

ZHI-BAI-DI-HUANG-WAN, A CLASSIC CHINESE MEDICINAL FORMULA IN RELIEVING MENOPAUSAL SYMPTOMS: A MULTI-CENTRE AND CONTROLLED TRIAL FROM UK AND CHINA

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## Abstract

**Background:** To explore the effects of Zhi-Bai-Di-Huang-Wan (ZBDHW), a classic formula of Chinese medicinal herbs in relieving menopausal symptoms in British and Chinese women.

**Methods and Materials:** Between May 2011 and May 2013, 224 Chinese and British women were divided into a ZBDHW group with 115 cases and a control group with 109 cases. The clinical menopausal symptoms were assessed by the modified Kupperman Index Scale. The serum levels of follicle stimulating hormone (FSH) and estradiol (E<sub>2</sub>) were respectively detected before and after the treatment.

**Results:** After 12 weeks of treatment, both groups' Kupperman index scores markedly decreased ( $P < 0.05$ ) and no significant difference existed between them ( $P > 0.05$ ). The serum levels of FSH did not change significantly after the treatment ( $P > 0.05$ ) and no significant difference existed between them ( $P > 0.05$ ). The serum levels of E<sub>2</sub> significantly increased in both of the two groups ( $P < 0.05$ ) and it increased more in the comparison group ( $P < 0.05$ ). No side-effect of the treatment was reported in both of the two groups during the period of the treatment.

**Conclusion:** The classic Chinese medicinal formula, ZBDHW, showed promise in relieving menopausal symptoms.

**Key words:** Chinese medicinal herb; Zhi-Bai-Di-Huang-Wan (ZBDHW); menopausal symptoms

## Introduction

As we know, menopause is the end of a woman's reproductive phase, which is defined as the permanent cessation of ovarian function (Sherman, 2005). Some women can experience menopausal symptoms beginning in their mid-to-late forties and the menopausal symptoms can last for 4-5 years or longer (Politi et al., 2008). Menopausal women may suffer from a variety of symptoms, such as hot flashes, night sweats, mood swings, insomnia, vaginal dryness, in addition to long-term complications such as osteoporosis (Ortmann and Lattrich, 2012; Roush, 2012). In 1998, there were more than 477 million menopausal women worldwide, and the number was expected to reach 1.1 billion by 2025 (Uhl, 2008). Nearly 80% of women in western countries and more than 60% of Chinese women suffer from menopausal problems (Kronenberg, 1994). Although menopause is an inevitable part of every woman's life, according to an American survey, approximately 25% of women required interventions (Kronenberg, 1990). Although hormone replacement therapy (HRT) is the most effective treatment for menopausal syndrome, for the women who are unwilling to receive HRT or cannot take HRT due to its contraindications, it is urgent to explore the use of alternative and complementary medicine, especially traditional Chinese medicine to relieve their menopausal symptoms (Kass-Annese, 2000;

Morelli and Naquin, 2002; Nedrow et al., 2006; Newton et al., 2002; Wong et al., 2009; Zheng et al., 2013; Zhong et al., 2013; Zhou et al., 2007; Zhou et al., 2011). In USA, 82% physicians recommended herbal remedies to their menopausal patients (Singh et al., 2005).

Zhi Bai Di Huang Wan (ZBDHW, Eight Flavor Rehmannia Pill), a classic Chinese medicinal formula is frequently given to menopausal women who are suffering from hot flushes and night sweats. However, little multi-centre research has been conducted on the effects of ZBDHW in alleviating menopausal symptoms. The present multi-centre and controlled trial from UK and China was then designed to address it.

## **Methods and Materials**

### **Subjects**

The clinical research was conducted between May 2011 and May 2013 in three hospitals in China (Women's Hospital, School of Medicine, Zhejiang University, Hangzhou; the 2<sup>nd</sup> Hospital, Heilongjiang University of Chinese Medicine, Harbin; and the 3<sup>rd</sup> People's Hospital of Yuhang District, Hangzhou) and a TCM clinic in UK, Acu-herb Consultant (Sheffield, S10 2PR, UK; the relevant blood tests were done by the laboratory in Royal Hallamshire Hospital of the University of Sheffield, UK). A total of 234 Chinese and British women were divided into a ZBDHW group with 118 cases and a control group with 116 cases according to their desire. All of the participants did not take drugs containing hormones, or herb with phytohormone (such as Soybean protein products) or affecting the cardiovascular system during the previous 6 months. A gynecologic examination and laboratory tests showed that they did not suffer from organic diseases of reproductive system. All of the subjects were accorded to the diagnostic criteria of menopausal syndrome after clinical and laboratory examination. None of the patients was under medical treatment or had metabolic, hepatic, renal, or endocrine disease. Smokers were excluded. Ethical approval and permission to conduct the study were obtained from the Local Ethical Committees (where in the UK and where in China?) and the administration based on international guidelines. Women were informed about the short- and long-term benefits of HRT. The aim and methodology of the present study was explained to the patients. Voluntary participation was requested and informed consent obtained.

### **Group and Administration**

#### **ZBDHW Group**

The ingredients in the formula of ZBDHW are as follows: Radix Rehmanniae Preparata (Shu Di Huang), Fructus Corni Officinalis (Shan Zhu Yu), Cortex Moutan Radicis (Paeonia Suffruticosa, Mu Dan Pi), Rhizoma Dioscoreae Oppositae (Shan Yao), Sclerotium Poriae Cocos (Fu Ling), Rhizoma Alismatis Orientalis (Ze Xie), Rhizoma Anemarrhenae Asphodeloidis (Zhi Mu), Cortex Phellodendri Chinensis (Huang Bo). ZBDHW was provided by Tong Ren Tang Pharmaceutical Co., Ltd (Beijing, China). Patients were instructed to take 30 pills (6g) orally twice a day with warm water for 12 consecutive weeks. A two-week supply was dispensed at each treatment visit. Subjects were asked not to modify their dietary pattern during the study period.

#### **Control Group**

The subjects were prescribed with oral Livial (Tibolone, made by Nanjing Oujianong Pharmaceutical Co., Ltd, Nanjing, China), in the dosage of one tablet a day (2.5mg/tab) for 12 consecutive weeks. All the patients included in the control group were from the three hospitals in China.

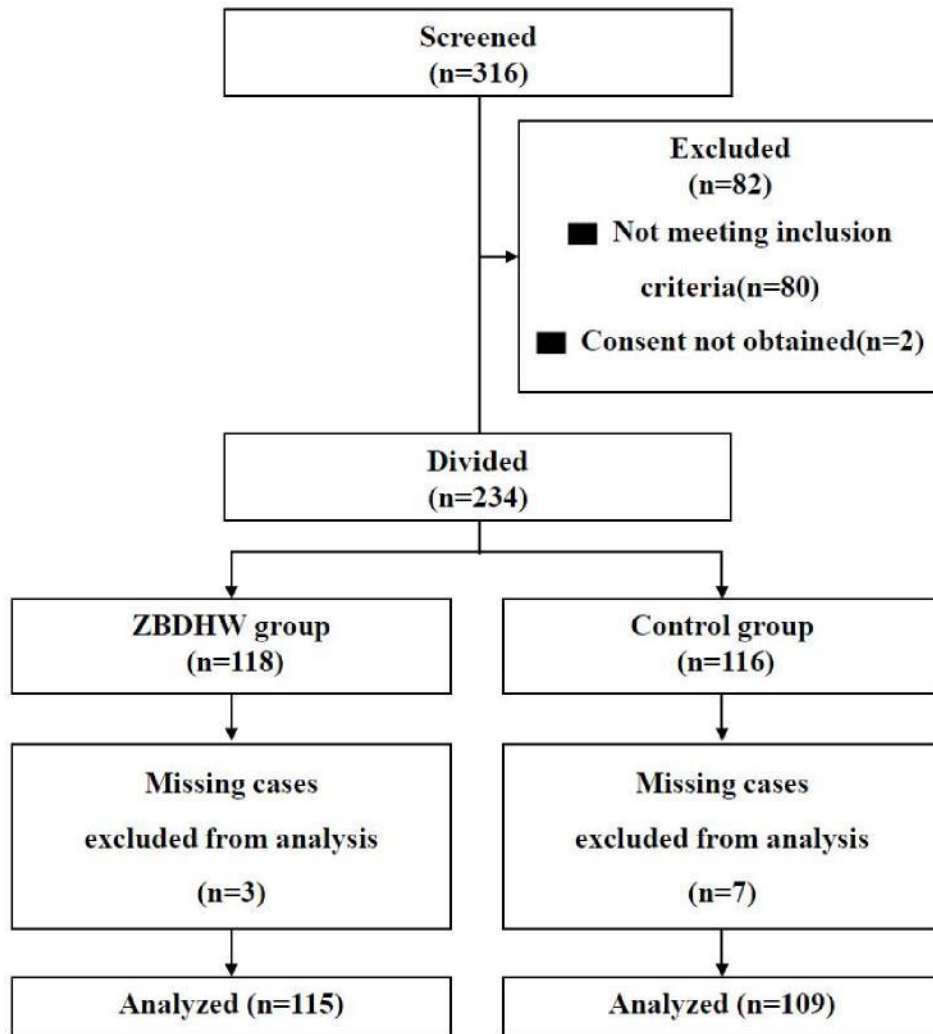
### **Index and Method**

Scoring criteria of menopausal symptoms: the degree of clinical symptoms was assessed by the modified Kupperman Scale respectively 1 day before the treatment and at the end of the treatment. Thirteen main symptoms were selected as heat and sweating, insomnia, nervousness, melancholia, sexual complaints, arthralgia and myalgia, vertigo, fatigue, headache, formication, urinary tract infection, heart palpitation,

paresthesia. Kupperman index was the sum of every multiplication product of symptom index and degree factor. The higher the score was the severe the symptom was. Kupperman indices before and after treatment of every patient were calculated. The serum levels of Follicle Stimulating Hormone (FSH) and estradiol (E<sub>2</sub>) were detected with ELISA. Each participant received a physical examination, routine blood examination, routine uronscopy, liver function test and renal function test respectively 3 days before the treatment and on the 3<sup>rd</sup> day after the treatment ended. In the statistical analysis, three cases in ZBDHW group and seven cases in control group were excluded as they went missing during the trial (Fig 1).

**Data Analysis**

Results were analyzed by an independent university statistician using Statistical Package for Social Sciences (SPSS 13.0 for Windows), a computer software. Non-parametric Mann–Whitney tests were used to analyze the inter-group and intra-group differences of Kupperman scores. Analysis of variance (ANOVA) was used to analyze the inter-group and intra-group differences of the serum levels of FSH and E<sub>2</sub>. A 5% significance level ( $P<0.05$ ) and two-tailed tests were used for all hypothesis tests. Ninety-five percent confidence intervals for the median differences were determined.



**Figure 1 :** The flow chart of the progress of participants through the trial.

## Results

### The Baseline Characteristics

There was no significant difference between ZBDHW group and control group in all the baseline characteristics ( $P>0.05$ ) (Table 1).

### Kupperman Index Scores

As shown in Table 2, after treatment for 12 weeks, Kupperman index scores in both of ZBDHW group and control group markedly decreased ( $P<0.05$ ) and no significant difference existed between the two groups ( $P>0.05$ ). As shown in Table 3, all the thirteen main symptoms were significantly relieved after treatment in ZBDHW group ( $P<0.05$ ). However, in control group, the vertigo symptom did not change markedly after the treatment ( $P>0.05$ ) and all the other symptoms were significantly relieved ( $P<0.05$ ).

**Table 1:** Participants' baseline characteristics

Item	ZBDHW group (n=115)	Control group (n=109)
Demographic characteristics		
Age (years)	48.66±4.66	46.70±4.55
Height(cm)	161.93±6.67	162.38±9.26
Weight(Kg)	62.79±7.18	61.13±11.91
Time since last menstrual period(months)	16.70±15.22	18.32±12.72
Married/living as married	106(92.2%)	101(92.7%)
Never married	2(1.9%)	3(2.8%)
Divorced/separated	7(6.1%)	5(4.6%)
Women with children	106(92.2%)	102(93.6%)
Area of residence		
Urban	72(62.6%)	69(63.3%)
Suburban	26(22.6%)	25(22.9%)
Rural	17(14.8%)	15(13.8%)
Educational background		
Less than high school	15(13.0%)	12(11.0%)
High school	18(15.7%)	18(15.6%)
Some college/university	82(71.3%)	79(72.5%)
Current employment status		
Full-time employment	63(54.8%)	59(54.1%)
Part-time employment	16(13.9%)	17(15.6%)
Registered unemployed /retired	36(31.3%)	33(30.3%)
Duration of the perimenopausal symptoms (month)	13.01±9.85	12.74±7.81

Notes: Values are given as mean±SD.

\*  $P<0.05$ , compared with the control group.

**Table 2:** Comparison of Kupperman index scores and the serum levels of FSH and E<sub>2</sub>

Items	ZBDHW group (n=115)		Control group (n=109)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FSH (mIU/ml)	61.57±25.65	55.90±35.40	55.97±28.42	35.68±21.64
E <sub>2</sub> (pg/ml)	52.08±52.38	78.76±96.32 * #	69.93±74.52	120.93±30.34 #
Kupperman Index	27.23±6.05	8.90±4.65 #	26.23±9.18	10.36±7.14#

Notes: Values are given as mean±SD.

\* P<0.05, compared with the control group.

# P<0.05, compared with pre-treatment in the same group.

**Table 3:** Comparison of the individual symptom in the Kupperman index scale

Symptoms	TCM group(n=115)		Control group(n=109)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Heat and sweating	8.66±3.09	2.26±2.26#	8.18±3.05	2.20±2.40#
Insomnia	3.70±1.90	1.23±1.07#	3.21±2.00	0.94±1.23#
Nervousness	3.22±1.73	1.15±1.16#	2.90±2.13	0.90±1.11#
Melancholia	0.94±0.82	0.45±0.55#	0.95±0.83	0.48±0.59#
Sexual complaints	1.65±1.62	0.59±0.95#	1.80±1.70	1.01±1.14#
Arthralgia, myalgia	0.97±0.92	0.35±0.48#	0.94±0.76	0.44±0.58#
Vertigo	0.71±0.71	0.23±0.42#	0.72±0.66	0.59±0.66
Fatigue	2.08±1.68	0.53±0.52#	0.85±0.69	0.42±0.55#
Headache	0.89±0.76	0.37±0.52#	0.94±0.78	0.68±0.62#
Formication	1.03±1.14	0.45±0.88#	1.78±1.52	1.05±1.29#
Urinary tract infection	1.10±1.11	0.47±0.89#	1.39±1.32	0.83±1.13#
Heart palpitation	0.97±0.64	0.26±0.44#	0.79±0.71	0.43±0.60#
Paresthesia	1.30±1.35	0.56±0.98#	1.78±1.50	0.40±0.81#

Notes: Values are given as mean±SD. # P<0.05, compared with pre-treatment in the same group.

### Serum Levels of FSH and E<sub>2</sub>

As shown in Table 2, after the treatment, the serum levels of FSH did not change significantly in both of ZBDHW group and control group (P>0.05) and no significant difference existed between them (P>0.05). The serum levels of E<sub>2</sub> significantly increased in both of the two groups (P<0.05) and it increased more in the control group (P<0.05).

### Adverse Result

No side-effect was reported in either group during the period of the research.

## Discussion

Menopausal symptoms occur frequently in premenopausal and early postmenopausal women, which negatively influence their physical and mental health as well as their quality of life at different levels (Gold et al., 2001; van der Mooren and Kenemans, 2004 not in the references section). The most recent research has shown relatively low risk of severe adverse events for HRT within the first 10 years of menopausal onset (Santen et al., 2010), however, as some menopausal women have contraindications to or are unwilling to use HRT, it is necessary to find some alternative medication for them. Both the patients and the physicians are increasingly interested in complementary therapies using natural products with good effectiveness and fewer side effects (Bair et al., 2008; Brett and Keenan, 2007; Flint, 2003; Hill-Sakurai et al., 2008; Thompson, 2010; Wong et al., 2009). We found in the present study that ZBDHW treatment for twelve weeks successfully decreased the Kupperman index scores of the menopausal women, without any difference compared to Livial and no side-effect of the treatment was reported during the period of the treatment.

It has been found that the main factors contributing to earlier onset of menopause and severity of menopausal symptoms were lower educational level, poor economic status, and smoking (Li et al., 2012). In the present study, the three factors were well controlled. The smokers were excluded from the study, and there were no significant differences between the ZBDHW and control groups on age, height, weight, time since last menstrual period, duration of the menopausal symptoms, marital status, area of residence, educational backgrounds and current employment status

In the present study, no side-effect was reported in either group during the period of the research, demonstrating that ZBDHW is a safe intervention to alleviate the menopausal symptoms in women. Findings from this study have implications for health care providers to consider administering ZBDHW, the classic Chinese medicinal formula in their clinical practices when caring for menopausal women who are unwilling to or cannot receive HRT. Further research should be done on the mechanism involved and more large-size, randomized, multicentre, double-blinded and placebo-controlled trials are supposed to be conducted in the future.

## Conclusion

The classic Chinese medicinal formula--ZBDHW showed promise in relieving menopausal symptoms.

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