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Black cohosh improves objective sleep in postmenopausal women with sleep disturbance

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Key words: BLACK COHOSH, POSTMENOPAUSAL, POLYSOMNOGRAPHY, SLEEP

ABSTRACT

Objective Sleep problems are prominent after menopause. The aim of our study was to look into the effect of black cohosh on both objective and subjective sleep in early postmenopausal women with sleep complaints.

Methods We performed a randomized, double-blind and placebo-controlled research during a 6-month period. Forty-eight postmenopausal women aged 45–60 years with sleep disturbance were enrolled and received daily administration of either black cohosh or placebo. Polysomnography and the Pittsburg Sleep Quality Index (PSQI) were performed at the initiation and termination of the study, as well as the Menopause-specific Quality of Life questionnaire and estradiol and follicle stimulating hormone tests. Liver and renal functions and breast and pelvic ultrasound were set as safety measures, carried out every 3 months.

Results Seventy-six women were interviewed, of whom 42 women completed the whole trial. Compared with placebo, black cohosh treatment led to significant polysomnographic changes, including increased sleep efficiency and decreased wake after sleep onset (WASO) duration, and tended to improve PSQI with a medium effect size. On average, 15.8% of WASO duration was reduced in the black cohosh group. Vasomotor and physical domains of life quality were improved compared with placebo. Safety measures did not yield any adverse event assigned to black cohosh.

Conclusions In early postmenopausal women with a major sleep complaint, black cohosh effectively improved sleep and might be a safe measure in managing menopausal sleep disturbance.

INTRODUCTION

Menopause is associated with a series of psycho-physiological changes, which persist from the menopausal transition for years in different severities. Besides vasomotor symptoms (VMS), sleep disturbance is another marker of menopause. Sleep is more likely to be disturbed in women than men at all ages and menopause brings about 3.4 times the risk of sleep disorders in postmenopausal women compared with premenopausal women¹. A large-scale study proved that sleep problems afflicted 25% of midlife women aged 50–64 years, 15% of which were suffering from even severe sleep disturbance². Sleep problems can vary with menopausal status. Early postmenopausal women experience lower sleep

efficiency (SE) and spend more time awake in bed than perimenopausal women³. Compared to early postmenopausal women, late postmenopausal women have a decreased proportion of slow-wave sleep (SWS) and increased arousals⁴. It is noteworthy that age-related sleep changes become prominent in late postmenopause, when physical aging is the principal concern^{5,6}. As sleep disturbance at menopause is multifactorial, primary menopausal insomnia should be defined as insomnia associated with menopause and cannot be explained by primary sleep disorders or other determinants^{7,8}. Along with other climacteric symptoms, self-reported sleep quality could be improved by hormone therapy, although its effects on objectively measured sleep are not always consistent^{9–12}. However, the duration, dose and indication of hormone

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therapy have been strictly limited by its potential risks for future heart attack, stroke and breast cancer. The demand for safe therapies to alleviate climacteric symptoms is increasing, leading gynecologists and researchers to focus on alternative medications for menopausal sleep problems⁷.

Black cohosh (*Cimicifuga racemosa*, BC) is the most prevalent alternative herbal remedy to hormone therapy in Europe for climacteric complaints that benefit from its non-estrogenic behavior, and its effect on overall climacteric symptoms has been confirmed for decades. More than 50 components have been derived from the crude drug and the key constituents of BC are triterpene glycosides, phenolic acids and *N*- ω -methylserotonin^{13,14}. The active compounds of BC mostly behave as neurotransmitters like 5-hydroxytryptamine (5-HT) and γ -aminobutyric acid (GABA). Serotonergic and GABAergic activities in relevant brain regions including the hypothalamus are essential in regulation of the normal sleep architecture, which is disrupted by the ovarian insufficiency in menopausal women^{15,16}. Three-month administration of BC could improve self-reported sleep quality in postmenopausal women with or without menopausal complaints, measured by daily diary and the subscore of the Menopause Rating Scale (MRS)^{17,18} or the Kupperman Menopause Index (KMI)¹⁹. To date, however, its effect on sleep architecture and nocturnal awakenings is still not known because of a lack of data on objective sleep measurement. Moreover, menopausal sleep disturbance is not the central issue of these studies.

An objective technique is provided by polysomnography (PSG), which is of great significance to both clinical examination and laboratory research, to capture features of sleep architecture dynamically and non-intrusively. Menopausal insomnia correlates with reduced rapid eye movement (REM) sleep, increasing arousals, low SE but long duration of SWS (stages 3 and 4) in PSG recordings^{20–22}. Very recently, PSG has been effectively applied to estimate the effects of acupuncture^{23,24}, therapeutic massage²⁵, yoga²⁶, physical therapy²⁷ and phytoestrogen²⁸ on menopausal women's sleep problems. Here we aim to investigate the effect of BC in the management of menopausal sleep disturbance through PSG as well as a sleep questionnaire.

BC has the superiority of safety to other hormonal therapies and has no clear contraindication in the current literature. There is still controversy regarding liver metabolism, and the administration of BC should be given cautiously with regard to potential hepatotoxicity²⁹. In our study, liver and renal functions were monitored for vital effects of drug metabolism. In regard to gynecologic organs, a 6-month treatment period of BC did not affect mammographic density in postmenopausal women^{30,31}, nor was there any increase of endometrial thickness during a 1-year treatment^{32,33}. In Chinese menopausal women, a recent controlled trial for tolerability showed that 20.7% of the participants experienced breast pain or enlargement during a 3-month administration of BC. Although this could not be causally interpreted, we examined the major target organs of estrogen as cautionary measures in the present study to further explore BC's safety.

METHODS

Participants

Seventy-six postmenopausal women with a chief complaint of sleep disturbance for at least 1 month were interviewed for further evaluation (Figure 1). All participants were collected in the 1st Affiliated Hospital of Harbin Medical University. Sleep disturbance in this study was defined as follows: having difficulty in initiating or maintaining sleep or experiencing non-restorative sleep for at least 1 month, without a history of insomnia prior to the menopausal transition (STRAW + 10: stages -2 and -1).

The inclusion criteria were as follows: age between 45 and 60 years old; body mass index (BMI) ≤ 30 kg/m²; 1 year \leq final menstrual period (FMP) ≤ 5 years (STRAW: stages +1b and +1c)⁶; serum follicle stimulating hormone (FSH) > 30.0 IU/l. The exclusion criteria consisted of the following conditions: induced menopause, i.e. bilateral oophorectomy and/or hysterectomy, artificial termination of ovarian function by chemotherapy and/or radiotherapy; poorly controlled clinical diseases, i.e. diabetes, systemic arterial hypertension, hepatic and/or nephritic dysfunction; history of thromboembolic events; historic and/or present clear psychiatric disorders such as schizophrenia, depression and anxiety according to DSM-IV-TR; self-reported and/or PSG-confirmed sleep-related respiratory disorders (i.e. sleep apnea, obstructive snoring) and movement disorders (i.e. restless leg syndrome); night shift work or irregular sleeping habit; systemic use of medications containing opioids, antiepileptics, anxiolytics, hypnotics and sedatives, antidepressants, and antihistamines within 3 months³⁴; use of estrogen, progestogen, androgen, or any other therapy against menopausal syndrome such as plant estrogen and Chinese medicine within 3 months; participation in another clinical trial within 3 months; alcohol consumption exceeding seven drinks per week or three per day (containing 14 g alcohol per drink); history of drug or substance abuse.

Forty-eight women who met the criteria agreed to participate after informed consent was obtained. The research protocol had received the approval of the Medical Ethics Committee of Harbin Medical University (HMU Res./Art. Ethics No. 201449) before the first participant was recruited.

Study design

This study was designed as a double-blind, randomized, placebo-controlled clinical trial (Figure 1). The candidates received: clinical interview: physical, medical and socioeconomic data, i.e. age, BMI, FMP, blood pressure, medical history, medication use, educational attainment (junior high school or less, senior high school, college or beyond), financial strain (difficulty in paying for living basics: not very, somewhat, very difficult)³⁵; indispensable laboratory tests: fasting blood glucose, serum FSH and estradiol levels, blood coagulation function, blood tests of liver and renal function; breast

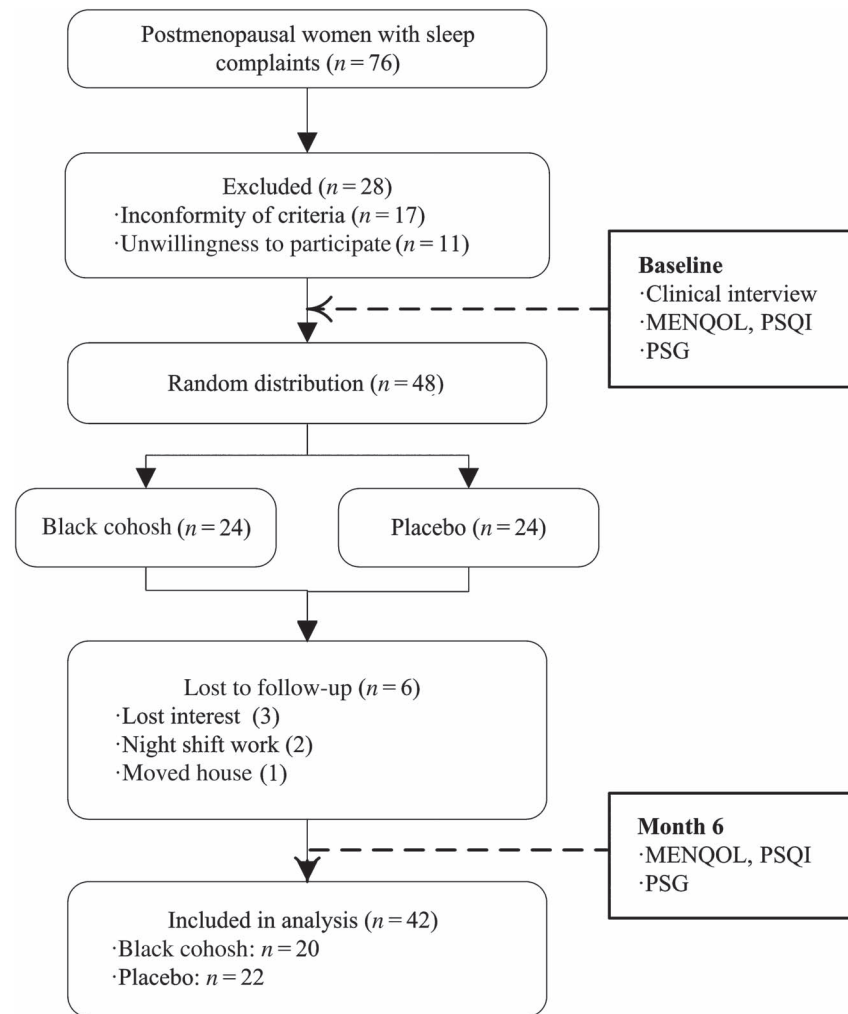


Figure 1 Flow chart of participants and study design. MENQOL, Menopause-specific Quality of Life; PSQI, Pittsburg Sleep Quality Index; PSG, polysomnography

and pelvic ultrasound. Then, the eligible candidates received the baseline PSG, after which those having sleep-related respiratory disorders and/or movement disorders were excluded. PSG was performed on two consecutive nights, of which the first night was for adaptation and the second night for data analysis. Women were asked to keep a healthy and regular sleep hygiene for at least 1 week before the baseline recording nights and to maintain the sleep schedule throughout the whole trial. PSG was recorded from lights off to lights on. After breakfast, women completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire, as well as the Menopause-specific Quality of Life (MENQOL) questionnaire.

Participants randomly received a standardized isopropanolic BC extract, containing extract of 20 mg crude drug per tablet (about 2.5 mg extract), or placebo. The randomization was conducted by a third party who was not involved in the rest of the study. BC tablets and placebo were prepared in uniform bottles with unique numbers. Both the researchers and the participants were blind to the intervention until the statistical

analysis was finished. The intervention lasted for 6 months, when both BC and placebo were orally administrated twice a day at fixed times after meals, one tablet each time. Adverse events were reported. The medication was supplied at the end of each month when the remaining tablets were returned to the researcher. Medication compliance was estimated at the end of the whole trial, by counting returned tablets at each visit. Tablet count was expressed as the percentage of taken tablets over total tablets and 100% represents perfect compliance. Participants who completed the whole trial were re-examined as follows: (1) PSG; (2) questionnaires: MENQOL, PSQI; (3) laboratory tests: serum FSH and estradiol levels, blood tests of liver and renal function; (4) breast and pelvic ultrasound. Examinations (2), (3) and (4) were performed in the morning after the second PSG recording night. Liver and renal function tests and ultrasound were also performed in the middle of the intervention for safety concerns.

Sleep was objectively assessed by PSG (Stellate Harmonie, Natus Medical Incorporated) and subjectively by PSQI. Sleep

electroencephalography (EEG) recordings were performed by a trained technician and analyzed by two EEG specialists, who were unaware of the intervention of individuals. Sleep stages were visually scored as wakefulness, stage 1, stage 2, stages 3 and 4 (SWS), and REM sleep. Polysomnographic parameters of total sleep time (TST), sleep stage percentages, sleep latency (SL), SE, REM sleep latency (RSL), duration of wake time after sleep onset (WASO), and arousals (alpha activity, 8–13 Hz, for at least 15 s per epoch) were also obtained³⁶. PSQI is a self-assessed questionnaire and consists of 24 items, evaluating sleep quality and disturbance. The total score ranges from 0 to 21 and higher scores indicate worse subjective sleep³⁷. MENQOL is also self-tested with 29 items. It has four domains (vasomotor, psychosocial, physical and sexual) and the score of each domain ranges from 1 to 8. The vasomotor domain is made up of three items concerning daytime hot flushes and night sweats; the psychosocial domain assesses memory loss and mood symptoms with seven items; the physical domain has 16 items of physical fatigue, somatic pain, sleep problems, digestive and urinary symptoms, aging skin and weight gain; the sexual domain measures sex drive and vaginal dryness with three items³⁸. Individuals spent 15–35 min completing the questionnaires. All the questionnaires were in the standardized Chinese edition and their reliability and validity had already been proved.

Statistical analysis

SPSS v19.0 was used for data analysis. The χ^2 test, Fisher's exact test, unpaired Student's *t* test and Mann–Whitney *U* test were used for inter-group comparison while Fisher's exact test, paired Student's *t* test and Wilcoxon rank test were adopted for intra-group comparison. In addition, analysis of covariance (ANCOVA) was also used for the analysis of MENQOL scores. For categorical data analysis, Cramer's *V* was measured for effect size³⁹. Pearson's correlation coefficient, *r*, was chosen to measure the effect size in the means comparisons and non-parameter tests according to Field³⁹. When *r* is 0.10, 0.30 or 0.50, it is equivalent to a small, medium or large experimental effect, respectively. The correlation between estradiol and sleep measures was assessed by the means of linear correlation or Spearman's rank correlation. Spearman's rank correlation was also performed to confirm whether MENQOL vasomotor correlated with WASO or arousals. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Twenty women in the BC group and 22 in the placebo group completed the whole trial and were included in the final statistical analysis (Figure 1). No one dropped out for the emergence of adverse events, disease onset or aggravation or sleep respiratory and movement disorders. The treatment compliance in this trial was good (BC group 99.0%, placebo group 98.2%).

Demographic and clinical data at baseline

The demographic and clinical characteristics are presented in Table 1. There was no significant difference between the two groups at baseline in age, BMI, FSH and estradiol levels, PSQI, MENQOL scores and polysomnographic parameters. The two groups were also similar in educational attainment ($p = 0.375$) and financial strain ($p = 0.737$). According to MENQOL, 59.5% of the women had VMS (MENQOL vasomotor > 1) and their prevalence was similar in the two groups at baseline (60.0% and 59.1%, $p = 0.601$). PSG data showed that 76.2% of the women had low SE ($< 85\%$). The percentages of women with low SE were similar in the two groups (70.0% and 81.0%, $p = 0.477$, Figure 2). Estradiol level did not significantly correlate with PSQI or any polysomnographic parameters. Nor was any correlation found between MENQOL vasomotor and WASO or arousals.

Clinical and polysomnographic assessment after treatment

It seemed that BC could not improve VMS ($p = 0.267$, Table 2). Concerning the women having VMS at baseline, however, the MENQOL vasomotor score was significantly lower in the BC group than that in the placebo group ($r = 0.480$, $p = 0.015$). In spite of a decline of MENQOL psychosocial score in both

Table 1 Baseline characteristics of demographic and clinical data expressed as mean (standard deviation)

	Black cohosh (<i>n</i> = 20)	Placebo (<i>n</i> = 22)	<i>p</i> Value
Age (years)	52.2 (5.5)	51.6 (4.9)	0.706
Body mass index (kg/m ²)	23.7 (3.7)	25.0 (3.0)	0.217
FSH (IU/l)	65.7 (10.9)	69.4 (13.7)	0.668
Estradiol (pg/ml)	14.9 (2.9)	14.0 (3.9)	0.268
MENQOL vasomotor (1–8)	3.5 (2.4)	3.7 (2.6)	0.754
MENQOL psychosocial (1–8)	4.8 (1.9)	4.7 (2.0)	0.574
MENQOL physical (1–8)	3.9 (0.9)	4.5 (1.17)	0.064
MENQOL sexual (1–8)	4.9 (2.2)	4.8 (1.9)	0.846
PSQI (0–21)	12.0 (3.6)	11.9 (3.2)	0.939
Total sleep time (min)	330.1 (39.8)	323.0 (49.9)	0.716
Sleep latency (min)	26.45 (17.2)	33.7 (20.5)	0.226
REM sleep latency (min)	131.4 (51.8)	137.5 (46.3)	0.689
Sleep efficiency (%)	78.8 (8.4)	76.6 (8.2)	0.402
Stage 1 (%)	15.9 (6.5)	19.1 (6.4)	0.124
Stage 2 (%)	49.3 (9.1)	45.8 (8.0)	0.187
Stages 3 and 4 (%)	18.5 (6.3)	20.8 (5.5)	0.22
REM sleep (%)	16.3 (5.1)	14.4 (4.2)	0.199
Wake after sleep onset (min)	60.6 (30.0)	70.1 (33.1)	0.335
Arousals (times)	121.6 (38.5)	113.5 (44.1)	0.529

FSH, follicle stimulating hormone; MENQOL, Menopause-specific Quality of Life; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement

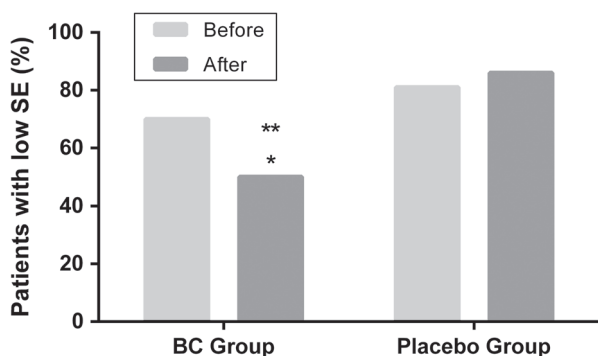


Figure 2 Percentage of participants with sleep efficiency (SE) < 85% before and after intervention in the two groups. **, $p = 0.003$ compared with baseline; *, $p = 0.011$ compared with placebo group. BC, black cohosh

the BC group ($p = 0.015$) and the placebo group ($p = 0.019$), no difference between groups was observed ($p = 0.487$, Table 2). For the physical symptom evaluation, the MENQOL physical score decreased in both groups ($p = 0.004$, 0.023) and it remained significant in the inter-group analysis ($r = 0.316$, $p = 0.041$, Table 2). Considering the p value of the MENQOL physical score at baseline ($p = 0.064$, Table 1), ANCOVA was performed to adjust for the baseline scores of this domain, whereas a small effect size was observed ($r = 0.161$). No change of MENQOL sexual score was detected in any analysis intra- or inter-group.

Table 2 Clinical data after intervention expressed as mean (standard deviation)

	Black cohosh ($n = 20$)	Placebo ($n = 22$)	p Value
FSH (IU/l)	66.5 (10.5)	69.4 (14.4)	0.451
Estradiol (pg/ml)	13.9 (3.1)	14.1 (2.6)	0.881
MENQOL vasomotor (1–8)	2.9 (1.9)	3.6 (2.5)	0.267
MENQOL psychosocial (1–8)	4.2 (1.6)	3.9 (1.5)	0.487
MENQOL physical (1–8)	3.4 (0.9)	4.0 (0.9)	0.041*
MENQOL sexual (1–8)	4.7 (1.9)	4.7 (1.4)	0.951
PSQI (0–21)	10.6 (2.9)	12.2 (3.0)	0.051
Total sleep time (min)	341.6 (38.9)	332.1 (34.2)	0.403
Sleep latency (min)	21.5 (12.4)	31.8 (22.2)	0.069
REM sleep latency (min)	137.8 (42.0)	136.7 (53.6)	0.922
Sleep efficiency (%)	81.8 (6.5)	75.7 (8.0)	0.01*
Stage 1 (%)	17.7 (8.8)	18.1 (7.3)	0.888
Stage 2 (%)	47.2 (11.2)	47.4 (9.5)	0.963
Stages 3 and 4 (%)	19.4 (5.7)	19.9 (6.5)	0.814
REM sleep (%)	15.7 (4.6)	14.7 (3.5)	0.45
Wake after sleep onset (min)	48.7 (24.1)	73.6 (31.7)	0.009**
Arousals (times)	101.5 (34.5)	120.9 (52.6)	0.17

MENQOL, Menopause-specific Quality of Life; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement
 **, $p < 0.01$; *, $p < 0.05$

PSQI was the subjective measure of perceived sleep quality in this trial and a reduction of PSQI score indicated an improvement. A decrease of PSQI was found in the BC group ($r = 0.601$, $p = 0.001$). Although the decrease vanished when compared with the placebo group ($r = 0.301$, $p = 0.051$, Table 2), there was a medium effect in this situation. For the objective measure of sleep, intra-group analysis of polysomnographic parameters showed that no change was observed in the placebo group, while in the BC group, SE ($r = 0.559$, $p = 0.008$) was higher and WASO ($r = 0.585$, $p = 0.005$) and arousals ($r = 0.517$, $p = 0.016$) were lower than those at baseline. When compared with the placebo group, the difference in SE ($r = 0.391$, $p = 0.010$) and WASO ($r = 0.404$, $p = 0.009$) remained significant (Table 2). Considering the proportion of low SE, the percentage of women with low SE in the BC group decreased from 70% to 50% (Cramer's $V = 0.655$, $p = 0.003$) and was significantly lower than that in placebo group (Cramer's $V = 0.393$, $p = 0.011$, Figure 2). In addition, we calculated the reduction of WASO duration in both groups, expressed as percentage of WASO reduction over WASO at baseline. BC reduced 15.8% of WASO duration at baseline on average ($r = 0.427$, $p = 0.005$, Figure 3). Significant changes in other polysomnographic parameters were not observed.

Safety evaluation

Blood tests of liver and renal functions and ultrasound examinations of breast and pelvic cavity were major measures for safety. Only one woman in the BC group was reported to have an increased aspartate aminotransferase (AST) level in the middle of the trial (AST = 48.6 U/l). She was asked to improve dietary hygiene and her AST returned to normal when re-examined 1 month later. For the others, no clinically significant abnormality was found in the tests of liver and renal functions, ultrasound of mammary gland, uterus and bilateral ovaries and no adverse event was reported. No difference in

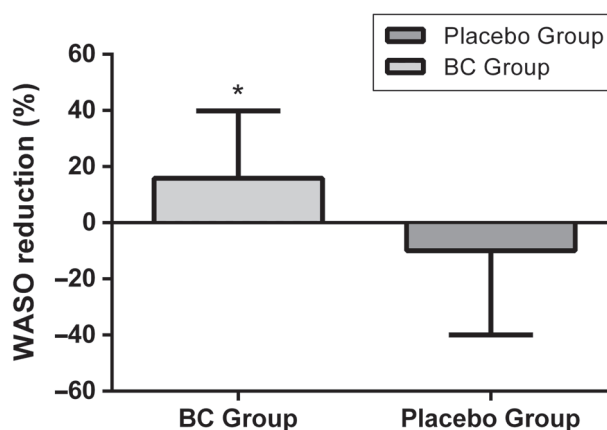


Figure 3 Reduction in wake after sleep onset (WASO) over WASO at baseline illustrated as mean and standard deviation in the two groups. *, $p = 0.005$ compared with placebo group. BC, black cohosh

FSH or estradiol level was observed in the comparisons intra- and inter-group, suggesting that BC did not affect the level of serum estrogen.

DISCUSSION

The present study demonstrated that the 6-month daily oral administration of a standardized isopropanolic preparation of BC improved objective sleep quality through increasing SE and decreasing WASO duration. It tended to ameliorate the subjective sleep complaints indicated by reducing PSQI in postmenopausal women with sleep disturbances. Life quality was also improved in the vasomotor and physical domains.

The prevalence of insomnia in Chinese menopausal women aged 40–65 years is increasing from 37.2% to 67.65%; insomnia is one of the most prevalent climacteric symptoms^{40,41}. Increasing numbers of menopausal women troubled with new-onset or aggravating sleep disturbances have been seeking safe medication other than hormone therapy in our clinics. By the very nature of estrogen, hormone therapy has invariably been associated with limited clinical indication and poor medical compliance. Despite the popularity of alternative therapies during these years, only a few studies have focused on menopausal sleep disturbance. Thus, PSG was first chosen as the principal assessment of sleep in the present study. Here we addressed the sleep issues related to menopause itself beyond the whole climacterium, while the primary sleep disorders and the definite psychological and psychiatric disorders were excluded. The age span and the menopausal stage were defined as early postmenopause following the menopausal transition. We also tried to control other confounding factors having the potential to affect sleep parameters such as BMI, sex hormone levels, systemic medication use, physical condition, financial and educational status, according to the SWAN (Study of Women's Health Across the Nation) sleep study³⁵. The randomization of our study was well performed as there was no significant difference in baseline data between the two groups.

The mechanisms of BC underlying sleep changes *in vivo* have not been well understood in the literature. The objective sleep improvement might be mostly attributed to the activities of 5-HT and GABA in the central nervous system. Bolton and her colleagues previously identified the serotonergic behaviors of BC compounds in their earlier *in vitro* studies; these behaviors were mostly attributed to *N*- ω -methylserotonin^{13,42}. It competitively binds to the 5-HT_{1A}, 5-HT_{1D} and 5-HT₇ subtypes of serotonin receptors and functions as a partial agonist^{13,42,43}. In mammals, 5-HT is involved essentially in various functions including the sleep–wake transition, cognition, sexual function, thermoregulation and food ingestion¹⁶. 5-HT plays a key role in the normal regulation of sleep initiation, duration and stage transformation. BC might alleviate the neuroendocrinal fluctuation of serotonin caused by menopause, resulting in reduced duration of WASO. GABA also participates in sleep regulation and GABA type A (GABA_A) receptor agonist can promote SWS and suppress wakefulness

with no influence on REM sleep¹⁵. Some of the isolated triterpene glycosides have been proven positively to modulate the GABA_A receptor *in vitro*⁴⁴. It appears that BC acts as an atypical GABA_A receptor agonist as it decreases wake time without affecting REM sleep, but a typical improvement of SWS was not observed in our study. Besides, Mimaka and colleagues found earlier that two types of triterpene glycoside were capable of promoting ACTH secretion of mouse pituitary tumor cell line⁴⁵. They also revealed that BC interacted with the hypothalamo–pituitary–adrenal axis and the sympathetic adrenomedullary system to buffer the systemic responses to stress events *in vivo*, probably through its neurotransmitter-mimetic activities in brain^{43,46}. Moreover, a recent *in vitro* study showed that a novel triterpene glycoside reduced the amyloid beta deposits, well known as the major pathological change in Alzheimer's disease, implying its protection of the central nervous system⁴⁷.

Postmenopausal women with sleep complaints often experience poor SE and, as we expected, 76.2% of the participants exhibited low SE at baseline in our study. BC could reduce the percentage of women suffering from low SE and induce a significant improvement of SE compared with placebo, suggesting its role in the maintenance of sleep. In addition to poor SE, postmenopausal women tend to spend more time awake at night, which is another marker of impaired sleep associated with menopause. Wuttke and colleagues examined whether BC impacted on sleeping behavior and showed that the average frequency of self-reported waking up per night was lower in the BC group than in the group receiving estrogen¹⁸. In our PSG analysis, similar results were achieved: 6-month administration of BC could significantly reduce WASO duration on the recording nights while no increase in stages 1 and 2 of non-REM sleep or REM sleep was observed, indicating that BC provided an amelioration of the impaired sleep continuity. However, BC failed to accelerate the initiation of sleep since no difference in SL was observed. Thus, we assume that BC might improve sleep continuity mainly through attenuating certain nocturnal arousals that are strong enough to cause total wakefulness, rather than shortening the latency to the onset of another sleep stage right after the arousal.

The beneficial effect of BC on perceived sleep quality during the menopausal transition and postmenopause has been confirmed¹⁷. BC is equivalent to conjugated estrogen and tibolone in the improvement of subjective sleep, as indicated by the sleep diary and KMI insomnia subscore^{18,19}. Geller and colleagues applied PSQI to measure the perceived sleep quality and showed, however, that 12-month administration of BC failed to be superior to placebo⁴⁸. It is worth noting that participants were primarily selected based on moderate to severe VMS in the previous study. Besides, the previous PSQI research administered up to 128 mg crude drug per day, namely about three times the dose in our study, as well as in the studies of positive findings by sleep diary and KMI insomnia subscore. In our study, although we also failed to observe a remarkable difference between groups concerning PSQI, a medium effect was achieved. In addition, serum estradiol did

not correlate with subjective or objective sleep parameters, consistent with a recent SWAN sleep study⁴⁹.

In our study, an isopropanolic extract of BC was used, which has been introduced since 2009. Before the formal introduction, Bai and colleagues performed a large-scale clinical trial in 2006 to prove its equivalent efficacy and superior safety to tibolone in managing menopausal complaints in Chinese peri- and postmenopausal women¹⁹. Our study again confirmed its effect on VMS. Although there is always a strong link between VMS and sleep disruption⁵⁰, no correlation between VMS and nocturnal wake periods or arousals was found in our study. VMS and menopausal sleep complaints might be isolated entities^{8,51,52}. It is well accepted that VMS are caused by a falsely reduced set point of body core temperature and the dysfunction of the hypothalamic thermoregulatory center results from estrogen deficiency and opioid withdrawal⁵³. BC might work through interaction with the endogenous opioid system and acting as a partial agonist^{54,55}. Another connection between BC and VMS is that BC modulates the activities of 5-HT_{1A} and 5-HT₇ receptors, which are mainly distributed in the hypothalamus. Although BC failed to be superior to placebo when dealing with the psychosocial domain, both groups reached a significant reduction of MENQOL psychosocial score. Recently, an *in vivo* study showed that certain hypothalamic nuclei, involved in the physical and psychological changes in menopause, might be the targets of BC. For instance, the suprachiasmatic nucleus (SCN) generates a mammalian circadian rhythm and is vital for maintaining the sleep-wake pattern, the endocrine system, metabolism and physiological rhythm⁵⁶. BC could up-regulate the neuron density of the impaired neurons of SCN in ovariectomized rats⁵⁷. The excitatory activities in SCN could be enhanced by estrogen as well, but their responses to various external environments were different from those treated with BC⁵⁷. The negative result in the sex domain in the present study was supported by another herbal therapy study. It was shown that systemic use of BC did not impact vaginal cytology and vaginal dryness score³². BC might not keep the same advantage of ameliorating menopausal sexual symptoms as in the other domains. Local use of estrogen is recommended for vaginal dryness in menopausal women⁵⁸.

In our study, a placebo effect was observed. A placebo effect is a neurobiological phenomenon associated with the central nervous system. Its mechanism has been widely studied in somatic pain, as well as depression, anxiety and Parkinson's disease⁵⁹. This effect might be remarkable in alleviating subjective symptoms rather than pathological disease, which is mainly due to strong expectations of certain therapies⁶⁰. In our study, the scores in the psychosocial and physical domains of MENQOL were reduced in the placebo group. The latest research in the literature also show that placebo could decrease the scores of MENQOL in postmenopausal women^{61,62}. In terms of objective symptoms, however, placebo did not impact any polysomnographic parameters.

One participant in the BC group in our study was found to have an abnormal liver enzyme and it could not be assigned to BC since the abnormality was slight and transient and was rectified with diet adjustment. A recent meta-analysis assessed five clinical trials of isopropanolic BC extract and showed that 3–6-month treatment did not cause liver impairment⁶³. Concerning the target organs of estrogen, BC was reported to present a protective effect against breast cancer and this anti-carcinogenic property might be mainly assigned to triterpenes⁶⁴. Another protective effect of triterpenes is that endometrial proliferation could be suppressed without any stimulation of estrogen receptor α ⁶⁵. Moreover, BC reduces 30% of the ultrasonic volume of uterine fibroids in midlife women⁶⁶. The circulating levels of estradiol and FSH did not change significantly in our study, supporting the non-estrogenic property of BC in treating estrogen-insufficient symptoms.

There are certain limitations to the present study. As we were limited by the small scale, we did not enroll women of different menopausal status and a wide age span. A larger sample size is needed to involve more covariate and subgroup analysis concerning menopausal status, age and the severity of climacteric symptoms. Also, the dynamic changes of clinical symptoms and polysomnographic parameters during the process of treatment were not evaluated. By conducting repeated measures for the next step, we will be able to investigate the effective treatment duration of BC.

CONCLUSION

We first investigated the effect of black cohosh on sleep disturbance related to menopause. Our study provided, for the first time, the profiles of black cohosh's effect on sleep architecture and process. In summary, PSG analysis revealed that 6-month daily oral administration of black cohosh is effective in the maintenance of objective sleep by increasing sleep efficiency and reducing time of being awake in early postmenopausal women with the major complaint of impaired sleep. Black cohosh also had the potential to ameliorate perceived sleep quality. Regarding menopausal quality of life, black cohosh could improve the vasomotor and physical domains in this population. The present study opens the possibility that black cohosh might be useful in menopause-related sleep disturbance. Future research is expected to reach a comprehensive understanding of its mechanisms in dealing with impaired sleep in menopausal women.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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References

- Kuh DL, Wadsworth M, Hardy R. Women's health in midlife: the influence of the menopause, social factors and health in earlier life. *Br J Obstet Gynaecol* 1997;104:923–33
- Polo-Kantola P. Sleep problems in midlife and beyond. *Maturitas* 2011;68:224–32
- Moreno-Frias C, Figueroa-Vega N, Malacara JM. Relationship of sleep alterations with perimenopausal and postmenopausal symptoms. *Menopause* 2014;21:1017–22
- Hachul H, Frange C, Bezerra AG, et al. The effect of menopause on objective sleep parameters: data from an epidemiologic study in Sao Paulo, Brazil. *Maturitas* 2015;80:170–8
- Edwards BA, O'Driscoll DM, Ali A, et al. Aging and sleep: physiology and pathophysiology. *Semin Respir Crit Care Med* 2010;31:618–33
- Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Climacteric* 2012;15:105–14
- Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. *Semin Reprod Med* 2010;28:404–21
- Bourey RE. Primary menopausal insomnia: definition, review, and practical approach. *Endocrine Pract* 2011;17:122–31
- Kalleinen N, Polo O, Himanen SL, et al. The effect of estrogen plus progesterin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women. *Climacteric* 2008;11:233–43
- Saletu-Zyhlarz G, Anderer P, Gruber G, et al. Insomnia related to postmenopausal syndrome and hormone replacement therapy: sleep laboratory studies on baseline differences between patients and controls and double-blind, placebo-controlled investigations on the effects of a novel estrogen-progestogen combination (Climodien, Lafamme) versus estrogen alone. *J Sleep Res* 2003;12:239–54
- Schussler P, Kluge M, Yassouridis A, et al. Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. *Psychoneuroendocrinology* 2008;33:1124–31
- Silva BH, Martinez D, Wender MC, et al. A randomized, controlled pilot trial of hormone therapy for menopausal insomnia. *Arch Women's Ment Health* 2011;14:505–8
- Powell SL, Godecke T, Nikolic D, et al. In vitro serotonergic activity of black cohosh and identification of N- ω -methylserotonin as a potential active constituent. *J Agric Food Chem* 2008;56:11718–26
- Nuntanakorn P, Jiang B, Einbond LS, et al. Polyphenolic constituents of *Actaea racemosa*. *J Nat Prod* 2006;69:314–18
- Steiger A. Neurochemical regulation of sleep. *J Psychiatr Res* 2007;41:537–52
- Monti JM. Serotonin control of sleep-wake behavior. *Sleep Med Rev* 2011;15:269–81
- Reed S, Newton K, LaCroix A, et al. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005;106:1111
- Wuttke W, Rauš K, Gorkow C, et al. Efficacy and tolerability of the Black cohosh (*Actaea racemosa*) ethanolic extract BNO 1055 on climacteric complaints: A double-blind, placebo- and conjugated estrogens-controlled study. *Maturitas* 2006;55:S83–91
- Bai W, Henneicke-von Zepelin HH, Wang S, et al. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. *Maturitas* 2007;58:31–41
- Toffol E, Kalleinen N, Urrila As, et al. The relationship between mood and sleep in different female reproductive states. *BMC Psychiatr* 2014;14:177
- Hachul H, Andersen LM, Bittencourt A, et al. Does the reproductive cycle influence sleep patterns in women with sleep complaints? *Climacteric* 2010;13:594–603
- Naoko T, Yoshiro S, Tachibana N, et al. Sleep characteristics of menopausal insomnia: a polysomnographic study. *Psychiat Clin Neurosci* 2004;58:179–85
- Hachul H, Garcia TK, Maciel AL, et al. Acupuncture improves sleep in postmenopause in a randomized, double-blind, placebo-controlled study. *Climacteric* 2013;16:36–40
- Yang SB, Mei ZG, Cai SJ, et al. [Efficacy comparison of different points combination in the treatment of menopausal insomnia: a randomized controlled trial]. *Zhongguo Zhen Jiu* 2014;34:3–8
- Oliveira Ds, Hachul H, Goto V, et al. Effect of therapeutic massage on insomnia and climacteric symptoms in postmenopausal women. *Climacteric* 2012;15:21–9
- Afonso RF, Hachul H, Kozasa EH, et al. Yoga decreases insomnia in postmenopausal women: a randomized clinical trial. *Menopause* 2012;19:186–93
- Llanas AC, Hachul H, Bittencourt LR, et al. Physical therapy reduces insomnia symptoms in postmenopausal women. *Maturitas* 2008;61:281–4
- Hachul H, Bittencourt L, Baracat E, et al. Isoflavones decrease insomnia in postmenopause. *Menopause* 2011;18:178–84
- Mahady GB, Low Dog T, Barrett ML, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause* 2008;15:628–38
- Hirschberg AL, Edlund M, Svane G, et al. An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. *Menopause* 2007;14:89–96
- Lundstrom E, Hirschberg AL, Soderqvist G. Digitized assessment of mammographic breast density – effects of continuous combined hormone therapy, tibolone and black cohosh compared to placebo. *Maturitas* 2011;70:361–4
- Reed SD, Newton KM, LaCroix AZ, et al. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. *Menopause* 2008;15:51–8
- Raus K, Brucker C, Gorkow C, et al. First-time proof of endometrial safety of the special black cohosh extract (*Actaea* or *Cimicifuga racemosa* extract) CR BNO 1055. *Menopause* 2006;13:678–91
- Kravitz HM, Avery E, Sowers M, et al. Relationships between menopausal and mood symptoms and EEG sleep measures in a multi-ethnic sample of middle-aged women: the SWAN sleep study. *Sleep* 2011;34:1221–32
- Hall MH, Matthews KA, Kravitz HM, et al. Race and financial strain are independent correlates of sleep in midlife women: the SWAN sleep study. *Sleep* 2009;32:73–82
- Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. UCLA Brain Information Service. California, USA: Brain Research Institute Los Angeles, 1968
- Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatr Res* 1989;28:193–213

38. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 2008;61:107–21
39. Field A. *Discovering Statistics using SPSS*. Thousand Oaks, LA: Sage Publications, 2009
40. Yang D, Haines CJ, Pan P, et al. Menopausal symptoms in mid-life women in southern China. *Climacteric* 2008;11:329–36
41. Chen R, Yu Q, Xu KH, et al. [Survey on characteristics of menopause of Chinese women with the age of 40–60 years at gynecological clinic from 14 hospitals]. *Zhong hua fu chan ke za zhi* 2013;48:723–7
42. Burdette JE, Liu J, Chen SN, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem* 2003;51:5661–70
43. Nadaoka I, Yasue M, Sami M, et al. Oral administration of Cimicifuga racemosa extract affects immobilization stress-induced changes in murine cerebral monoamine metabolism. *Biomed Res* 2012;33:133–7
44. Cicek SS, Khom S, Taferner B, et al. Bioactivity-guided isolation of GABA(A) receptor modulating constituents from the rhizomes of Actaea racemosa. *J Nat Prod* 2010;73:2024–8
45. Mimaki Y, Nadaoka I, Yasue M, et al. Neocimicigenosides A and B, cycloartane glycosides from the rhizomes of Cimicifuga racemosa and their effects on CRF-stimulated ACTH secretion from AtT-20 cells. *J Nat Prod* 2006;69:829–32
46. Nadaoka I, Yasue M, Kitagawa Y, et al. Oral administration of Cimicifuga racemosa extract attenuates psychological and physiological stress responses. *Biomed Res* 2012;33:145–52
47. Findeis MA, Schroeder F, McKee TD, et al. Discovery of a novel pharmacological and structural class of gamma secretase modulators derived from the extract of Actaea racemosa. *ACS Chem Neurosci* 2012;3:941–51
48. Geller SE, Shulman LP, van Breemen RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause* 2009;16:1156–66
49. Sowers MF, Zheng H, Kravitz HM, et al. Sex steroid hormone profiles are related to sleep measures from polysomnography and the Pittsburgh Sleep Quality Index. *Sleep* 2008;31:1339–49
50. Joffe H, Crawford S, Economou N, et al. A gonadotropin-releasing hormone agonist model demonstrates that nocturnal hot flashes interrupt objective sleep. *Sleep* 2013;36:1977–85
51. Young T, Rabago D, Zgierska A, et al. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. *Sleep* 2003;26:667–72
52. Freedman RR, Roehrs TA. Lack of sleep disturbance from menopausal hot flashes. *Fertil Steril* 2004;82:138–44
53. Freedman RR. Pathophysiology and treatment of menopausal hot flashes. *Semin Reprod Med* 2005;23:117–25
54. Rhyu MR, Lu J, Webster DE, et al. Black cohosh (Actaea racemosa, Cimicifuga racemosa) behaves as a mixed competitive ligand and partial agonist at the human mu opiate receptor. *J Agric Food Chem* 2006;54:9852–7
55. Reame NE, Lukacs JL, Padmanabhan V, et al. Black cohosh has central opioid activity in postmenopausal women: evidence from naloxone blockade and positron emission tomography neuroimaging. *Menopause* 2008;15:832–40
56. Meijer JH, Michel S. Neurophysiological analysis of the suprachiasmatic nucleus: a challenge at multiple levels. *Methods Enzymol* 2015;552:75–102
57. Hui Z, Xiaoyan M, Mukun Y, et al. Effects of black cohosh and estrogen on the hypothalamic nuclei of ovariectomized rats at different temperatures. *J Ethnopharmacol* 2012;142:769–75
58. de Villiers TJ, Pines A, Panay N, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013;16:316–37
59. Meissner K, Bingel U, Colloca L, et al. The placebo effect: advances from different methodological approaches. *J Neurosci* 2011;31:16117–24
60. Colloca L, Jonas WB, Killen J, et al. Reevaluating the placebo effect in medical practice. *Zeitschrift Psychol* 2014;222:124–7
61. Yang H, Yang J, Wen Z, et al. Effect of combining therapy with traditional chinese medicine-based psychotherapy and herbal medicines in women with menopausal syndrome: a randomized controlled clinical trial. *Evid Based Complement Alternat Med* 2012;2012:354145
62. Caan B, LaCroix AZ, Joffe H, et al. Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes: a placebo-controlled randomized trial. *Menopause* 2014 Nov 17. Epub ahead of print
63. Naser B, Schnitker J, Minkin MJ, et al. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. *Menopause* 2011;18:366–75
64. Rebbeck TR, Troxel AB, Norman S, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. *Int J Cancer* 2007;120:1523–8
65. Alves DL, Lima SM, da Silva CR, et al. Effects of Trifolium pratense and Cimicifuga racemosa on the endometrium of Wistar rats. *Maturitas* 2008;61:364–70
66. Xi S, Liske E, Wang S, et al. Effect of isopropanolic Cimicifuga racemosa extract on uterine fibroids in comparison with tibolone among patients of a recent randomized, double blind, parallel-controlled study in Chinese women with menopausal symptoms. *Evid Based Complement Alternat Med* 2014;2014:717686