Complementary Therapies in Medicine (2014) 22, 549—566

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Effectiveness and safety of Wuling capsule for post stroke depression: A systematic review

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Available online 6 May 2014

KEYWORDS
Wuling capsule;
Conventional treatment;
Post stroke depression (PSD);
Systematic review;
Meta-analysis

Summary

Objective: To review the effectiveness and safety of Wuling capsule for post stroke depression (PSD) systematically.

Methods: We searched electronic databases for randomized controlled trials (RCTs) that compared either Wuling capsule with placebo, no treatment or Wuling capsule plus conventional treatment with conventional treatment alone in adults with post stroke depression. Relevant resources were also retrieved. Two reviewers screened the citations, assessed the risk of bias and extracted data independently.

Results: A total of 16 studies involving 1378 patients were identified for this review. There were 3 trials comparing Wuling capsule with no treatment control and 13 trials comparing Wuling capsule plus conventional treatment (Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram) with conventional treatment alone. Meta-analyses indicated Wuling capsule used alone or integrated with conventional treatment was effective for PSD in terms of HAMD (Hamilton depression scale) scores, response rate and with less adverse effects, of which, HAMD scores decreased significantly in favor of Wuling capsule from onset time to 1 week (SMD = 1.27, 95%CI: 0.71—1.83, $P < 0.00001$), 2 weeks (SMD = 1.45, 95%CI: 0.57—2.33, $P = 0.001$), 4 weeks (SMD = 2.84, 95%CI: 2.15—3.52, $P < 0.00001$), 6 weeks (SMD = 2.70, 95%CI: 2.15—3.24, $P < 0.00001$), and 8 weeks (SMD = 4.53, 95%CI: 3.55—5.50, $P < 0.00001$) and overall effect (SMD = 2.40, 95%CI: 1.75—3.05, $P < 0.00001$) (SMD = standardized mean difference).

Conclusion: Wuling capsule appeared to present certain antidepressant effect compared to no treatment control. With a combination of several Western medicines, Wuling capsule could be helpful in strengthening efficacy and reducing the incidence of adverse events as an alternative choice in the treatment of PSD. However, due to the limited number of included trials and relatively moderate methodological quality in the majority of studies, further large scale and rigorously designed trials are warranted to confirm the effectiveness and safety of Wuling capsule for post stroke depression.

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http://dx.doi.org/10.1016/j.ctim.2014.04.005

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Introduction

As the third leading cause of death in the world, stroke is a major health issue in elderly population because it not only affects physical impairment, but also leads to a high risk of disability, social nonparticipation (handicap) and psychological problem.[1,2] Of those, depression is the most common neuropsychiatric comorbidity of a stroke.[3] Post stroke depression(PSD) is often accompanied by disorders of recognition, causing adverse influence on patient recovery and it has been the most serious factor causing low quality of life in patients.[4] The incidence of post stroke depression varies from 23.0% to 76.1% in China.[5] Mortality in depressed stroke patients has been estimated between 3.5 and 10 times higher than in non-depressed stroke patients; suicide ideation can be observed in 11.3% of stroke patients too.[6] Although depression may influence functional recovery and quality of life after stroke, such condition is often ignored. In fact, only a minority of patients is diagnosed and even fewer are treated in the common clinical practice.[7]

Currently, pharmacotherapy, psychotherapy, or electroconvulsive therapy was selected in the treatment of depression in patients with stroke. The main therapeutic approach of PSD is essentially pharmacological.[7] Drugs therapy showed the importance of antidepressant medications, particularly with SSRIs (selective serotonin reuptake inhibitors) as this may improve not only the life expectancy of post stroke patients but also their quality of life.[8]

However, concerns have been raised about the effectiveness of these drugs treating patients with persistent depression, as well as the risks, especially of seizures, falls, and delirium.[9] Simultaneously, treatments of PSD are often more prone to side effects and interactions among different drugs rather than general population.[7] Hence, effective medications without (or with comparatively few) adverse effects, would achieve a major advance in the management of PSD. Complementary therapies seem to meet these criteria avoiding the well-known adverse effects of standard antidepressant agents.[10] Recent years, traditional Chinese medicine (TCM) as complementary and alternative therapy has been well recognized for safety and effectiveness in alleviating symptoms of depression.[11] According to the theory of traditional Chinese medicine, the causes of depression have been attributed to liver qi stagnation (a comprehensive manner the state of the symptom including mental stress, hypochondriac and hernial pain, or lumps in the breasts, irregular menstruation, etc.).[12] Despite the fact that many traditional Chinese medicines and empirical formula were used to treat the depression by dispersing stagnant liver qi,[13,14] Wuling capsule as pure Chinese patent medicine has been approved by China Food and Drug Administration(CFDA) for treating depression, anxiety or insomnia in 1998 after being evaluated in clinical trials, which are only partly published in the Chinese medical literatures.[15,16] Wuling capsule mainly comprises Wuling mycelia, which is extracted from *Xylaria* sp. (a kind of scarce of fungi) and is refined by modern bioengineering technology. The constituents of Wuling mycelia contain adenosine, adenine, uridine, guanosine, polysaccharide, mannitol, ergosterol, cholesterol, β-sitosterol and 19 kinds of amino acids including aspartic acid, glutamic acid, γ-aminobutyric acid, ysine (of which, 9 kinds are regarded as essential for humans). Additionally, Wuling mycelia contains microminerals and micronutrients (Fe, Zn, Mn, Cu, P, Mg, Ca, and Ge) as well as vitamins (B_1, B_2, B_6, E, A, D_2, and K_1).[16] The mechanism of *Xylaria* sp. may tonify the kidney and invigorate the brain, tranquilize the mind by nourishing the heart, sooth the liver and dispel the stagnation (according to the theory of traditional Chinese medicine). It also can strength the organic immunity, eliminate or improve anxiety and depressive symptom effectively.[17] Wuling capsule is widely available in China and is a nonprescription drug reimbursed through health care insurance system.

At present, Wuling capsule either used alone or integrated with conventional antidepressants has been widely chosen for the treatment of depression in China.[16] Although some studies reported its effectiveness for post stroke patients, the conclusions were inconsistent, and adverse effects in the treatment of post stroke depression still remains uncertainty. And no systematic review specifically addressing Wuling capsule for the treatment of PSD is available. The aim of this study is to comprehensively examine the effectiveness and adverse effects of Wuling capsule in the treatment of PSD: (1) to determine whether Wuling capsule is effective or not compared with placebo or no treatment for treating PSD; (2) to assess the effectiveness of Wuling capsule adding conventional treatment versus only conventional treatment with treating depression; and (3) to compare the adverse effects of Wuling capsule and determine the safety of Wuling capsule in the treatment of PSD.

Methods

Criteria for considering studies for this review

Type of studies

We only included randomized controlled trials (RCTs), which were published in English or Chinese. And studies not presenting any outcome data and such data were not available from the authors, were excluded.

Types of participants

Patients, male or female, over the age of 18, were diagnosed post stroke depression. Studies adopted stroke diagnostic criteria which included neuroimaging verification of pathological alterations in the brain (thromboembolic stroke or intracerebral hemorrhages) such as CT (computed tomography) or MRI (Magnetic Resonance Imaging), or ''Key Points for Diagnosing Cerebrovascular Diseases'' modified in the 4th National Cerebrovascular Disease Seminar by the China Medical Society in 1995.[18] Participants with no prior history of depression, and no dysphasia or severe disarticulation, as demonstrated by their ability to correctly answer questions were included.[19] The additional diagnosis of depressive disorders should be made based on International Classification of Diseases (ICD-9, ICD-10),[20,21] Chinese Classification of Mental Disorders (CCMD-3),[22] or Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IIIR, DSM-IV, DSM-IV).[23–26]

Types of interventions

Either comparison of Wuling capsule with placebo, no treatment or comparison of Wuling capsule integrated with conventional treatment versus (vs.) conventional treatment alone for PSD, and any regimens of drugs were included in this review.

Types of outcome measures

Primary outcome was evaluated by differences in means of change-from-baseline in 17, 21 or 24-item HAMD (Hamilton depression scale). Secondary outcomes were response rate (number of patients who responded to treatment showing a reduction of at least 50% at the HAMD out of the total number of randomized patients, intention-to-treat (ITT) analysis), safety (accessed according to incidence of treatment-effect adverse effects, laboratory investigations, proportion of patients discontinuing the study).

Search strategies

Electronic searches

A comprehensive literature search for relevant publications was performed in the following electronic databases: CENTRAL (Cochrane Central Register of Controlled Trials, from 1991 to April 2013), PubMed (from 1966 to April 2013), Embase (from 1974 to April 2013), CBM (Chinese Biomedicine Database, from 1978 to April 2013), CNKI (China National Knowledge Infrastructure, from 1994 to April 2013), VIP (Chinese Scientific Journals Database, from 1989 to April 2013), Wanfang database (from 1998 to April 2013). The key words including ''wuling'', ''wu ling'', ''wu-ling'' were used as

English and corresponding Chinese search terms to identify studies from aforementioned databases. Reference lists of all included relevant studies were also searched for publications satisfying the inclusion criteria.

Searching other resources

In addition, seven key relevant journals were retrieved by hand from January 1998 through April 2013, they were Chinese Journal of Psychiatry, Chinese Journal of Nervous and Mental Diseases, World Journal of Integrated Traditional and Western Medicine, Chinese Journal of Integrative Medicine, Journal of Chinese Integrative Medicine, Journal of Traditional Chinese Medicine and Journal of Beijing University of Traditional Chinese Medicine. We also searched conference proceedings and dissertation abstracts, and contacted pharmaceutical company for unpublished studies.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved were downloaded to the reference management database (Endnote5.0), duplicates were removed, and the remaining references were examined by two reviewers (LP, XZ) independently. The eligibility of retrieved papers was assessed independently by the same authors (LP, XZ). Those studies that clearly did meet the inclusion criteria were included, and copies of the full-text were obtained. Disagreements were resolved by discussion with the third reviewer (DK). Reasons for exclusion were documented too.

Data extraction and management

Two reviewers (LP, XZ) independently extracted data using a standard form. In case of disagreement, consensus was achieved by discussion with a third reviewer (DK). We extracted the following information from all included study: participant characteristics, intervention details, measured outcomes and the trial designs. Data on the characteristics of study participants (age, sex), sample sizes in each group, diagnosis criteria and setting were abstracted. Where possible, the number of subjects randomized and the number included in outcome evaluation were extracted from each study. Intervention details included drug, medication doses, therapeutic regimen and treatment duration. For continuous outcomes, the number of patients included in the analysis and the mean change from baseline to the particular endpoint or, if the mean change was unavailable, the mean scores at baseline and at end point, along with the standard deviation (SD) or standard error of this value were extracted.[27,28]

Assessment of risk of bias in included studies

The quality of the studies was assessed by two reviewers (LP, XZ) independently on the basis of whether the following quality criteria had been adequately fulfilled: adequacy of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; and selective outcome reporting, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[27] Disagreements were resolved by discussion with the third author (DK).

Statistical analysis

The demographic and pre-period clinical characteristics of the study population were described using rate for categorical data and using mean and standard deviation for continuous data. If it was feasible and meaningful, data were pooled by means of meta-analyses carried out on the full ITT population, using the Review Manager 5.1 (Cochrane Collaboration). A model of the fixed-effects or random-effects was used to calculate the pooled-effect estimate, with analysis of continuous data using the mean difference (MD) or the standardized mean difference (SMD); with analysis of dichotomous data using relative risk (RR), including 95% confidence intervals (CIs). Statistical significance was assumed for $P < 0.05$. Heterogeneity of effect sizes was assessed with the I^2 statistic; pooled estimates were calculated using a random-effects model if substantial heterogeneity was observed ($I^2 > 50\%$ or $P < 0.1$). If statistical heterogeneity was present, sensitivity analyses were conducted when appropriate to assess possible sources of heterogeneity, such as variations in characteristics of the study population or in the methodological quality of studies. The following subgroup analyses were planned in advance: between trials using different follow up durations, and published versus unpublished trials. A statistical test of funnel plot asymmetry, which may indicate the presence of publication bias, was performed if possible.[29]

Results

Study selection

The search in electronic databases yielded 1476 citations, 36,957 references were from manual-search journals and 36 articles were from conference proceedings and dissertation abstracts. No additional studies were identified in retrieving relevant reference lists. And it was not possible to contact manufacturer to request unpublished studies on account of various reasons. Finally, a total of 16 studies met the inclusion criteria. Further details, including reasons for exclusion, are presented in Fig. 1.

Characteristics of included studies

Characteristics of trials included in this review were summarized in Table 1 . All identified trials were conducted in China and published in Chinese, of which, three studies[30–32] compared Wuling capsule with no treatment control and thirteen trials compared Wuling capsule plus conventional antidepressants (Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram) with conventional antidepressants alone. The sample size ranges from 60 to 180 with a mean size of 86. Three trials,[33,39,40] observed the drop-outs and only one trial[37] reported source of funding Patients recruited in 16 studies were diagnosed as having post stroke depression (PSD), which was based on criteria of CT, MRI, Key Points for Diagnosing Cerebrovascular Diseases (KPDCD), or CCMD-3. All participants were $\geq$18 years, males constituted about half of the sample in most studies, and the dose of Wuling capsule was 2970 mg/d in all trials but patients in

Table 1 Characteristics of included studies.

Study	Number of participants		Dropouts	Comparisons		Diagnostic criteria	Depression degree	Fund status
	Experiment	Control		Experiment	Control			
Chen 2009[30]	61	61	No	Wuling capsule	No treatment	KPDCD, CCMD-3	HAMD-24 ≥ 9	NR
Hu 2008[31]	30	30	No	Wuling capsule	No treatment	CT,KPDCD,CCMD-3	HAMD(NS)	NR
Meng 2011[32]	43	43	No	Wuling capsule	No treatment	KPDCD, CCMD-3	HAMD ≥ 9(NS)	NR
Fu 2008[33]	40	40	5	Wuling capsule plus Deanxit	Deanxit	CT or MRI,KPDCD, CCMD-3	HAMD-17 ≥ 9	NR
Ran 2010[34]	32	32	No	Wuling capsule plus Deanxit	Deanxit	CT or MRI,KPDCD, CCMD-3	HAMD ≥ 17(NS)	NR
Zhang 2010[35]	45	45	No	Wuling capsule plus Deanxit	Deanxit	CT or MRI,KPDCD, CCMD-3	HAMD ≥ 9(NS)	NR
Wu 2013[36]	35	35	No	Wuling capsule plus Deanxit	Deanxit	CT or MRI,KPDCD, CCMD-3	18 ≤ HAMD < 36(NS)	NR
Liu 2009[37]	41	41	No	Wuling capsule plus Fluoxetine	Fluoxetine	KPDCD	HAMD(NS)	Yes
Liu 2011[38]	50	50	No	Wuling capsule plus Fluoxetine	Fluoxetine	CT	HAMD ≥ 17(NS)	NR
Xu 2007[39]	38	38	4	Wuling capsule plus Fluoxetine	Fluoxetine	CT or MRI,CCMD-3,	HAMD ≥ 17(NS)	NR
Shi 2008[40]	30	30	4	Wuling capsule plus Fluoxetine	Fluoxetine	CCMD-3	HAMD-17 ≥ 9	NR
Hu 2009[41]	45	45	No	Wuling capsule plus Sertraline	Sertraline	KPDCD, CCMD-3	HAMD-17 > 17	NR
Wang 2007[42]	40	40	No	Wuling capsule plus Sertraline	Sertraline	CT or MRI,KPDCD, CCMD-3	HAMD > 17(NS)	NR
Wan 2006[43]	35	35	No	Wuling capsule plus Paroxetine	Paroxetine	CT	HAMD ≥ 17(NS)	NR
Xiang 2006[44]	92	88	No	Wuling capsule plus Paroxetine	Paroxetine	KPDCD, CCMD-3	HAMD > 18(NS)	NR
Ran 2012[45]	34	34	No	Wuling capsule plus Citalopram	Citalopram	CT or MRI,KPDCD, CCMD-3	HAMD > 17(NS)	NR

Study	Age		Gender (%, male)		Baseline HAMD (mean ± SD)		Dose (mg/d)		Duration (weeks)	Setting
	Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control		
Chen 2009[30]	46—78(65.2)		NR	NR	18.23 ± 2.36	18.12 ± 2.25	2970	No	6	Inpatients
Hu 2008[31]	62 ± 6.48	60.83 ± 7.01	66.7	60	28.77 ± 8.15	25.5 ± 4.94	2970	No	8	Inpatients
Meng 2011[32]	43—78	45—76	53.5	51.2	29.95 ± 7.84	30.26 ± 6.02	2970	No	6	NR
Fu 2008[33]	52.5 ± 5.3		NR	NR	20.76 ± 4.87	20.22 ± 4.99	2970	21	6	Inpatients, outpatients
Ran 2010[34]	65.1 ± 11	64.5 ± 13	46.9	53.1	28.38 ± 7.21	28.22 ± 6.35	2970 + 10	0 + 10	8	NR
Zhang 2010[35]	44—76	45—74	64.4	66.7	28.67 ± 6.86	29.23 ± 7.08	2970 + (10.5—21)	0 + (10.5—21)	6	Inpatients
Wu 2013[36]	70.2 ± 5.3	69.5 ± 5.8	51.4	42.9	25.28 ± 3.19	25.19 ± 3.15	2970 + 21	0 + 21	8	Outpatients

Table 1 (*Continued*)

Study	Age		Gender (%, male)		Baseline HAMD (mean ± SD)		Dose (mg/d)		Duration (weeks)	Setting
	Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control		
Liu 2009[37]	57.4 ± 10.6	56.8 ± 11.2	56.1	53.7	25.83 ± 6.11	24.92 ± 6.22	2970 + 20	0 + 20	6	Outpatients
Liu 2011[38]	64.1 ± 11.2	64.5 ± 10.1	64.0	60.0	28.33 ± 6.77	27.99 ± 6.69	1000 + 20	0 + 20	12	NR
Xu 2007[39]	61.1 ± 10.2	63.4 ± 10.6	52.8	55.6	29.52 ± 7.32	28.24 ± 6.27	2970 + 20	0 + 20	12	NR
Shi 2008[40]	65.7	63.4	50.0	56.7	16.6 ± 4.4	16.2 ± 4.1	2970 + 20	20	6	NR
Hu 2009[41]	56.42 ± 5.18	55.38 ± 6.3	64.4	71.1	27.55 ± 3.26	26.89 ± 3.43	2970 + (50–100)	0 + (50–100)	6	Inpatients, outpatients
Wang 2007[42]	44–70	46–78	47.5	50.0	29.42 ± 7.31	28.33 ± 6.25	2970 + (50–100)	0 + (50–100)	12	NR
Wan 2006[43]	59.23 ± 8.30	60.13 ± 8.70	62.9	68.6	21.71 ± 5.97	22.03 ± 6.12	2970 + 20	0 + 20	6	Inpatients
Xiang 2006[44]	58.75 ± 9.2	56.41 ± 11.1	52.2	58.0	21.63 ± 2.12	20.89 ± 1.87	2970 + 20	0 + 20	12	Inpatient, outpatients
Ran 2012[45]	65.1 ± 11	64.5 ± 13	52.9	58.8	31.38 ± 7.11	30.22 ± 6.75	2970 + 20	0 + 20	8	NR

Abbreviations: KPDCD, Key Points for Diagnosing Cerebrovascular Diseases; CCMD-3, Chinese Classification of Mental Disorders Version 3, HAMD, Hamilton depression scale; NR, not reporting; SD, standard deviation; NS, not stated the version of HAMD.

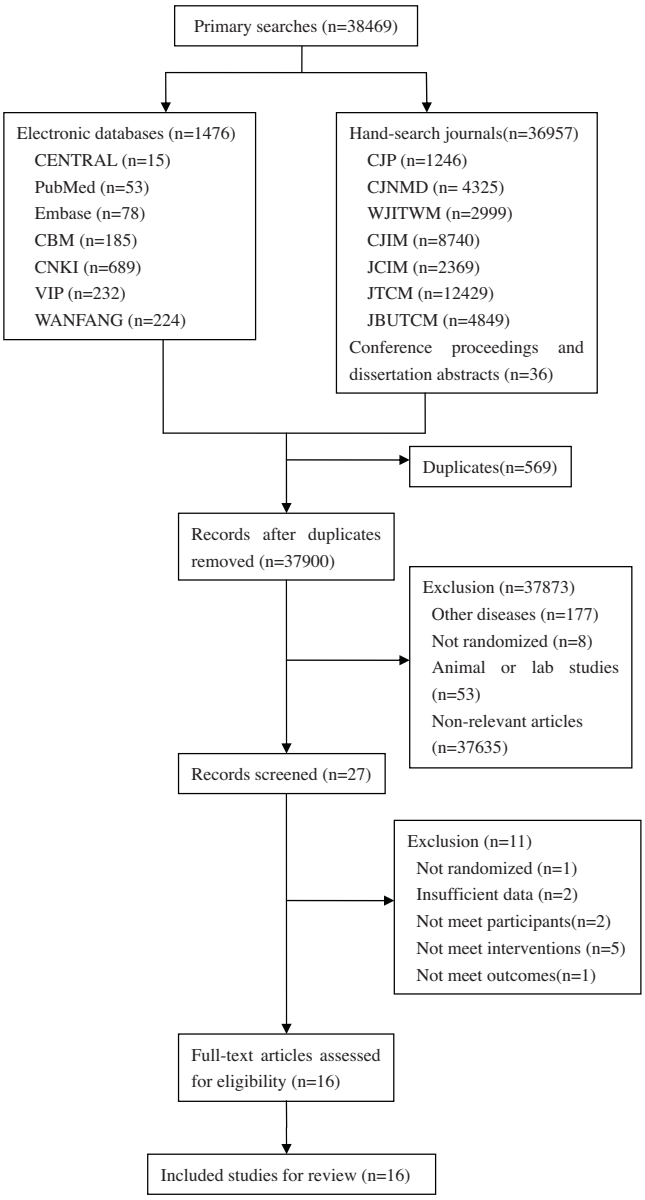

Figure 1 Flow diagram of the selection process. *Abbreviations*: CENTRAL, Cochrane Central Register of Controlled Trials; CBM, Chinese Biomedicine Database; CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journals Database; CJP, Chinese Journal of Psychiatry; CJNMD, Chinese Journal of Nervous and Mental Diseases; WJITWM, World Journal of Integrated Traditional and Western Medicine; CJIM, Chinese Journal of Integrative Medicine; JCIM, Journal of Chinese Integrative Medicine; JTCM, Journal of Traditional Chinese Medicine; JBUTCM, Journal of Beijing University of Traditional Chinese Medicine.

one study[38] were administered 1000 mg/d, the dosage of Western medicines were flexible. The follow-up time varied considerately from 6 to 12 weeks with a mean length of 8 weeks. Four studies[30,31,35,43] were carried out in hospital, two trials[36,37] enrolled participants in outpatients setting, three trials[33,41,44] recruited both inpatients and outpatients, while the seven remaining trials did not describe setting. HAMD scores were used as primary outcome in all identified

studies, but versions of HAMD were not mentioned in most studies. Baseline scores of HAMD were ≥9, 17 or 18 points, respectively.

Assessment of risk of bias in included studies

The assessment of risk of bias in included studies was represented in Table 2. The quality of reporting in the reviewed studies was generally poor, providing insufficient information to reach conclusions whether or not the random sequence generation, allocation concealment and blinding were adequate. Inadequate reporting raises the possibility of bias and carries a risk for the validity of this review. Of those, 5 studies[33,34,39,43,45] used random number table, one study[41] used stratified randomization, one study[36] used odd or even number to generate random sequence, the nine remaining trials just mentioned randomization but did not describe the method of allocation; details on how allocation being concealed were unclear in 15 studies and one study[36] described an improper method of allocation concealment; none of the 16 studies described blinding of participants and personnel, two studies[33,35] were blind to outcome assessor and one study[43] was not, the rest of 13 studies did not provide sufficient information regarding outcome assessor blinding. Fifteen studies either reported that all patients had completed the trial or provided the number and reasons of dropouts, but 1 trial did not mention reasons of loss to follow-up as well as not use ITT analysis. We could not assess whether selective reporting or other important risk of bias existed due to insufficient information in all included studies.

Primary outcomes

HAMD scores changes: Wuling capsule vs. no treatment

Random effects model was used to evaluate the pooled treatment effects of Wuling capsule verse no treatment, HAMD scores decreased significantly in favor of Wuling capsule from onset time to 1 week (SMD = 1.27, 95%CI: 0.71—1.83, $P < 0.00001$), 2 weeks (SMD = 1.45, 95%CI: 0.57—2.33, $P = 0.001$), 4 weeks (SMD = 2.84, 95%CI: 2.15—3.52, $P < 0.00001$), 6 weeks (SMD = 2.70, 95%CI: 2.15—3.24, $P < 0.00001$), 8 weeks (SMD = 4.53, 95%CI: 3.55—5.50, $P < 0.00001$) and overall effect (SMD = 2.40, 95%CI: 1.75—3.05, $P < 0.00001$). The enlarging trend of HAMD scores changes could be observed after 1 week, 2 weeks and 4 weeks of treatment (Fig. 2).

HAMD scores changes: Wuling capsule plus Deanxit vs. Deanxit alone

A total of 4 trials compared combination of Wuling capsule plus Deanxit versus Deanxit alone, significant decreases on HAMD scores were observed in favor of combined therapy after 2 weeks (SMD = 0.84, 95%CI: 0.52—1.16, $P < 0.00001$), 4 weeks (SMD = 0.68, 95%CI: 0.40—0.97, $P < 0.00001$), 6 weeks (SMD = 1.26, 95%CI: 0.18—2.34, $P = 0.02$) and overall effect (SMD = 0.89, 95%CI: 0.55—1.22, $P < 0.00001$), however, there were no significant improvement at 1 week (SMD = 0.29, 95%CI: −0.12 to 0.71, $P = 0.17$) and 8 weeks (SMD = 1.24, 95%CI: −0.55 to 3.04, $P = 0.17$) (Fig. 3).

HAMD scores changes: Wuling capsule plus Fluoxetine vs. Fluoxetine alone

HAMD scores changes were pooled by a fixed effects model within 4 studies, HAMD scores changes of combined treatment were significantly superior than that of monotherapy after 1 week (SMD = 1.05, 95%CI: 0.49—1.61, $P = 0.0003$), 2 weeks (SMD = 0.59, 95%CI: 0.05—1.13, $P = 0.03$), 4 weeks (SMD = 0.64, 95%CI: 0.28—1.00, $P = 0.0004$), 6 weeks (SMD = 0.73, 95%CI: 0.38—1.07, $P < 0.0001$), 12 weeks (SMD = 1.11, 95%CI: 0.79—1.43, $P < 0.00001$) and overall effect (SMD = 0.84, 95%CI: 0.66—1.01, $P < 0.00001$). We also view an increasing trend of HAMD scores changes from 2 weeks to 12 weeks after treatment (Fig. 4).

HAMD scores changes: Wuling capsule plus Sertraline vs. Sertraline alone

Two trials compared the effectiveness of Wuling capsule plus Sertraline with Sertraline alone. Significant improvements were found on HAMD scores in the combination group after 1 week (SMD = 1.12, 95%CI: 0.68—1.57, $P < 0.00001$), 2 weeks (SMD = 0.91, 95%CI: 0.04—1.79, $P = 0.04$), 4 weeks (SMD = 0.74, 95%CI: 0.43—1.05, $P < 0.00001$), 6 weeks (SMD = 1.30, 95%CI: 0.85—1.76, $P < 0.00001$), 8 weeks (SMD = 1.57, 95%CI: 1.06—2.07, $P < 0.00001$) and 12 weeks (SMD = 0.96, 95%CI: 0.49—1.42, $P < 0.0001$) and overall effect (SMD = 1.02, 95%CI: 0.76—1.28, $P < 0.00001$) of treatment (Fig. 5).

HAMD scores changes: Wuling capsule plus Paroxetine vs. Paroxetine alone

Two trials assessed the efficacy of Wuling capsule plus Paroxetine in comparison with Paroxetine alone. There were no significant differences in pooling treatment effect after 2 weeks (SMD = 0.29, 95%CI: −0.18 to 0.77, $P = 0.22$), 4 weeks (SMD = 0.38, 95%CI: −0.10 to 0.85, $P = 0.12$) and 6 weeks (SMD = 0.25, 95%CI: −0.22 to 0.72, $P = 0.30$). Significant benefit was found after 12 weeks (SMD = 2.62, 95%CI: 2.22—3.02, $P < 0.00001$) and overall effect (SMD = 1.04, 95%CI: 0.81—1.26, $P < 0.00001$) in favor of the combination group (Fig. 6).

HAMD scores changes: Wuling capsule plus Citalopram vs. Citalopram alone

There was only one study comparing the effects of Wuling capsule plus Citalopram with Citalopram alone. Significant greater reductions on HAMD scores were observed within Wuling capsule plus Citalopram group after 4 weeks (MD = 4.50, 95%CI: 2.00—7.00, $P = 0.0004$), 8 weeks (MD = 4.72, 95%CI: 2.17—7.27, $P = 0.0003$) and overall effect (MD = 4.61, 95%CI: 2.82—6.39, $P < 0.00001$) of treatment (Fig. 7).

Secondary outcomes

Response rate: Wuling capsule vs. no treatment

Two trials assessed the effectiveness of Wuling capsule ($n = 73$) on response rates in comparison with no treatment ($n = 73$). A random effect meta-analysis displayed significant difference on response rates in favor of Wuling capsule (RR = 2.90, 95%CI: 1.36—6.20, $P = 0.006$) (Fig. 8).

Table 2 Assessment of risk of bias in included studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Other sources of bias
Chen 2009[30]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Hu 2008[31]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Meng 2011[32]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Fu 2008[33]	Random number table	Unclear	Unclear	Yes	No	Unclear	Unclear
Ran 2010[34]	Random number table	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Zhang 2010[35]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Wu 2013[36]	Odd or even number	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Liu 2009[37]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Liu 2011[38]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Xu 2007[39]	Random number table	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Shi 2008[40]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Hu 2009[41]	Stratified randomization	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Wang 2007[42]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Wan 2006[43]	Random number table	Unclear	Unclear	No	Yes	Unclear	Unclear
Xiang 2006[44]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Ran 2012[45]	Random number table	Unclear	Unclear	Unclear	Yes	Unclear	Unclear

Annotation: Yes = low risk of bias; No = high risk of bias; Unclear = uncertain risk of bias.

Response rate: Wuling capsule plus Deanxit vs. Deanxit alone

There were 4 trials comparing the effects of Wuling capsule plus Deanxit ($n = 152$) on clinical response with Deanxit alone ($n = 152$). Pooled analysis across 4 trials indicated that patients in combination groups had significantly higher response rate than control groups (RR = 1.23, 95%CI: 1.07—1.41, $P < 0.003$) (Fig. 9).

Response rate: Wuling capsule plus Fluoxetine vs. Fluoxetine alone

Two studies compared response rate of Wuling capsule plus Fluoxetine ($n = 66$) with that of Fluoxetine alone ($n = 66$). Pooled results were statistically significant in favor of combined therapy (RR = 1.26, 95%CI: 1.02—1.54, $P = 0.03$) (Fig. 10).

Response rate: Wuling capsule plus Sertraline vs. Sertraline alone

There were 2 trials comparing Wuling capsule plus Sertraline ($n = 85$) with Sertraline alone ($n = 85$). A fixed meta-analysis demonstrated that patients treated with combination therapy achieved significantly higher response than patients receiving Sertraline alone (RR = 1.22, 95%CI: 1.01—1.48, $P = 0.04$) (Fig. 11).

Response rate: Wuling capsule plus Paroxetine vs. Paroxetine alone

Only one study reported response rate of Wuling capsule plus Paroxetine ($n = 35$) with that of Paroxetine ($n = 35$). There were no significant differences on clinical response between two groups (RR = 1.03, 95%CI: 0.91—1.17, $P = 0.64$) (Fig. 12).

Response rate: Wuling capsule plus Citalopram vs. Citalopram alone

There was only one study evaluating the effect of Wuling capsule plus Citalopram with Citalopram alone on response rate. No statistical significances were observed on response rate between combined therapy and Citalopram-treated group (RR = 1.08, 95%CI: 0.81—1.44, $P = 0.58$) (Fig. 13).

Response rate: Wuling capsule plus antidepressants vs. antidepressants alone

Finally, we reanalyzed the response rate of Wuling capsule integrated with all above antidepressants (Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram) vs. antidepressants alone Ten trials reported the response rates of Wuling capsule plus antidepressants ($n = 372$) with that of antidepressants alone ($n = 372$). The meta-analysis showed there were significant higher response rate on the combination group compare to the antidepressants using alone in the fixed effects model (RR = 1.19, 95%CI: 1.10—1.30, $P < 0.0001$) (Fig. 14).

Table 3 Incidence of adverse effects.

Adverse effect	Wuling capsule plus Deanxit vs. Deanxit Ran 2010,[34] Zhang 2010[35]			Wuling capsule plus Fluoxetine vs. Fluoxetine Xu 2007,[39] Shi 2008[40]			Wuling capsule plus Paroxetine vs. Paroxetine Xiang 2006[44]			Wuling capsule plus Citalopram vs. Citalopram Ran 2012[45]		
	Experiment ($n=77$) no.(%)	Control ($n=77$) no.(%)	P^*	Experiment ($n=66$) no.(%)	Control ($n=66$) no.(%)	P^*	Experiment ($n=92$) no.(%)	Control ($n=88$) no.(%)	P^*	Experiment ($n=34$) no.(%)	Control ($n=34$) no.(%)	P^*
Flatulence	1(1.30)	0	1.00	2(3.03)	4(6.06)	0.68	0	0	–	1(2.94)	0	1.00
Dry mouth	2(2.60)	3(3.90)	1.00	0	0	–	0	0	–	1(2.94)	2(5.88)	1.00
Headache	0	1(1.30)	1.00	0	0	–	4(4.35)	5(5.68)	0.74	0	0	–
Dizziness	0	0	–	0	0	–	5(5.43)	4(4.55)	1.00	0	1(2.94)	1.00
Insomnia	0	0	–	2(3.03)	2(3.03)	1.00	0	0	–	0	1(2.94)	1.00
Constipation	0	0	–	0	0	–	8(8.70)	5(5.68)	0.44	0	0	–
Hand tremor	1(1.30)	1(1.30)	1.00	0	0	–	0	0	–	0	0	–
Nausea/Vomiting	0	0	–	6(9.09)	5(7.58)	1.00	10(10.87)	6(6.82)	0.34	0	0	–
Blurred vision	0	0	–	0	0	–	7(7.61)	8(9.09)	0.72	0	0	–
Tachycardia	0	0	–	0	0	–	8(8.70)	6(6.82)	0.64	0	0	–
Somnolence	0	0	–	0	0	–	8(8.70)	9(10.23)	0.73	0	0	–
Fatigue	0	0	–	0	0	–	9(9.78)	8(9.09)	0.87	0	0	–
Anorexia	0	0	–	5(7.58)	5(7.58)	1.00	0	0	–	0	0	–
Weight gain	0	0	–	0	0	–	4(4.35)	5(5.68)	0.74	0	0	–
Orthostatic hypotension	0	0	–	0	0	–	3(3.26)	2(2.27)	1.00	0	0	–

Annotation:

* Fisher exact test or Chi-square test was used to compare incidence of adverse effects across two groups.

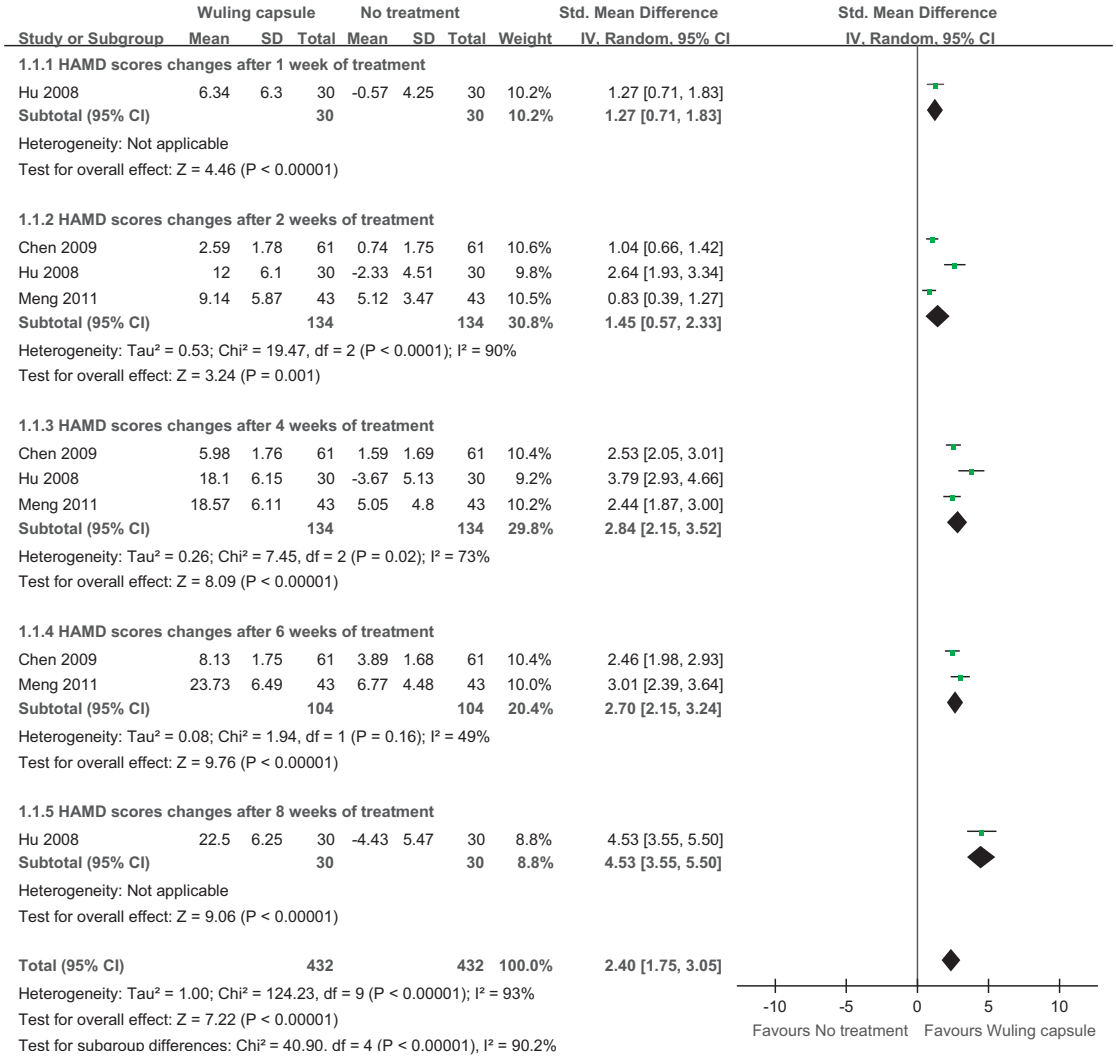

Figure 2 Meta-analysis of treatment effect of Wuling capsule vs. No treatment on HAMD scores changes.

Safety evaluation

No adverse effects were observed in 5 trials.[30–32,36,42] Adverse reactions related to treatment occurring in 6 studies are shown in Table 3. In 6 trials with a total of 534 patients, the most common treatment emergent adverse effects (occurring in ≥5% of patients in either group) were nausea/vomiting, fatigue, somnolence, tachycardia, constipation, blurred vision, dry mouth, headache, weight gain and dizziness. However, no significant differences of the incidence of side effects were observed. Besides, one study[45] reported a decrease of serum lipids after therapy; there were 5(6.25%) dropouts in one trial[33] without reporting the reasons; in one study,[39] 4(5.56%) participants left study owing to severe vomiting; in one trial,[40] 2(3.33%) patients left the trial because they did not adhere to medication and other 2(3.33%) patients discontinued the treatment for flatulence in Fluoxetine-treated group; five studies[33,37,38,41,43] did not report safety evaluation or have a poor reporting.

Publication bias

A funnel plot analysis of the 10 trials comparing Wuling capsule plus antidepressants to antidepressants on response rate was generated to determine the potential publication bias, and it manifested an insignificant asymmetry in Fig. 15.

Discussion

Although several clinical studies reporting Wuling capsule for treating PSD patients ranged from case reports, case series, controlled trials to randomized controlled trials, there was no systematic review specially dealing with its effectiveness and safety in the treatment of PSD. So this is the first review to explore the efficacy and adverse reactions of Wuling capsule for post stroke depression. A total of 16 RCTs involving 1378 patients were identified for this review, with the comparison of Wuling capsule with no treatment control ($n = 3$) and the comparison of Wuling capsule

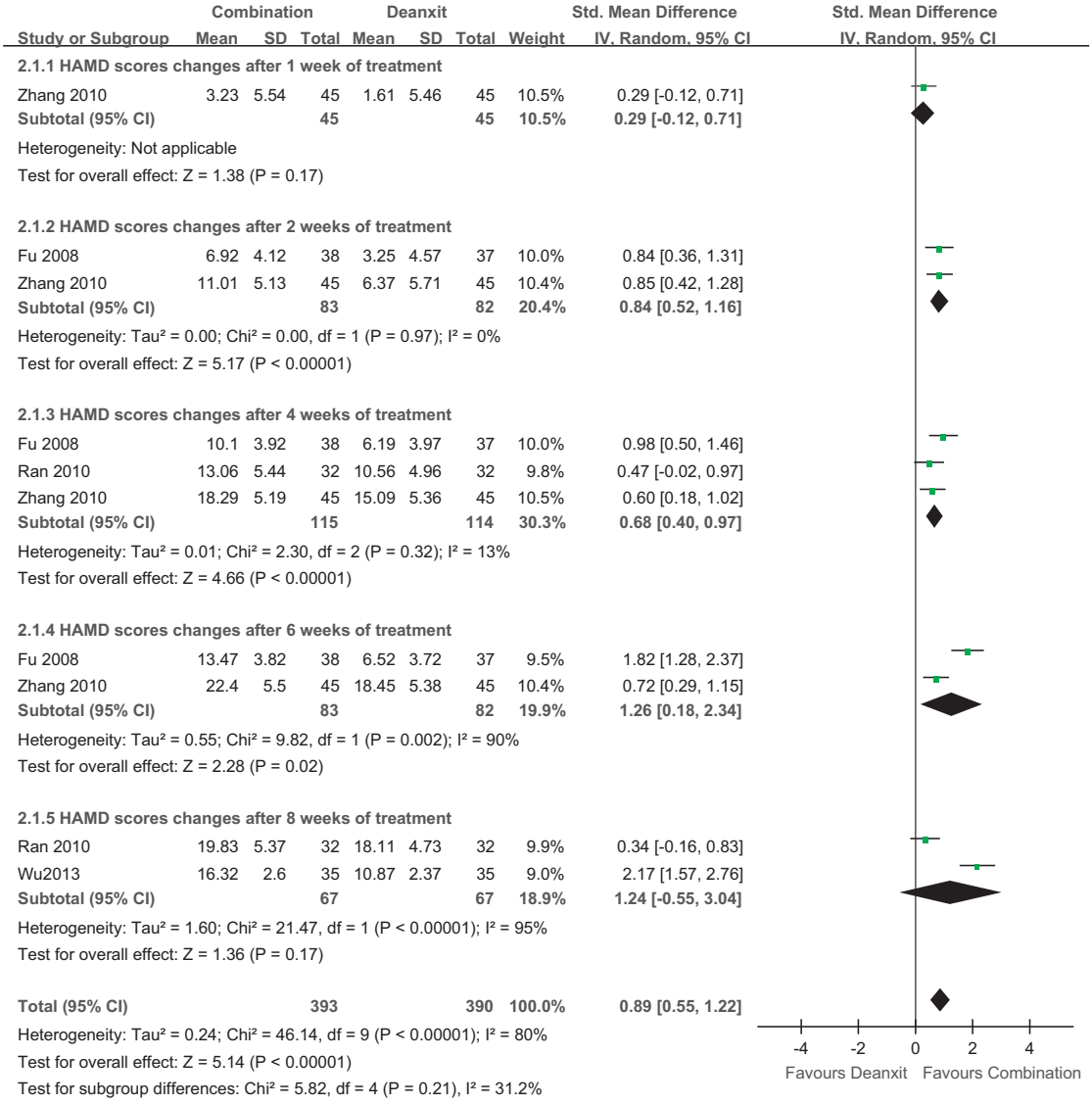

Figure 3 Meta-analysis of treatment effect of Wuling capsule plus Deanxit vs. Deanxit on HAMD scores changes. *Annotation*: Combination = Wuling capsule plus Deanxit.

plus conventional treatment with conventional treatment (Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram) alone ($n = 13$). The pooled analyses suggested that Wuling capsule was effective for treating patients with PSD in terms of HAMD scores changes and response rate. Subjects treated with Wuling capsule plus antidepressants had significantly higher HAMD scores changes and response rates than those treated with antidepressants alone. In addition, no extra adverse reactions were observed in Wuling capsule compared to no treatment control. Participants administering Wuling capsule plus pharmaceuticals had less side effects compared to those received monotherapy. Based on the meta-analyses of the outcome on HAMD scores changes, clinical response rates and safety evaluation, Wuling capsule either used alone or combined with antidepressants seems beneficial for treating PSD with no or fewer adverse effects.

The mild effectiveness of Wuling capsule either single use or integrated with standard antidepressants on PSD could be, at least partially explained by the multiple therapeutic effects of Wuling mycelia, one major component of Wuling capsule. Wuling mycelia is rich in amino acids, vitamins, microminerals and micronutrients. Of those, glutamate (Glu) takes the highest proportion of amino acids. It is not only a key compound in energy metabolism and protein synthesis,[46] but also an important neurotransmitter that plays a key role in long-term potentiation and is important for learning and memory.[47] Glu also can generate the inhibitory γ-aminobutyric acid (GABA) in GABA-ergic neurons catalyzed by glutamate decarboxylase (GAD).[46] Pharmacological researches demonstrated that Wuling mycelia could improve the permeability of excitatory neurotransmitter Glu and Vitamin B_6 in brain tissue so as to strengthen activity of GAD, increase the synthesis of GABA and improve activity of its receptor, therefore exert a sedation and sleep-promoting properties.[17] Animal studies also indicated that Wuling mycelia might possess the ability to facilitate the entry of Glu and GABA into the brain, to activate the receptors of GABA and thus to mediate the function of

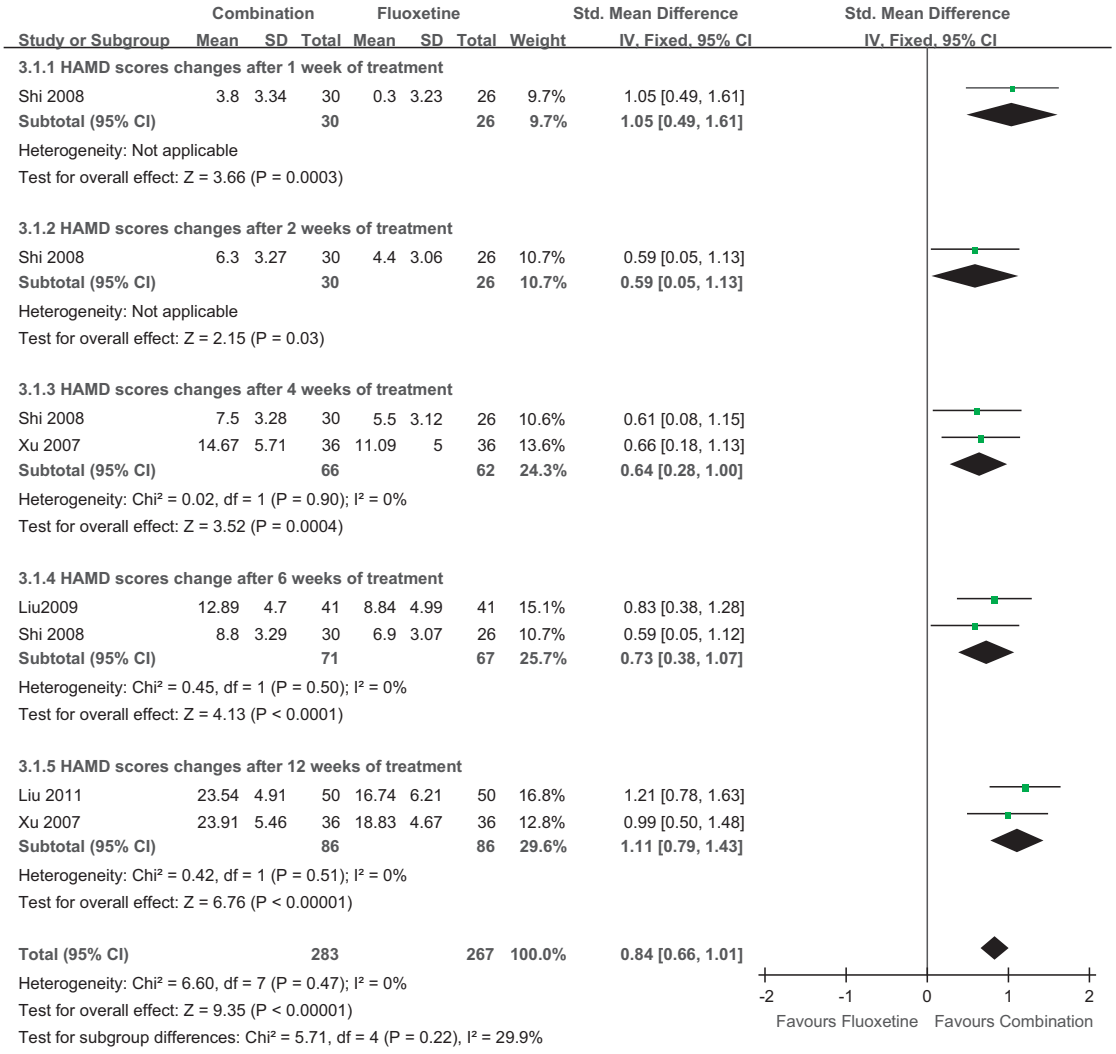

Figure 4 Meta-analysis of treatment effect of Wuling capsule plus Fluoxetine vs. Fluoxetine on HAMD scores changes. Annotation: Combination = Wuling capsule plus Fluoxetine.

the central nervous system.[46,48] Some researchers used ^{1}H-magnetic resonance spectroscopy (^{1}H MRS) to measure the concentration of GABA in occipital lobe in depression patients and found it was notably lower than normal person.[49] Analogously, the mechanism of Wuling capsule on human beings might be interpreted that Wuling mycelia enhanced synthesis of GABA and promoted activity of its receptor in brain cell, meanwhile, it could increase brain energy reserve, reduce energy expenditure and have an protective effect on injured brain cells. Therefore, it has an antidepressant effect as well as ameliorate brain energy metabolism, thus to accelerate the rehabilitation of patients' nerve cells.[33] It could not only alleviate depression severity of patients, but also enhance the rehabilitation of physiological function of brain and improve the ability of daily life with the action of Glu.[50]

On the other hand, as Wuling mycelia contains many pharmaco-active substances, what kind of dose range should be considered, especially the hormesis dose response need to be concerned seriously in the drug development. Hormesis is an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response.[51] Regard to Wuling mycelia, the hormesis maybe exist too, however, the dose range, especially low dose, cannot be ensured due to lack of findings from toxicity researches or pro-clinical trials.

Within this review, we carried out a comprehensive and rigorous systematic search with a coverage of relevant studies across several electronic databases and other resources. We also calculated and analyzed the effect sizes to determine the clinical meanings of the results. In addition, this paper provides readers with the opportunity to access the original studies published in Chinese journals that many would otherwise be unable to read. It also has the potential to be a useful addition to the published researches and generates a sound basis for further clinical investigations in this area.

We should regard several limitations before accepting the findings of this review. First, most of the included studies were prone to some methodological issues and potential risk of bias. The quality of reporting in general was poor with few

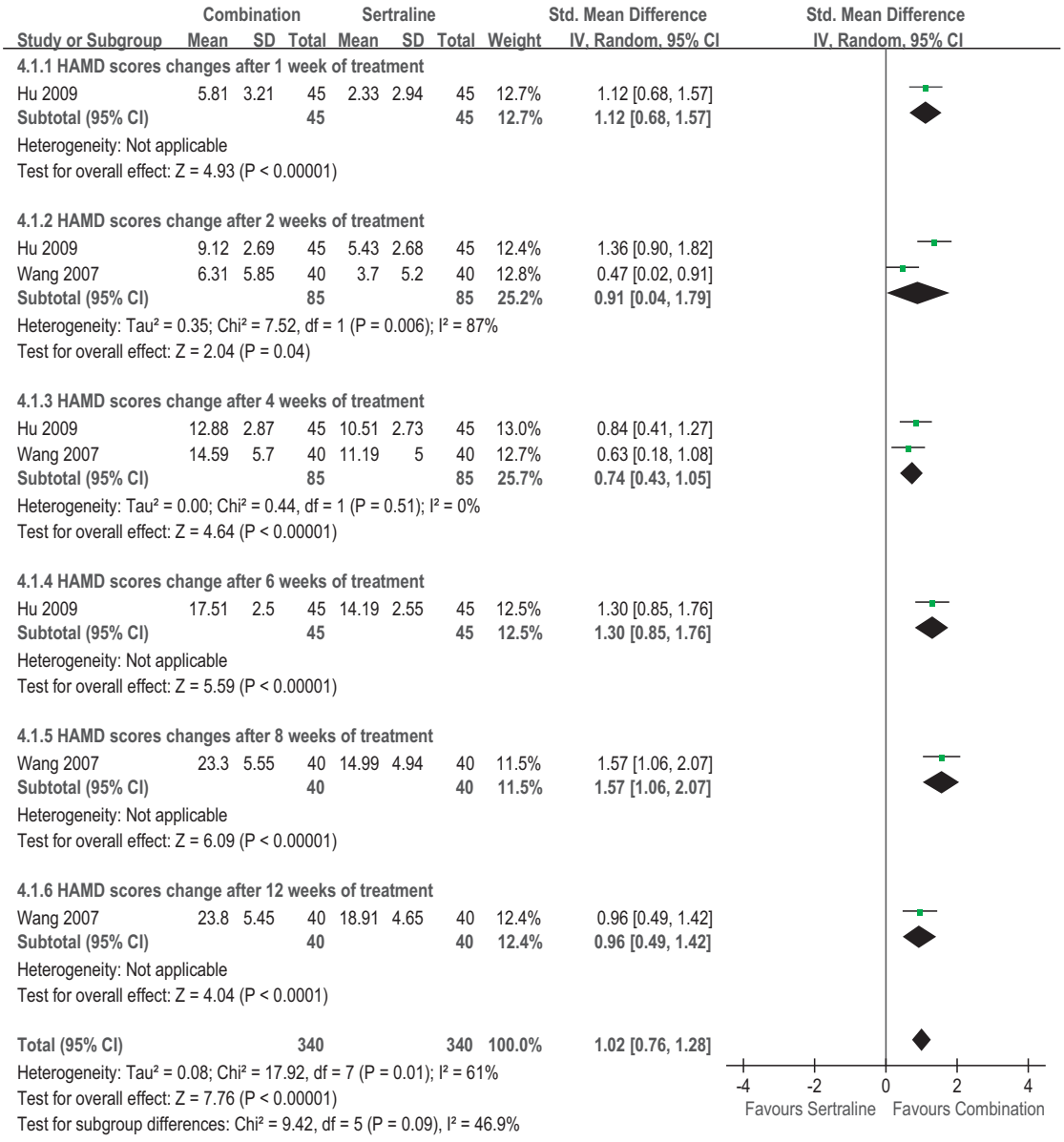

Figure 5 Meta-analysis of treatment effect of Wuling capsule plus Sertraline vs. Sertraline on HAMD scores changes. *Annotation*: Combination = Wuling capsule plus Sertraline.

authors detailing the random sequence generation, allocation concealment, and level of blinding. Consequently, there was potential for a high risk of selection bias with unclear randomization and allocation concealment, although the baseline characteristics of patients were balanced. Neglect of the use of placebo would remove the possibility of blinding (at least for the patients, and possibly also for others involved in the trial) and so increase the possibility of performance bias and detection bias during the period of trial and reporting bias at outcome. The method of sample size determination was also not mentioned in all included studies. The authors of most studies were contacted to provide additional methodological and statistical information by e-mail or telephone, however, none response was obtained. In addition, the potential for harm is an important consideration for all medicines, but the poor reporting on adverse events in several included trials limit the exploration of safety of Wuling capsule. Moreover, source of funding may affect the validity and reliability of this treatment, but only one trial reported funding status.

Second, heterogeneity may be another problem in this systematic review. Several factors might lead to heterogeneity such as the versions of HAMD scores, stroke type of patients, the degree of depression, setting and dosage. These may result in heterogeneity and so influence the treatment effect. The small number of studies within comparisons, and the lack of trials with low risk of bias prevented us using sensitivity analysis or meta-analysis to have a further investigation of the heterogeneity and its impact on treatment effects or adverse effects.

Third, publication bias might be serious in studies of traditional Chinese medicine. Liu et al. found that some

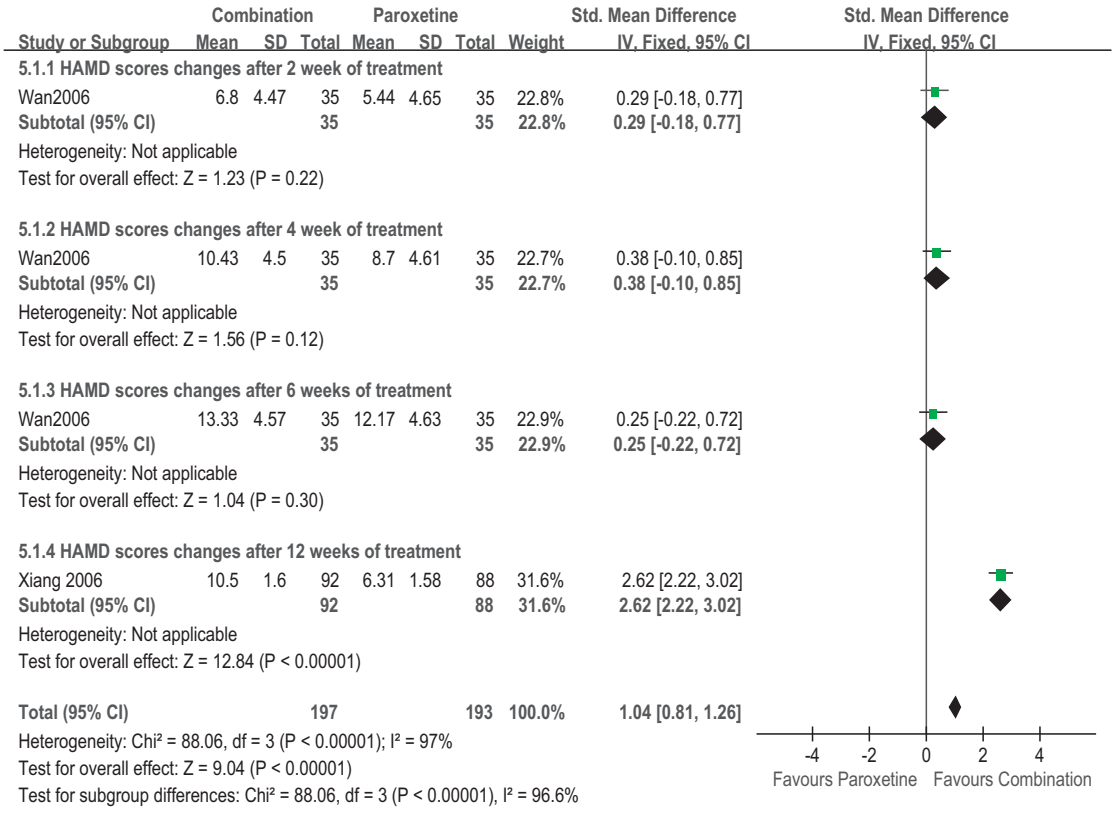

Figure 6 Meta-analysis of treatment effect of Wuling capsule plus Paroxetine vs. Paroxetine on HAMD scores changes. *Annotation*: Combination = Wuling capsule plus Paroxetine.

Asian countries including China published unusually high proportions of positive results.[52] Although two authors independently selected the studies strictly according to inclusion and exclusion criteria, none study with negative finding was identified in this review. Considering all of the sixteen trials identified are in Chinese and conducted in China, as well as 13 out of 16 trials that the HAMD scores at baseline in the intervention group were higher than in the control group, the probability of that happening (i.e. of 13 trials being in one direction) is about 0.0106, this could be a chance occurrence but might be due to some selection bias in recruitment to the trials, however, we cannot rule out the possibility that some studies may be missed although our search was comprehensive as well as a statistical test of funnel plot failed

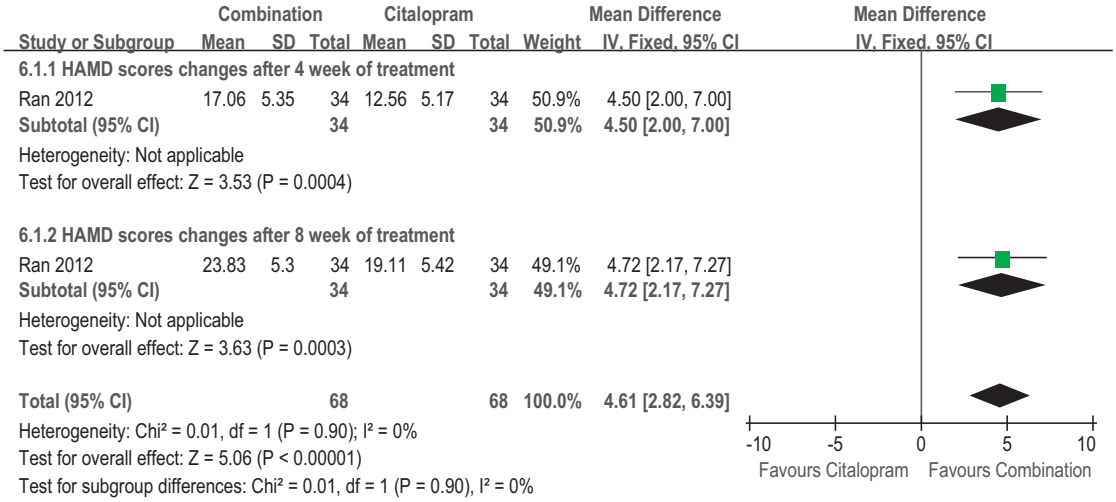

Figure 7 Meta-analysis of treatment effect of Wuling capsule plus Citalopram vs. Citalopram on HAMD scores changes. *Annotation*: Combination = Wuling capsule plus Citalopram.

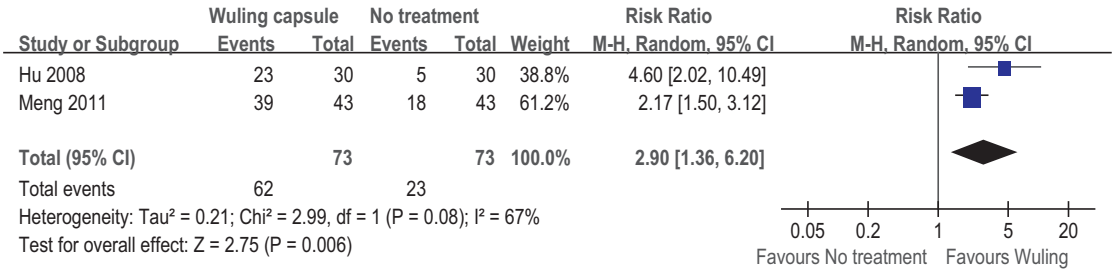

Figure 8 Meta-analysis of treatment effect of Wuling capsule vs. No treatment on response rate.

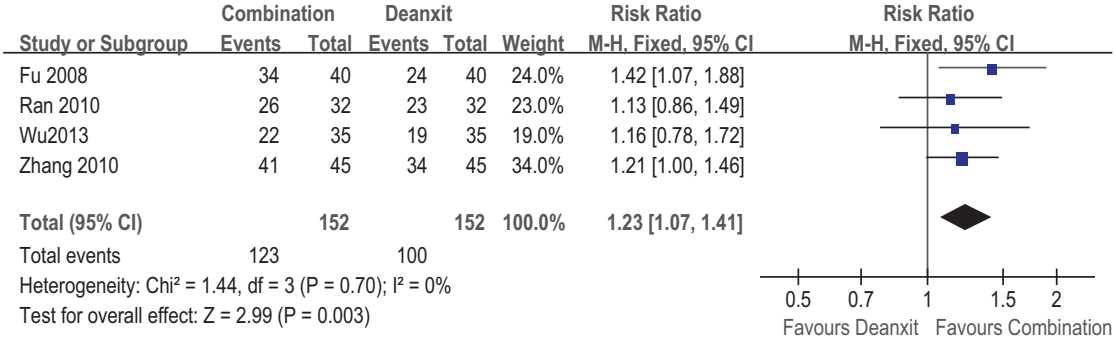

Figure 9 Meta-analysis of treatment effect of Wuling capsule plus Deanxit vs. Deanxit on response rate. *Annotation*: Combination = Wuling capsule plus Deanxit.

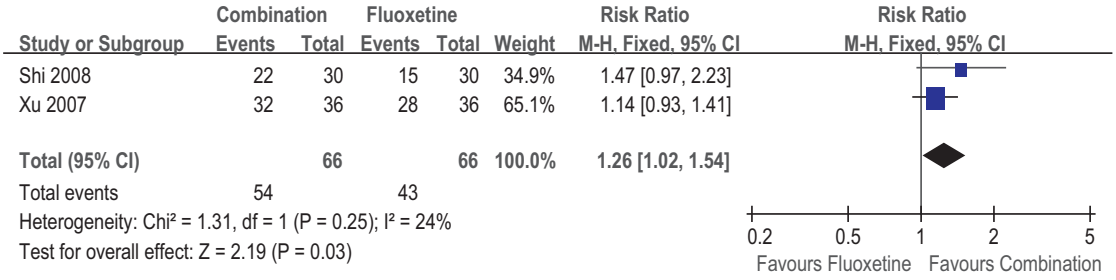

Figure 10 Meta-analysis of treatment effect of Wuling capsule plus Fluoxetine vs. Fluoxetine on response rate. *Annotation*: Combination = Wuling capsule plus Fluoxetine.

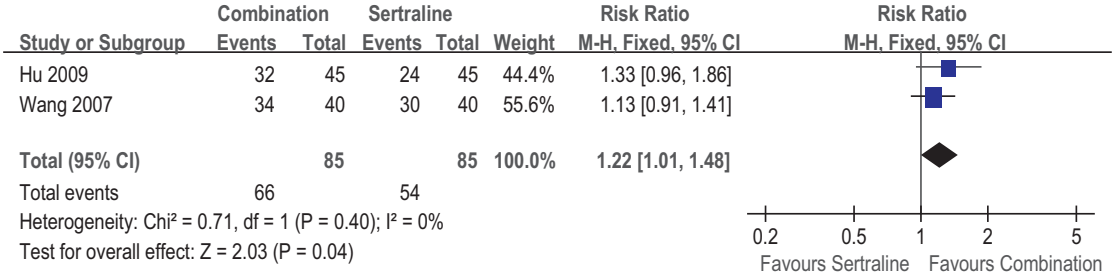

Figure 11 Meta-analysis of treatment effect of Wuling capsule plus Sertraline vs. Sertraline on response rate. *Annotation*: Combination = Wuling capsule plus Sertraline.

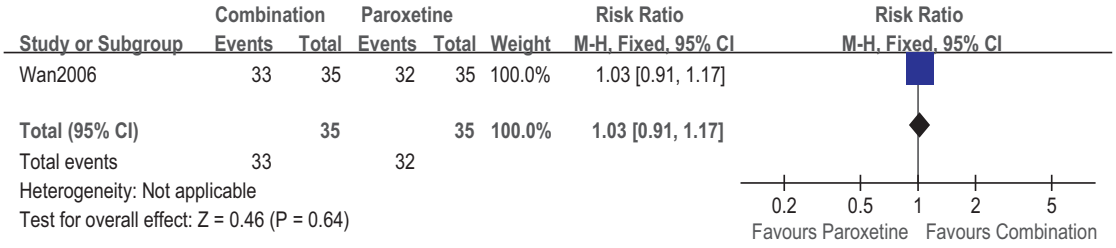

Figure 12 Meta-analysis of treatment effect of Wuling capsule plus Paroxetine vs. Paroxetine on response rate. *Annotation*: Combination = Wuling capsule plus Paroxetine.

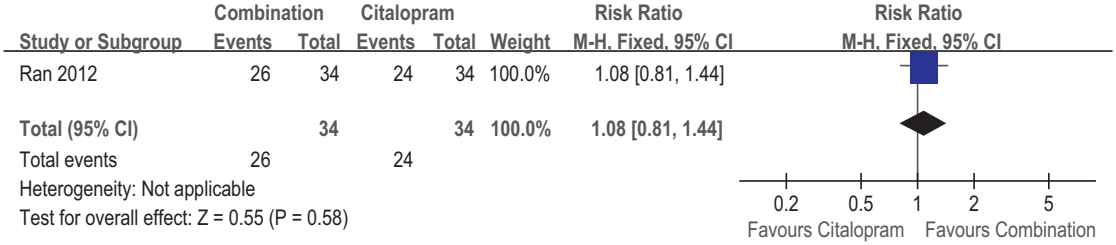

Figure 13 Meta-analysis of treatment effect of Wuling capsule plus Citalopram vs. Citalopram on response rate. *Annotation*: Combination = Wuling capsule plus Citalopram.

to find the presentation of publication bias, moreover, we could not obtain unpublished studies from the manufacturer.

Overall, Wuling capsule is more effective than no treatment control, or there is an additive benefit from Wuling capsule when used in combination with standard antidepressants (Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram). Wuling capsule may be an alternative and complementary option for patients suffering from post stroke depression. However, due to the possible limitations presented in this review, evidence for its effectiveness and safety is needed to be testified in next step and recommendations for clinicians should be cautious.

Regard to the small number of studies within comparisons, and lack of trials with low risk of bias, further well-designed randomized controlled trials are required to explore the effectiveness of Wuling capsule for patients with different degrees of depression and various types of stroke. Besides, there is also a need to improve the quality of reporting of future trials in accordance with CONSORT Statement.[53]

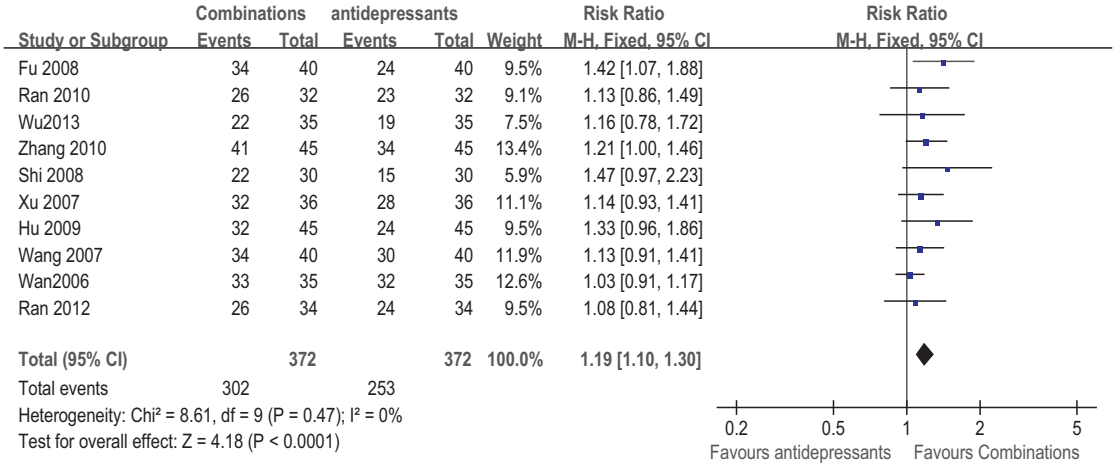

Figure 14 Meta-analysis of treatment effect of Wuling capsule plus antidepressants vs. antidepressants on response rate. *Annotation*: Combination = Wuling capsule plus antidepressants; antidepressants = Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram.

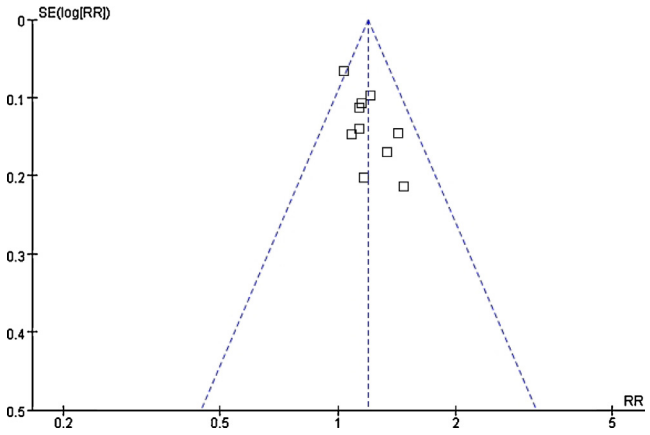

Figure 15 Funnel plot. *Annotation*: Comparison = Wuling capsule plus antidepressants vs. antidepressants; outcome = response rate; antidepressants = Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram.

Conclusion

Wuling capsule appeared to be effective for treating PSD, and there is an additive benefit from Wuling capsule when used in combination with standard antidepressants (Deanxit, Fluoxetine, Sertraline, Paroxetine or Citalopram). However, due to possible methodological flaws, limited number and small sample size of included studies, the effectiveness and safety of Wuling capsule in the treatment of PSD could not be fully substantiated based on current evidence, and recommendations for practice should be cautious. From a clinical point of view, further large scale and high quality clinical trials are needed. In addition, studies should also be reported in accordance with CONSORT Statement.[53]

Funding

No external current funding sources for this study.

Author's contribution

DK conceived and designed the study. LP and XZ performed literature searches, trial selection, critical appraisal, data extraction, as well as contacting authors for additional data. LP, XZ and XL carried out analysis and interpretation of the data. LP and QH drafted the article. All authors read and approved the final version of the manuscript.

Conflicts of interest

All authors declared that there are no conflicts of interest.

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