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Original article

Improving sleep quality in climacteric women with insomnia: A randomized, head-to-head trial between *Jia-Wei-Shiau-Yau San* (*JWSYS*) and *Suan-Zao-Ren Tang* (*SZRT*)

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Abstract

Background: *Jia-Wei-Shiau-Yau San* (*JWSYS*) was reported to reduce various menopausal-related symptoms, and *Suan-Zao-Ren Tang* (*SZRT*) is a frequently prescribed Chinese herbal formula for insomnia. We performed a double-blind, randomized trial to compare the efficacy of *SZRT* with that of *JWSYS* for insomnia in climacteric women.

Methods: A total of 60 subjects 40–60 years of age with a history of insomnia at least 1 month were recruited from the Taipei City Hospital. The participants were instructed to take 4 g 3 times per day of either *SZRT* ($n = 30$) or *JWSYS* ($n = 30$) for a period of 4 weeks. The primary outcome measures were the mean component scores of the Pittsburgh Sleep Quality Index (PSQI). Secondary outcome parameter was the global score on the World Health Organization Quality of Life questionnaire – Taiwan brief version.

Results: Of the initial 60 intent-to-treat participants, 54 completed the 4-week study. The mean domain and individual scores of PSQI decreased significantly under both treatments, reflecting improved daytime vitality and concentration ability. Mixed model analysis showed that *SZRT* was more effective in improving habitual sleep efficiency and prolonging sleep duration, while *JWSYS* was more effective in improving sense of well-being. Both formulas were associated with good compliance and safety. Serum cholesterol decreased slightly after 4 weeks of *SZRT* treatment.

Conclusion: *SZRT* appears to be more effective than *JWSYS* for improving sleep efficiency and duration, but the latter seems to be more effective in improving well-being. The potential effect of *SZRT* on serum total cholesterol level deserves further study.

Keywords: *Jia-Wei-Shiau-Yau San* (*JWSYS*); *Suan-Zao-Ren Tang* (*SZRT*); Randomized clinical trial; Sleep quality; Traditional Chinese medicine; Climacteric

Introduction

Insomnia is associated with menopausal transition and is a major determinant affecting women's quality of life (QOL) [1–4]. Despite significant progress made in the pharmacologic treatment of menopausal insomnia in the last few years [5,6], therapeutic side effects [7–9] and the risks of hypnotic-drug dependence have led to poor compliance with either hormone therapy or hypnotic suggestion among climacteric women [10,11]. Not surprisingly, many women have turned to traditional medicine to manage their own symptoms, partly because these medications are natural and have less subjective residual effects.

Jia-Wei-Shiau-Yau San (*JWSYS*) and *Suan-Zao-Ren Tang* (*SZRT*) have been in widespread use for thousands of years in traditional Chinese medicine and are two of the most popular formulas used by climacteric women in Taiwan [12,13]. Both have been approved by the Committee on Chinese Medicine and Pharmacy, Department of Health, in Taiwan and both are sold as over-the-counter dietary supplements in the North America.

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Table 1
Compositions of the trial herbal preparations *Jia-Wei-Shiau-Yau San* and *Suan-Zao-Ren Tang*, 4 g three times daily, total 12 g per day.

Pharmaceutical name	Chinese pinyin	Latin botanical name	Percentage of mixture (%)
Jia-Wei-Shiau-Yau San			
Radix Angelicae Sinensis	Dang Gui	*Angelica polymorpha* Maxim. Varsinensis Olive	12.1
Radix Paeoniae Lactiflorae	Bai Shao	*Paeonia albiflora* Pallas, var. trichocarpa, B	12.1
Rhizoma Atractylodis Macrocephalae	Bai Zhu	*Atractylodesovata*, Thunb	12.1
Sclerotium Poriae Cocos	Fu Ling	*Poria cocos* (Schw.) Wolf	12.1
Radix Bupleuri	Chai Hu	*Bupleurum falcatum* L.	12.1
Radix Glycyrrhizae Uralensis	Gan Cao	*Glycyrrhizaglabra* L. var. glandulifera, Rega	6.1
Cortex Moutan Radicis	Mu Dan Pi	*Paeonia suffruticosa* Andr.	7.6
Fructus Gardeniae Jasminoidis	Zhi Zi	*Gardenia florida*, L.	7.6
Rhizoma Zingiberis Officinalis	Sheng Jiang	*Zingiber officinale*, Boscoe.	12.1
Herba Menthae Haplocalycis	Bo He	*Mentha arvensis*, L.	6.1
Suan-Zao-Ren Tang			
Semen Zizyphi Spinosae	Suan Zao Ren	*Zizyphus vulgaris* Lam. var. spinosa (Bunge.) Huex H.F. Chow	45.4
Radix Glycyrrhizae Uralensis	Gan Cao	*Glycyrrhiza glabra* L. var. glandulifera, Rega	9.2
Anemarrhena Rhizome	Zhi Mu	*Anemarrhena aspodeloidea* Bunge.	9.2
Sclerotium Poriae Cocos	Fu Ling	*Poria cocos* (Schw.) Wolf	18.1
Radix Ligustici Chuanxiong	Chuan Xiong	*Conioselinum unvittatum*, Turcz.	18.1

JWSYS and *SZRT* consist of ten and five Chinese herbs, respectively, as shown in Table 1. *JWSYS* is indicated for relieving hot flush and other menopausal symptoms [14,15]. And in the classical literature, *SZRT* is said to nourish the blood and calm the nerves, eventually producing a tranquilizing sensation. It is believed to be an excellent formula for insomnia, restlessness, anxiety, and palpitations-symptoms frequently encountered in women during their climacteric years which was supported by recent observational study [16]. However, the clinical evidence regarding the efficacy between *JWSYS* and *SZRT* for menopausal insomnia is uncertain or lacking. Thus, we performed a blinded, randomized, trial using standardized questionnaires to compare the effect of *SZRT* with that of *JWSYS* in climacteric women with poor sleep quality.

Subjects and methods

This prospective, patient- and evaluator-blinded, randomized, study was performed between April 2009 and March 2011 at the Yang-Ming Branch of the Taipei City Hospital, Taipei, Taiwan. All study nurses and physicians attended a training session to ensure standardization of procedures and fulfillment of Good Clinical Practice guidelines prior to the start of the study. Approval of the study was obtained from the Institutional Review Board of Taipei City Hospital, and all participants provided signed and informed consents before taking part in the study. Women were recruited from the general population by advertisement and this trial was conducted in accordance with the Helsinki Declaration. At the initial screening visit, the subjects enrolled in the study were climacteric women, ranging in age from 40 to 60 years, with a Pittsburgh Sleep Quality Index (PSQI) of greater than six. All women spent 30 min or more falling asleep per night, slept less than 6 h each night three times per week, and had this issue continuously for at least one month. To be eligible, women could not have participated in any other medical trial for at least three months prior to the enrollment and should have discontinued taking current medications prior to screening: 2 weeks for any herbal medications, melatonin, acetylcholine, glutamate, serotonin, norepinephrine, GABA, histamine, adenosine, prostaglandins, narcotics, prescribed psychotropic drugs, and hypnotics; 12 weeks for estrogens or progestational agents. Additionally, subjects who had jet lag- or shift work-induced insomnia, any sign of cancer or treatment with chemotherapy or radiation therapy, any disease that might cause sleep difficulty including psychosis, depression, thyroid dysfunction, obstructive sleep apnea syndrome, restless legs syndrome, and cardiac disease, or showed evidence of renal or liver dysfunction were excluded from the study.

Baseline data (information about personal demographics, sleep quality, and quality of life) were obtained after the initial screening visit. Participants also received a physical examination, complete blood count, and biochemical function and hormone tests. These data were collected to ensure that each woman met the minimum eligibility criteria and to screen out respondents with potential poor compliance. The selected participants were randomly allocated to receive 4-week treatment with *JWSYS* or *SZRT*. The powder of trial drugs were administered orally at a dose of 4 g 3 times a day after meals which dose selection was according to experts' opinion and relevant published human studies [14,16]. Patients, investigators and study nurses maintained strict blinding throughout the study. The sealed envelope containing the group allocation was opened after data analysis was completed. The standardized extracts of *JWSYS* and *SZRT* which were packed in aluminum foil bags, identical in appearance, volume, and colour, were manufactured by a Taiwan pharmaceutical company (the Kaiser Pharmaceutical Company, Taipei, Taiwan) certified in herbal GMP (Good Manufacturing Practice). For quality assurance of the active ingredients in study formulas, high performance liquid chromatography and thin layer chromatography were employed to identify substances and to confirmed herbal plants in the final product as shown in Table 1 and Appendix A. No animal products, endangered species, or restricted herbal ingredients were used in this study. Each batch was also tested for *E. coli*,