patients were identified. The results of this study solid indicate that Shuganjieyu capsule therapy is related to a higher effective rate, lower HAM-D score, lower NIHSS score, lower UPDRS score and lower PSQI score. Subgroup analysis suggested that Shuganjieyu capsule did not significantly reduce HAM-D scores in Parkinson's disease, but did significantly reduce NIHSS scores when combined with chemical antidepressants compared to chemical antidepressants without Shuganjieyu capsule. These findings might assist in more accurately determining the efficacy of Shuganjieyu capsule treatment in neurologic disorder patients with co-morbid depression and can help physicians select appropriate treatment strategies.

Consistent with other meta-analyses, in this study Shuganjieyu capsule group had a favorable effective rate and lower HAM-D score than the control group, which suggests that shuganjieyu is an effective therapy for depression (Zhang *et al*., 2014; Zhen *et al*., 2018; Yi *et al*., 2018). Despite these observations, patients with Parkinson's disease had a lower HAM-D score without a statistically significant difference compared to non-SGJY group. Thus, large-scale trials are recommended to evaluate the benefits of Shuganjieyu capsule in Parkinson's disease. Shuganjieyu capsule significantly reduced NIHSS scores only when combined with chemical antidepressants. Studies have reported that synergistic effects occur when chemical antidepressants are co-administered (Hou *et al*., 2016; Yang *et al*., 2021; He *et al*., 2021; Pałucha-Poniewiera., 2022). Subgroup analysis showed that the main sources of heterogeneity for effective rate outcome were in Shuganjieyu capsule group compared to the placebo group. After subgroup analysis and sensitivity analysis, the heterogeneity still existed within HAM-D scores, indicating that participant selection may represent a heterogeneity source.

Supplementary materials

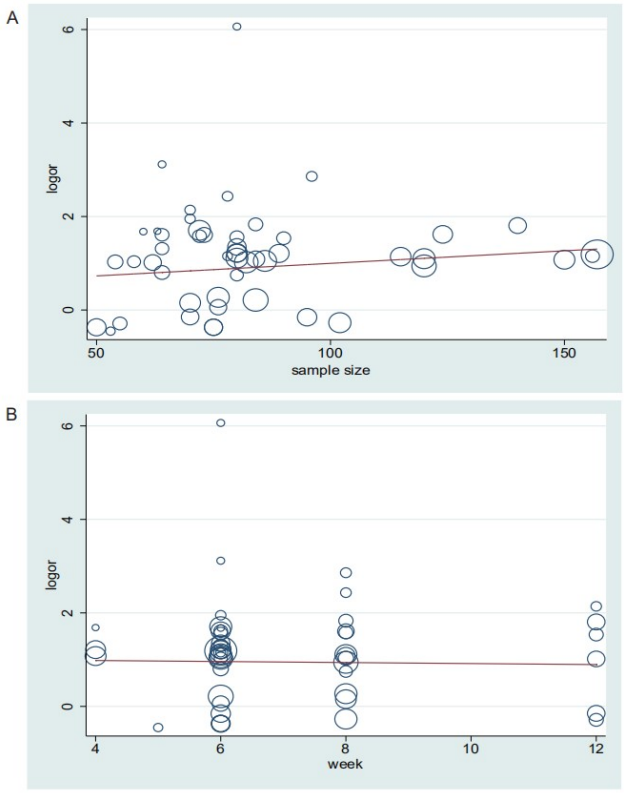

Fig. 1: Meta-regression plot displaying the effect of sample size (A) and course of treatment (B) for the effective rate.

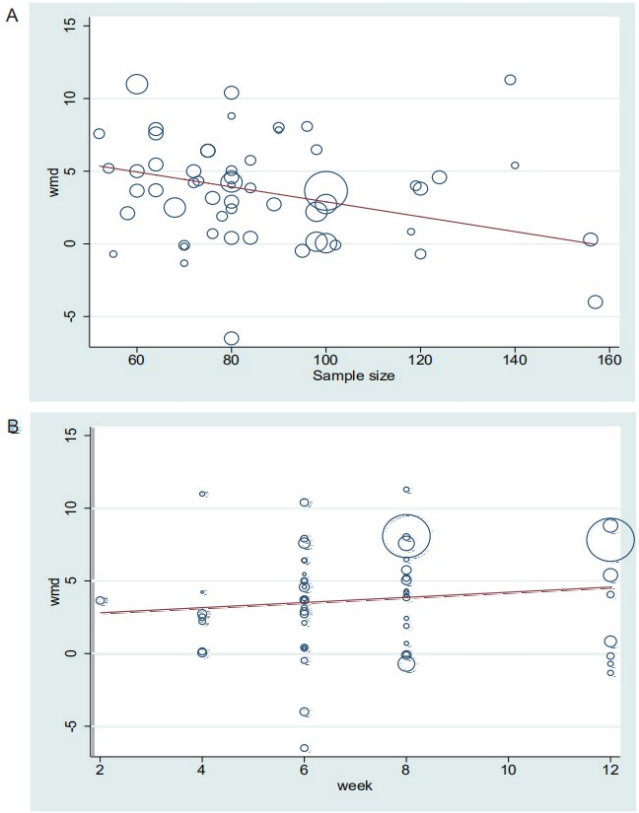

Fig. 2: Meta-regression plot displaying the effect of sample size (A) and course of treatment (B) for the HAM-D score.

For the strengths, this is the first meta-analysis to systematically review the literature and analyze the efficacy of Shuganjieyu capsule in neurologic disorders with co-morbid depression. Second, this study assessed improved symptom of neurologic disorders. Quantitative assessment of Shuganjieyu capsule treatment indicated that the efficacy of Shuganjieyu capsule treatment was more obvious than that of any individual study to date. Despite these strengths, however, our study does have a few limitations, which are as follows: (1) many included studies were of poor quality, which might affect the summary results; (2) only positive results were reported, which might result in potential publication bias; (3) Shuganjieyu capsule is a Chinese herbal medicine widely used in China. Therefore, all included studies were only carry out and published in China; (4) individual data was unavailable. Detailed analysis may yield more comprehensive results.

CONCLUSION

The findings of the present meta-analysis indicate that patients with neurologic disorders who receive Shuganjieyu capsule treatment had higher effective rate, lower HAM-D scores, and lower NIHSS, UPDRS and PSQI scores, especially when Shuganjieyu capsule was combined with chemical antidepressants. More large-scale and high-quality RCTs are required to provide more solid conclusive results for the efficacy of Shuganjieyu capsule treatment for neurological disorders and depression.

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