Tropical Journal of Pharmaceutical Research November 2019; 18 (11): 2447-2454
ISSN: 1596-5996 (print); 1596-9827 (electronic)
© Pharmacotherapy Group, Faculty of Pharmacy, University of Benin, Benin City, 300001 Nigeria.

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v18i11.31

Original Research Article

Clinical efficacy and safety of xiaoyao pill in post-stroke depression: A systematic review and meta-analysis of randomized controlled trials

Yue Xu[1,2], Qing Zhang[3], Fang Yang[1,2], Suoguo Jing[1,2], Xiangning Zhang[1,2], Xuemei Qiu[1,2], Weiyin Chen[1,2]*

[1]School of Clinical Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, [2]Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, [3]School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, PR China

For correspondence: **Email: chenwydoctor@sina.com; **Tel:** +86-28-61801001*

Sent for review: 17 June 2019 *Revised accepted: 27 October 2019*

Abstract

Purpose: *To review the efficacy and safety of the xiaoyao pill in the treatment of post-stroke depression.*
Methods: *A meta-analysis was conducted using eligible studies found in relevant electronic databases [e.g., Embase, Baidu Scholar, Google Scholar, PubMed, Cochrane Library, Science and Technology Periodical Database (VIP) in China, Chinese Biomedical Database, Wanfang, and China National Knowledge Infrastructure]. Statistical analyses were performed using Stata (version 12) and Review (version 5.3).*
Results: *Eleven articles with a total of 1007 patients were included in this study. Overall, the results of the published studies show that xiaoyao pill combined with conventional drug therapy increases clinical response by 20 %. In contrast, Hamilton Depression Scale score and Scandinavian Stroke Scale score were significantly ($p < 0.05$) lower in xiaoyao pill treatment group than in control group. As an adjuvant therapy, xiaoyao pill reduces potential adverse reactions, suggesting that it can be used as a supplementary therapy in the management of post-stroke depression patients.*
Conclusion: *The review and meta-analysis provide preliminarily proof that xiaoyao pill can improve the clinical symptoms of patients with post-stroke depression and has a higher safety profile than conventional drug therapy. These findings suggest that xiaoyao pill can be used as an alternative or complementary drug for the management of post-stroke depression.*

Keywords: *Post-stroke depression, Xiaoyao pill, Meta-analysis*

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Post-stroke depression (PSD) is a common complication in stroke patients that occurs anywhere from 2 months to 3 years following stroke. with an incidence of 20 to 70 % [1]. This complex affective disorder disease has multiple mental and physical symptoms. The main clinical manifestations of PSD, depression and loss of interest in life, hinder the recovery of neurological function, seriously affect the quality of life of patients and their families, increase the social

© 2019 The authors. This work is licensed under the Creative Commons Attribution 4.0 International License

burden of patients and their families, and can even cause death [2]. How to effectively treat PSD is a problem of wide concern. Serotonin (5-HT) reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, escitalopram, and citalopram, are commonly used for the treatment of PSD [3]. However, increased prescription use of SSRIs may increase the risk of bleeding and fatal strokes and may even lead to suicide [4,5]. Serotonin and norepinephrine (NE) reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, are also used to treat PSD [6]. These drugs have varying degrees of side effects [7,8].

The effectiveness and safety of natural drugs in the treatment of diseases have recently attracted more and more attention [9,10]. The xiaoyao pill (XYP) is a traditional medication that includes *Bupleurum chinense*, *Angelica sinensis (Oliv.) Diels*, *Cynanchum otophyllum*, *Atractylodes macrocephala Koidz.*, *Poria cocos (Schw.) Wolf*, *Glycyrrhiza uralensis Fisch*, *Mentha haplocalyx Briq.*, and *Zingiber officinale Roscoe*. In traditional Chinese medicine, XYP is widely used as a basic drug in the treatment of PSD and has achieved good clinical effects with few side effects [11]. More recently, modern pharmacological studies have found that XYP improves the microcirculation of the brain, regulates dopamine and NE systems in the cerebral cortex and striatum, and has certain immune regulation and antioxidant functions. Additional studies have shown that the herbs in XYP regulate mood and have an anti-depression effect [12-14]. Decades of clinical application have proved that XYP has a good therapeutic effect on PSD, but there are no systematic and comprehensive reports on this beneficial clinical effect. Therefore, this systematic meta-analysis on the efficacy and safety of XYP in the treatment of PSD was conducted in order to provide evidence for and promote the clinical application of XYP.

METHODS

Search criteria and inclusion criteria

A search of all the clinical research literature on XYP was conducted using Embase, Baidu Scholar, Google Scholar, PubMed, The Cochrane Library, Science and Technology Periodical Database (VIP), Chinese Biomedical Database (CBM), Wanfang and China National Knowledge Infrastructure (CNKI), and other electronic databases. The release time was selected from the date of establishment of the database to May 10, 2019. There was no limit due to language. Search terms included the following: "stroke", "depression", "post-stroke depression", "cerebrovascular accident", "xiaoyao pill", "randomized controlled trial", and "clinical trial". This search took into account all possible studies that met the inclusion criteria. A manual search of the bibliography of the identified references that met the criteria was also performed. To ensure that the included studies were comprehensive enough to avoid publication bias, gray literature was also searched. Two independent researchers performed the literature search.

Study selection

Inclusion criteria for literature selection were as follows: (1) clear domestic and foreign recognized PSD diagnostic criteria; (2) randomized controlled trials (RCT) of adult PSD; (3) the treatment group was treated with XYP alone or combined with other drugs, and the control group was treated with conventional PSD drugs. Exclusion criteria included the following: (1) *in vitro* and *in vivo* non-human species experiments; (2) observational and retrospective studies, case reports, expert experience, reviews, and non-randomized controlled trials; (3) studies that were duplicate publications or had data errors, incomplete data, or data unavailability; (4) studies with PSD as a secondary outcome or with the co-occurrence of PSD and other diseases.

Two researchers performed the literature search independently, and a third party helped decide when there was a disagreement. The primary outcome measure was the number of patients for which XYP was clinically effective (NPE). The secondary outcome measures were changes in the Hamilton Depression Scale (HAMD) score and the Scandinavian Stroke Scale (SSS) score. The incidence of adverse events (AEs) was used as the main index of safety.

Data extraction

The experimental data extracted included first author, time of publication, sample size, patient age, patient gender, course of disease, details of intervention measures, duration of intervention, AEs, total clinical response, mean change of care indicators, and standard deviation (SD). The two researchers who independently completed the literature extraction also contacted the author to supplement missing data as often as possible. This study included all RCTs about XYP therapy for PSD in journals and papers, without language limitations. The risk of bias assessment tool recommended by the Cochrane collaborative network, which was used in this study, includes

randomization (selection bias), random hiding method (selection bias), blindness of the investigator and subject during treatment (performance bias), result measurement blind method (detection deviation), integrity of results data (attrition bias), evaluation of selective reporting of results (reporting bias), and evaluation from other sources (other bias). The two researchers independently completed the risk of bias assessment for the included literature, and a bias risk map was completed using Revman (5.2.4) software.

Statistical analysis

Total clinical response and AEs were used as dichotomous variables to determine overall relative risk (RR) and 95% confidence interval (CI). The HAMD and SSS scores were used as continuous variables. Either the standard method (SMD) or weight method (WMD) was used as an effective indicator to give the point estimation and 95% CI. Subgroup analysis was used to exclude clinical heterogeneity of different interventions. Statistical heterogeneity between studies ($p < 0.01$) was evaluated using the chi-square test and the I^2 test; an I^2 value of >50% was considered to indicate greater heterogeneity. When the heterogeneity was large, the random effect size model was adopted; otherwise, the fixed effect size model was used. A funnel plot was used to evaluate the possibility of publication bias (only for indicators >10 in the studies involved). The asymmetry of the funnel plot was evaluated by the Begg and Egger test; a p value of <0.1 was considered an indication of publication bias. Sensitivity analysis was used to evaluate the stability of the combined results. Briefly, the included studies were removed one by one, and the remaining studies were re-analyzed to compare the difference between the new combined effect value and the results before the removal. The Stata (version 12) and Review (version 5.3) programs were used for all statistical analyses.

RESULTS

Characteristics of studies

During the initial search, a total of 550 studies were identified. Of these, 171 duplicates were deleted leaving 379 remaining. By reading the title and abstracts, 175 apparently unrelated studies were also excluded. Combined with the previously described inclusion criteria, 11 RCTs [15-25] were eventually included in this meta-analysis (n = 1,007 participants). The literature selection process is shown in Figure 1. The selected studies were published between 2008 and 2018, and all clinical trials were completed in China and published in Chinese. In our included study, XYP was used in combination with other drugs in the treatment group, and conventional Western medicine was used in the control group. The duration of each experiment varied from 2 to 12 weeks, with an average intervention time of 6.09 weeks. The baseline characteristics and intervention details included in the study are shown in Tables 1 and 2.

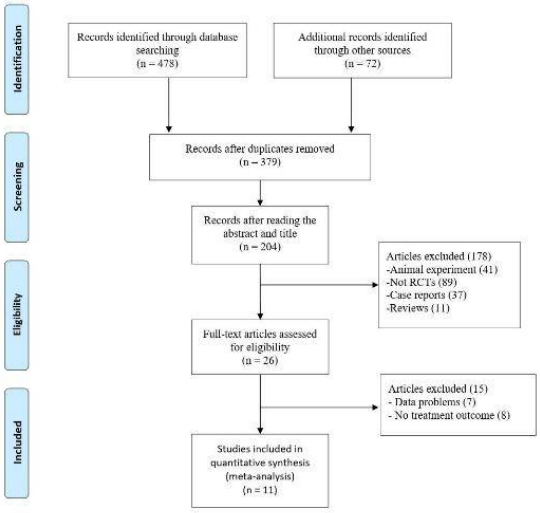

Figure 1: Flow chart of trial selection process

Risk of bias

After assessing the risk of bias in the included studies, most trials were found to be of low or moderate quality. Although all 11 studies mention random grouping, only five references mention specific randomization methods [17-19,23,24], such as random number table method, random drawing, etc. The 11 studies did not involve randomized concealment or double-blind trials, which was considered an uncertain risk of bias. The risk profile for each study is shown in Figure 2.

Clinical efficacy of XYP on PSD

The main outcome indicator, NPE, was reported in all studies (n = 1,007) [15-25]. The fixed effect model ($p > 0.001$, $I^2 = 0\%$) was used to analyze the results of 11 studies. The results show that compared with conventional Western medicine alone, combined XYP (RR = 1.20, 95% CI = 1.13–1.27, $p = 0.568$) significantly improved the clinical efficiency of PSD patients. Also, there was no statistical heterogeneity between these studies (Figure 3).

Table 1: Characteristics of the included RCTs

Author	Year	Case T/C	Sex T; C (male/female)	Age T; C (years) mean	Disease course T; C (month) range, mean	Diagnostic criteria	Reference
Zou *et al*	2009	30/30	18/12; 19/11	67.90; 66.80	27±7.5; 26±6.7	CT, MRI, NS	15
Wang *et al*	2008	36/36	19/17; 18/18	68.30; 69.30	NA	CT, MRI, NS	24
Wang *et al*	2014	60/52	35/25; 33/19	55.10; 56.70	NA	CT, MRI, NS	16
Peng *et al*	2014	49/49	55/43	60.35	NA	CT, MRI, NS	20
Zhang *et al*	2008	102/94	55/47; 51/43	59.20; 58.50	NA	CT, MRI, NS	23
Fan *et al*	2008	51/49	30/21; 30/19	43.32; 42.82	NA	HAMD	18
Zeng *et al*	2018	43/43	23/20; 25/18	57.53; 59.10	NA	HAMD、NS	21
Zou *et al*	2013	40/40	26/14; 24/16	67.20; 66.90	NA	CT, MRI, HAMD	17
Zhang *et al*	2014	40/40	28/12; 30/10	62.60; 63.10	NA	HAMD	25
Gao *et al*	2013	32/31	13/19; 12/19	60.30; 61.20	10.5±6.9; 11.5±3.2	CT, MRI,NS, HAMD	19
Zhu *et al*	2010	30/30	17/13; 16/14	65.80; 63.70	NA	CT, MRI, NS, HAMD	22

Key: T, trial group; C: control group; CT: computed tomography; NA: not available; MRI, nuclear magnetic resonance imaging; NS: national standard; HAMD: Hamilton Depression Scale

Table 2: Intervention and adverse events of included studies

Study	Year	Intervention		Duration (week)	Outcome measures	Reference
		Trial group	*Control group*			
Zou *et al*	2009	XYP + CD	Deanxit	6	NPE, HAMD, SSS	15
Wang *et al*	2008	XYP + CD	Fluoxetine	12	NPE, AR	24
Wang *et al*	2014	XYP + CD	Deanxit	2	NPE, HAMD, AR	16
Peng *et al*	2014	XYP + CD	Fluoxetine	4	NPE, HAMD	20
Zhang *et al*	2008	XYP + CD	Shuxuening injection	3	NPE, AR	23
Fan *et al*	2008	XYP + CD	Paroxetine	8	NPE, HAMD、AR	18
Zeng *et al*	2018	XYP + CD	Fluoxetine	4	NPE, HAMD	21
Zou *et al*	2013	XYP + CD	Venlafaxine	4	NPE, HAMD, SSS, AR	17
Zhang *et al*	2014	XYP + CD	Zoloft	8	NPE, AR	25
Gao *et al*	2013	XYP + CD	Mirtazapine	8	NPE, HAMD	19
Zhu *et al*	2010	XYP + CD	Fluoxetine	8	NPE, HAMD	22

Key: T, trial group; C, control group; XYP, xiaoyao pill; CD, conventional drugs; NPE, the number of patients for which XYP was clinically effective (i.e., reaching clinical efficacy); HAMD, Hamilton Depression Scale; SSS, Scandinavian Stroke Scale; AR, adverse reaction

Symmetrical funnel plots suggest that there was no publication bias (Figure 4), and Egger and Begg tests also confirm that there was no obvious publication bias (Table 3). In the sensitivity analysis, the included studies were removed one by one, and the results were recombined. No significant difference was found after comparison with the previous results, indicating that the combined results were very stable (Figure 5).

Improved HAMD scores

Changes in HAMD scores were reported in eight studies (n = 659) [15-22]. As shown in Figure 6, XYP combined with other conventional drugs reduced the HAMD score (WMD = 3.90, 95% CI = 5.83–1.97). Despite the obvious heterogeneity of these studies ($p < 0.001$, $I^2 = 98.20\%$), the results of all the studies showed that the HAMD score of the treatment group was lower than that of the control group at the end of treatment. Egger test results reveal that there was no publication bias (Table 3).

Improved SSS Scores

Only two studies (n = 140) had changes in SSS scores [15, 21], and the combined results suggest that the combination regimen was more

effective at reducing SSS scores (WMD = 4.28, 95% CI = 5.58–2.99). The results are shown in Figure 7.

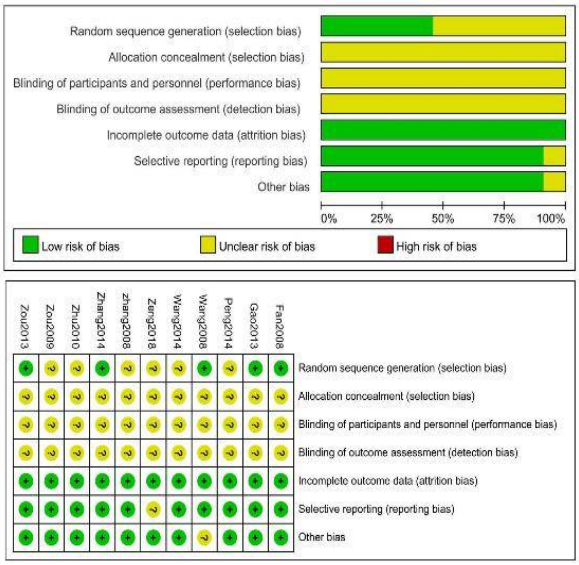

Figure 2: Risk profile for included studies

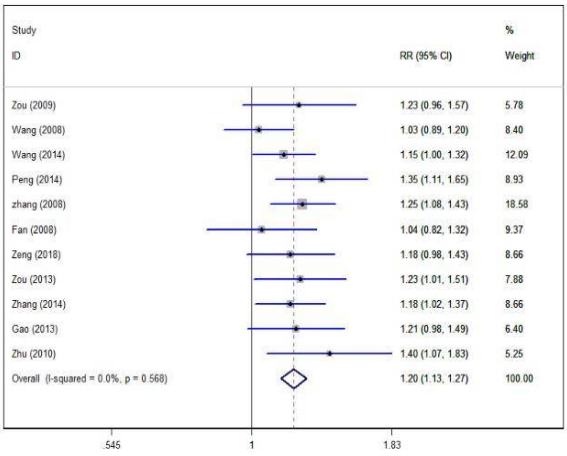

Figure 3: Statistical analysis results of NPE

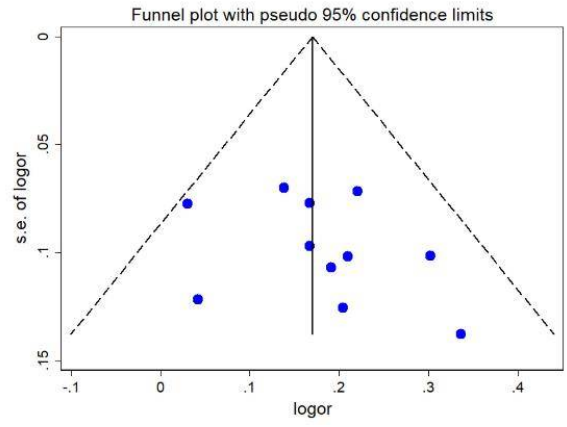

Figure 4: Funnel plots of NPE

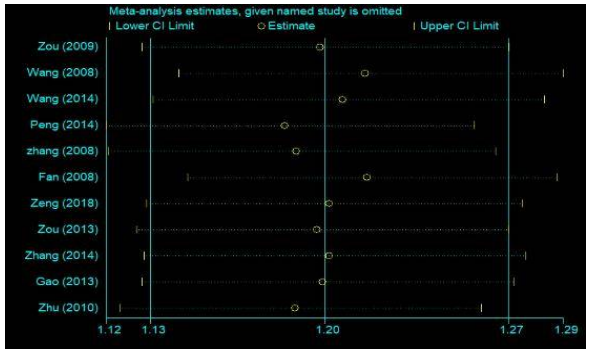

Figure 5: Sensitivity analysis of NPE

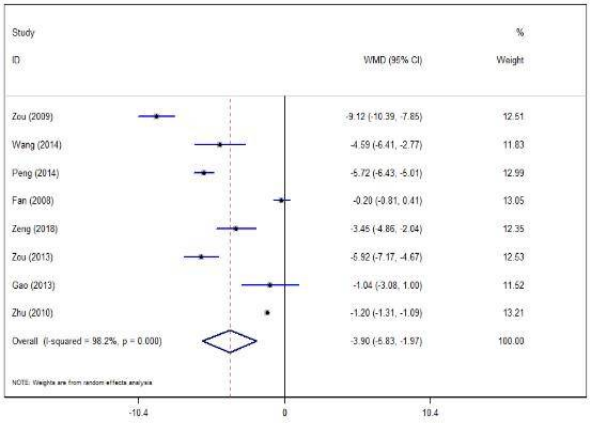

Figure 6: Sensitivity analysis of HAMD scores

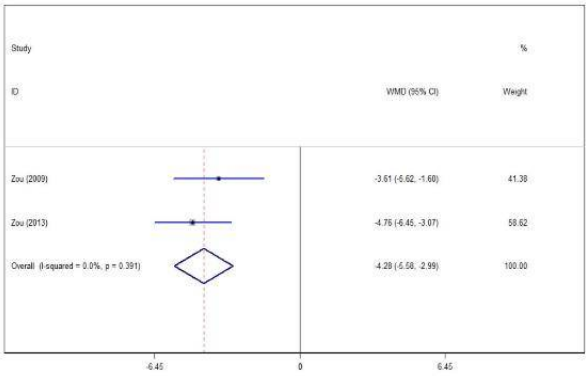

Figure 7: Sensitivity analysis of SSS scores

Clinical safety of XYP for PSD

Adverse reactions (ARs) were reported in six trials (n = 640) [16-18,23-25]. Common ARs included nausea, vomiting, headache, insomnia, dizziness, and drowsiness, but these ARs were not serious AEs and did not require special treatment (Figure 8). Overall, this meta-analysis showed that compared with conventional Western medicine therapy, XYP adjuvant therapy can reduce the risk of AEs (RR = 0.19, 95% CI = 0.04–0.91).

Table 3: Statistical analyses

Outcome measures	Analytical model	Effect size	Point estimates	95% confidence intervals (CI)	Heterogeneity		Publication bias	
					I^2	P	Begg	Egger
NPE	Fixed effect model	RR	1.20	1.13, 1.27	0%	0.568	0.350	0.326
HAMD	Random effect model	WMD	-3.90	-5.83, -1.97	98.20%	0.000	/	0.072
SSS	Fixed effect model	WMD	-4.28	-5.58, -2.99	0%	0.391	/	/
AE	Random effect model	RR	0.19	0.04, 0.91	85.40%	0.000	0.452	0.012

Key: RR, risk ratio; WMD, weighted mean difference; NPE, the number of patients reaching clinical efficacy; HAMD, Hamilton Depression Scale; SSS, Scandinavian Stroke Scale; AE, adverse event

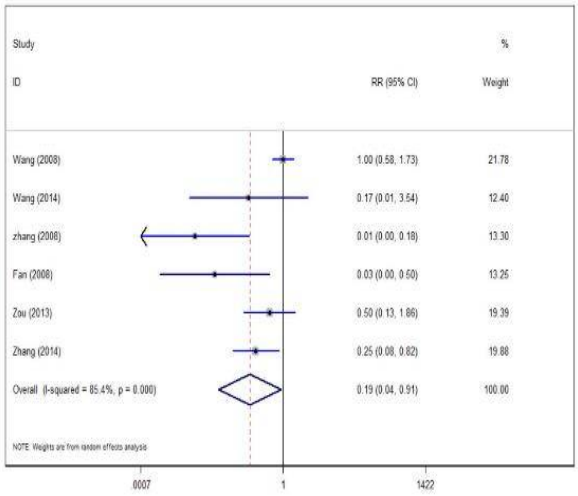

Figure 8: Sensitivity analysis of clinical safety

DISCUSSION

PSD, a common complication in stroke patients, not only affects the recovery of patients' neurological function but also increase the clinical disability rate and mortality. The HAMD scale is the most commonly used scale in the clinical evaluation of depression. The SSS has also been widely used in clinical studies to assess neurological impairment and recovery of stroke patients. The combination of HAMD and SSS is more extensive and authoritative in evaluating the therapeutic effect of drugs.

The results of this meta-analysis show that, compared with conventional Western medicine treatment alone, XYP adjuvant therapy significantly improves the clinical efficacy in PSD patients (20%) and reduces the HAMD and SSS scores of the patients. The ARs in the treatment group were lower than those in the control group. In summary, current work suggests that XYP can be used as an effective alternative strategy for clinical PSD.

However, this meta-analysis has some limitations. First, all 11 included studies were in Chinese and the results were all positive, which may pose a potential risk of publication bias. At the same time, small sample size and short intervention cycle (2–12 weeks, on average 6.09 weeks) could not evaluate the long-term effect of XYP on PSD. In addition, the quality of the evaluation results of the studies was ranked medium and low, which may affect the reliability of the meta-analysis results. Although more large samples and long-term studies are needed to further determine the clinical efficacy and safety of XYP for PSD, the current preliminary results clearly support the use of XYP as an adjuvant therapy for the management of PSD patients when safety, efficacy, and economy are taken into consideration.

CONCLUSION

Natural therapies associated with traditional Chinese medicine have been attracting more and more attention in adjuvant therapy and alternative therapy. The XYP is a classical Chinese prescription for the treatment of PSD in ancient Chinese medicine that has a long history of application, good clinical effect, and no serious ARs. XYP is also widely used in modern clinical practice. To systematically and comprehensively evaluate the clinical efficacy and safety of XYP treatment for PSD, a meta-analysis of the existing clinical trial data was conducted. The results of this meta-analysis suggest that XYP improves clinical efficacy in PSD patients compared with traditional Western treatments, reduces HAMD and SSS scores, and can be used as an adjuvant therapy for PSD.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. *Jiao JT, Cheng C, Ma YJ, Huang J, Dai MC, Jiang C, Wang C, Shao JE. Association between inflammatory cytokines and the risk of post-stroke depression, and the effect of depression on outcomes of patients with ischemic stroke in a 2-year prospective study. Exp Ther Med 2016; 12: 1591-1598.*
2. *Bogousslavsky J. William Feinberg lecture 2002: emotions, mood, and behavior after stroke. Stroke 2003; 4: 1046-1050.*
3. *Eum Y, Yim J. Literature and art therapy in post-stroke psychological disorders. Tohoku J Exp Med 2015; 235: 17-23.*
4. *Montejo-Gonzàlez A, Llorca G, Izquierdo JA, Ledesma A, Bousono M, Calcedo A. Fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex & Marital Ther 1997; 23: 176-194.*
5. *Smoller JW, Allison M, Cochrane BB, Curb JD, Perlis RH, Robinson JG, Rosal MC, Wenger NK, Wassertheil-Smoller S. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. Arch Intern Med 2009; 22: 2128–2139.*
6. *Shyn SI, Hamilton SP. The genetics of major depression: Moving beyond the monoarnine hypothesis. Psychiatr Clin North Am 2010; 1: 125-140.*
7. *Hosenbocus S, Chahal R. SSRIs and SNRIs: A review of the Discontinuation Syndrome in Children and Adolescents. J Can Acad Child Adolesc Psychiatry 2011; 1: 60-67.*
8. *Schoretsanitis G, Haen E, Hiemke C, Endres K, Ridders F, Veselinovic T, Gründer G, Paulzen M. Pharmacokinetic correlates of venlafaxine: associated adverse reactions. Eur Arch Psychiatry Clin Neurosci 2019; 1: 1-7.*
9. *Peng W, Han P, Yu LY, Chen Y, Ye BZ, Qin LP, Xin HL, Han P. Anti-allergic rhinitis effects of caffeoylquinic acids from the fruits of Xanthium strumarium in rodent animals via alleviating allergic and inflammatory reactions. Rev Bra de Farmac 2019; 29: 46-53.*
10. *Zhang Q, Peng W, Wei SJ, Wei DN, Li RL, Liu J, Peng LY, Yang S, Gao YX, Wu CJ, Pu XF. Guizhi-Shaoyao-Zhimu decoction possesses anti-arthritic effects on type II collagen-induced arthritis in rats via suppression of inflammatory reactions, inhibition of invasion & migration and induction of apoptosis in synovial fibroblasts. Biomed Pharmacother 2019; 118: 109367*
11. *Geng JH. Discussion on the early application of xiaoyao pill in the treatment of depression after stroke. Public Med Forum Magazine 2004; 8: 542-542.*
12. *Jia GC, Tian JS, Zhou YZ. Screening study on the anti-depression effects of xiaoyaosan prescription and its components. Liaoning J Trad Chin Med 2012; 39: 11-14.*
13. *Son WX, Hu SY. Effect of xiaoyao pill on hippocampal synapse mRNA expression in depression model rats. The Chin J Clin Pharmacol 2010; 26: 53-56.*
14. *Bao L, Chen J, Huang L. Effect of xiaoyao pill on depression and stress in mice. Chin Trad Herbal Drugs 2008; 31: 1360-1364.*
15. *Zou LH, Li H, Meng W, Chen XD, Qi JY. Clinical observation of Deanxit combined with Xiaoyao Pill treatment for post-stroke depression. J Community Med 2009; 7: 2-3.*
16. *Wang JQ, Ni XL. Observation on the efficacy of fluoperazide and triaxine combined with xiaoyao pill in the treatment of poststroke depression. Pract J Card Cereb Pneumal Vasc Dis 2014; 22: 45-46.*
17. *Zou LH, Li H, Chen XD. Clinical study of Xiaoyao Pill combined with venlafaxine on post-stroke depression. J Liaoning Univ Tradit Chin Med 2013; 15: 166-168.*
18. *Fan DC,Li WH, Kong FX. Clinical observation of xiaoyao pill and liuwei dihuang pill in the treatment of 51 cases of post-stroke depression. Henan Tra Chin Med 2008; 28: 65-66.*
19. *Gao MY. Dangui xiaoyao pill combined with mirtazapine tablets in the treatment of 32 cases of post-stroke depression. Trad Chin Med Research 2013; 26: 39-41.*
20. *Peng XW. The clinical effect of modified xiaoyao pill combined with fluoxetine in the treatment of post-stroke depression. Pract Clin J Trad Chin Med 2014; 14: 50-51.*
21. *Zeng ML, Chen L, Li B, Chen KL, Zhi HY, Zheng YT, Hu WH. Effects of Xiaoyao Pill Combined with Fluoxetine in Treating Post-stroke Depression and its Influence on the Serum 5-Serotonin Level. Zhejiang J Trad Chin Med 2018; 28: 997-999.*
22. *Zhu AH. Clinical observation of xiaoyao pill plus or minus plus prozac in the treatment of 60 cases of post-stroke depression. Clin J Chin Med 2010; 02: 53-54.*
23. *Zhang ZY, Zhu SF, Wei YY. Clinical study of xiaoyao pill combined with shuxuening injection in the treatment of post-stroke depression. J Hebei Med Col Cont Edu 2008; 25: 29-30.*

24. Wang ZY. Efficacy of fluoxetine combined with modified xiaoyao pill in the treatment of poststroke depression. J Med Forum 2008; 29: 75-76.

25. Zhang MM, Guo YH, Chen XY, Huang H. Clinical efficacy of luofu combined with danzhi xiaoyao pill in the treatment of post-stroke depression. Guide Chin Med 2014; 3: 67-69.