Journal of Ethnopharmacology 145 (2013) 320–327

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Efficacy and safety of Wuling capsule, a single herbal formula, in Chinese subjects with insomnia: A multicenter, randomized, double-blind, placebo-controlled trial

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ARTICLE INFO

Article history:
Received 14 September 2012
Received in revised form
26 October 2012
Accepted 1 November 2012
Available online 23 November 2012

Keywords:
Wuling capsule
Insomnia
Clinical trial
Multi-center randomized trial

ABSTRACT

Ethnopharmacological relevance: Wuling Capsule is a single herbal formula from *mycelia of precious Xylaria nigripes* (*Kl.*) *Sacc* and its pharmacological function have a tranquilizing effect on the central nervous system. The aim of the study to evaluate the efficacy and safety of Wuling capsule in treatment of insomnia.

Materials and methods: We performed a multicenter, randomized, double-blind, placebo-controlled study. The participants received either placebo ($n=92$) or Wuling capsule ($n=94$) for 4 weeks and a follow-up period for 2 weeks.

Results: Compared between pre-treatment and post-treatment, the global Pittsburgh sleep quality index (PSQI) scores in both Wuling capsule group and placebo group improved significantly ($P<0.01$). However, there was no significant difference between Wuling capsule group and placebo group ($P>0.05$). Scores of clinical global impressions scale (CGI-I) at each week in Wuling capsule group was similar to those in placebo group ($P>0.05$). Compared between pre-treatment and post-treatment, scores of the four components of world health organization on quality of life brief scale (WHOQOL-BREF) in both Wuling capsule group and placebo group improved significantly ($P<0.01$). However, there were no difference between the two groups ($P>0.05$). The rate of adverse events was 10.10% in Wuling group, and 6.73% in placebo group ($P>0.05$).

Conclusions: Wuling capsule can improve insomnia when compared with pre-treatment for 4 weeks and be a well tolerated by all the patients at the 6 weeks of study period. However, there are no significant in the results of the variables tested when compared with placebo control. Further additional rigorous randomized clinical trials are still required.

0. Introduction

Insomnia is a highly prevalent and often debilitating condition. The American Academy of Sleep Medicine Work Group defines insomnia disorder as sleep difficulties associated with daytime impairment or distress about the difficulty sleeping (Edinger et al., 2004). Prevalence estimates of chronic insomnia ranged from 10% to 15% in the adult population who suffers from insomnia with the presence of symptoms for at least 1 month, while an additional 25% to 35% have transient or occasional insomnia (Doghramji, 2006). Evidence-based management of insomnia may include pharmacological treatments and the collectively nonpharmacological approaches (Morgan et al., 2011). Currently, the results of the Bettering the Evaluation and Care of Health (BEACH) program from April 2006 to March 2008 showed that medications are prescribed to 95.2% of insomniac cases, even as high as 81.7% of new insomniac cases (Charles et al., 2009). However, hypnotic medicines might have a pool of potential harms such as hangover effects, drug tolerance, rebound insomnia, and risk of addiction.

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http://dx.doi.org/10.1016/j.jep.2012.11.009

In addition, chronic users of hypnotic medications for insomnia have more regular nighttime awakenings than insomniacs not taking medications (Ohayon and Caulet, 1995). Thus, there are rising number of insomniac patients resort to various kinds of complementary and/or alternative medicine (CAM) worldwide. An analysis of the United States National Health Interview Survey data from 2002 by Pearson et al. (2006) revealed that 4.5% of adult population had used CAM to treat insomnia or trouble sleeping during the previous 12 months. However, the only extensively researched herbal medicine for insomnia to date is valerian (either as a monotherapy or in combination with kava or hops), suggesting that further research on other herbal medicines with potential hypnotic effects is encouraged as current research in these areas is in their infancy (Sarris and Byrne, 2011).

The most appreciable distinction between China and the west in treating insomnia is the use of traditional Chinese medicine (TCM) therapy, which includes Chinese herbal medicine (CHM), acupuncture and other nonmedication therapies. TCM has played an important role in the medical care of insomnia patients for thousands of years in China. For example, *Suan Zao Ren* decoction has a long history of use as part of the traditional *Chinese pharmacopoeia* first documented in the classical Chinese text *Jin Gui Yao Lue* (essential prescriptions from the golden cabinet) about 210 A.D. by Zhong-Jing Zhang (Yeh et al., 2011). In modern time, herbs are still prevalent attractive CAMs to many patients with sleep disorders (Gyllenhaal et al., 2000; Sarris et al., 2011). Wuling capsule is a single herbal formula from *mycelia of precious Xylaria nigripes (Kl.) Sacc* and was approved in 1999 by the China State Food and Drug Administration (Authorized Document Number: Z19990048 in Chinese medicine) for the treatment of neurasthenia (insomnia, amnesia, neurosis, vertigo, exhaustion syndrome) and depression, anemia, women's menstrual disorder, diseases during climacterium and geriatric of men as well as women. As a modern Chinese patent herbal preparation, Wuling capsule carried out standard for quality and purity according to *Chinese Pharmacopoeia* (version 2005) and now *Chinese Pharmacopoeia* (version 2010). On the basis of the *Chinese Pharmacopoeia*, content determination of polysaccharides and adenosine has been proposed as the quality control of Wuling capsules. Thus, the processing of the product was subjected to strict quality control, and the ingredients were subjected to standardization. Recently, some new methods were reported for determining the chemical composition and/or for quality control of Wuling capsules. For example, Chen et al. (2012) established a method for the content determination of multiple constituents, including 5-methylmellein, 5-hydroxymellein, 5-carboxylmellein and genistein, in Wuling capsules simultaneously by high performance liquid chromatography (HPLC); Lu et al. (2011) established a method of specific chromatogram analysis of chemical constituents by reverse phase-HPLC with diode array detector for the quality control of Wuling capsules, and 5-methylmellein was extracted as the characteristic component of Wuling capsules; He and Liu (2010) established an analytical method for detecting 14 kinds of amino acid in Wuling capsule by HPLC with fluorescence detection.

Wuling capsule has been used in clinic for many years and claimed to be effective in improving the signs of insomnia and cognitive deficits (Li et al., 2011). The preliminary evidences from clinical studies suggested the significant benefits of Wuling capsule for some patients with insomnia (Yin and Zhang, 2011).

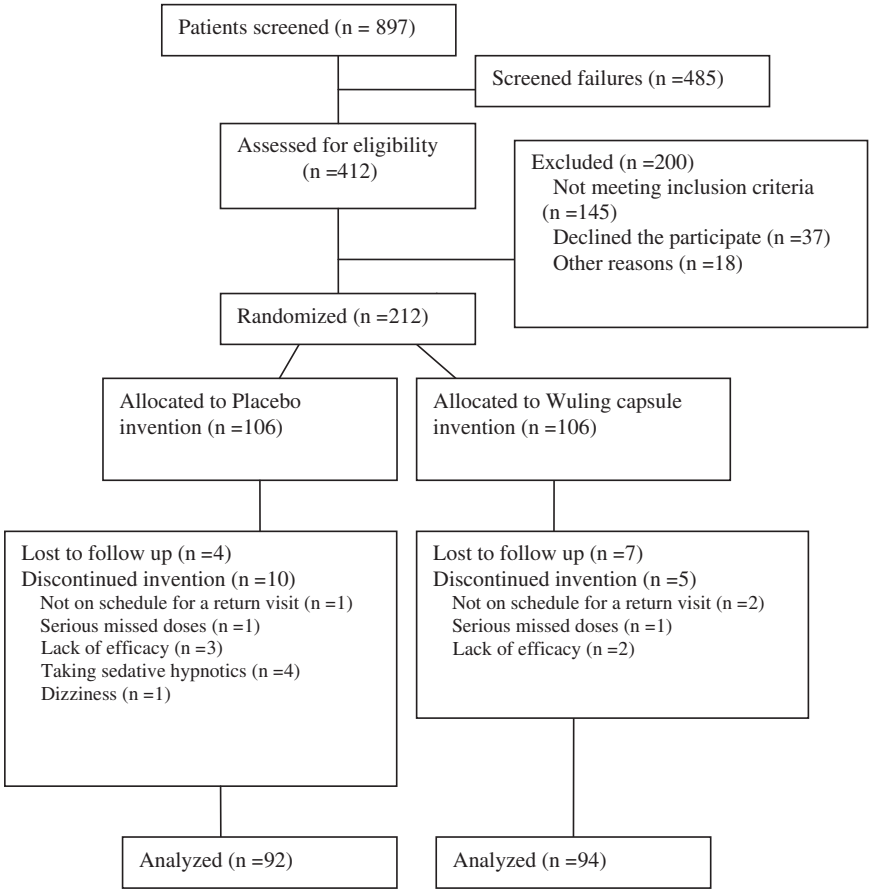

Fig. 1. Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis).