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Finished Herbal Product as an Alternative Treatment for Menopausal Symptoms in Climacteric Women

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ABSTRACT

Background: There is a paucity of scientific evidence supporting the efficacy of herbal medicines in treating menopausal symptoms.

Objective: The aim of this study was to evaluate safety and efficacy of the finished herbal product TMN-1 in the treatment of menopausal symptoms in climacteric women.

Design and setting: A multicenter, prospective, observational follow-up study was conducted from July 2003 to December 2004 in four hospitals in Taiwan.

Participants: Initially, 126 women were included who were between 45 and 55 years of age, were experiencing hot flashes, and were without hormone replacement therapy. Women were excluded if they had any signs of active cancer. Of the participants, 82% completed the study. The reasons for withdrawal included adverse effects ($n = 7$), failed to return ($n = 7$), lack of efficacy ($n = 6$), and from protocol deviation ($n = 3$).

Intervention: Every participant received TMN-1 treatment 4 g, 3 times per day, for 12 weeks.

Main outcome measure: Primary measures were change in frequency of hot flashes and severity of menopausal symptoms measured by Kupperman Index (KI). Secondary outcomes included changes in quality of life and adverse events.

Results: Significant improvement in scores of hot flashes and KI were found at weeks 4 and 12 in the 50 peri- and 53 postmenopausal women who completed this study ($p < 0.001$). Logistic regression analyses showed that perimenopausal women with hot flashes had sevenfold (95% confidence interval [CI], 1.8–28.0) odds of improvement in favor of treatment, whereas that of the postmenopausal group was 1.5 (95% CI, 0.5 to 4.2). Further analyses showed that TMN-1 produced superior benefit in women with moderate and severe menopausal symptoms (KI $\geq$21), compared to those with mild symptoms. It also improved symptoms of insomnia, nervousness, melancholia, and palpitation in perimenopausal women. Five (5) adverse drug reactions were detected: three single events of nausea, abdominal pain, and abdominal fullness; and two events of diarrhea.

Conclusions: This study provides evidence that 12 weeks of TMN-1 therapy is a viable alternative treatment to consider in perimenopausal women with hot flashes, particularly in those with palpitations, emotional disturbance, and insomnia.

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INTRODUCTION

Hot flashes are a hallmark of the menopausal transition.[1] They occur in about 75% of perimenopausal and recently postmenopausal women, and typically persist for up to 4 years.[2–6] Despite this high prevalence in half of the population, the full extent of neuroendocrine events surrounding this life transition is not completely understood. The perimenopausal phase is characterized by fluctuations in a woman's hormonal milieu,[7,8] and eventually the postmenopausal phase is characterized by hypoestrogenism.[8,9] The climacteric phase is sufficiently challenging for many women that they seek medical assistance.[10] Treatment of the primary symptom—hot flashes—has therefore become a therapeutic challenge for many clinicians.[11,12]

Estrogen or hormone therapy has long been considered a preferred treatment and is effective both in treating hot flashes and in improving quality of life.[13,14] Recent findings of the Women's Health Initiative (WHI), however, indicate that the benefits of taking estrogen plus progestin are outweighed by serious risks, including coronary heart disease, stroke, pulmonary embolism, breast cancer, and dementia.[15,16] These clear limitations of hormonal therapy have led clinicians to search for alternative options. These have included nonhormonal therapies such as clonidine, venlafaxine, fluoxetine, and paroxetine.[17–20] Although few studies have been conducted, these alternatives have been found to be less effective than hormonal therapy in treating symptoms, in addition to producing troublesome side effects.[21,22] Not surprisingly, many women have turned to traditional medicine to manage their own symptoms.[15,23]

Traditional Chinese Medicine (TCM) has been an important part of health care in Taiwan for hundreds of years and remains popular today.[24,25] Finished herbal products such as *Jia-Wey Shiau-Yau San* (JWSYS), *Zhi Bo Di Huang Wan* (ZBDHW), and *Xiang Sha Liu Jun Zi Tang* (XSLJT) are commonly prescribed by TCM practitioners for menopausal symptoms. These are currently covered by the Taiwan National Health Insurance. China and Korea have a similar history of TCM use. Their current insurance programs also cover these three ancient herb formulations. In the United States, these same herbal mixtures are available but as over-the-counter dietary supplements.[26,27] Despite the long history of wide use of TCM, the fact that few formulations have been clinically characterized has resulted in uncertainty in the medical profession[26,28] about their use.

TCM practitioners in Taiwan have accumulated considerable experience in treating climacteric women with hot flashes, but these menopausal formulations also remain clinically uncharacterized. A new formulation called TMN-1 has been created using a combination of the three herb mixtures mentioned above. The purpose of this study was to document the effect of TMN-1 on menopausal symptoms, especially frequency of hot flashes.

MATERIALS AND METHODS

Herbal preparation and treatment schedule

TCM clinicians use the TMN-1 product primarily to reduce menopausal hot flashes. This product contains a fixed ratio of the three commercially available traditional Chinese medicines, JWSYS, ZBDHW, and XSLJT. All three preparations have traditionally been individually prescribed and are well documented in ancient Chinese medicinal texts (e.g., JWSYS in Prescriptions of the Bureau of Taiping People's Welfare Pharmacy; ZBDHW in Key to Therapeutics of Children's Diseases; and, XSLJY in Collected Exegesis of Recipes).[29] Documents on these exact preparations have existed for more than two centuries. All three preparations have also been approved in Taiwan by the Committee on Chinese Medicine and Pharmacy, Department of Health. They are also reimbursed by the National Health Insurance system of Taiwan.[25] TMN-1 is a mixture of the following 21 plant species: *Angelicae sinensis,* radix; *Atractylodis macrocephalae,* rhizome; *Albus paeoniae lactiflorae,* radix; *Glycyrrhizae uralensis,* radix; *Poriae cocos, sclerotium*; *Bupleurum chinense,* radix; *Paeonia suffruticosa,* cortex; *Gardeniae jasminoidis,* fructus; *Mentha haplocalyx,* herba; *Zingiberis officinalis,* rhizome; *Rehmanniae glutinosae,* radix; *Alismatis orientalis,* rhizome; *Dioscoreae oppositae,* radix; *Anemarrhenae asphodeloidis,* rhizome; *Phellodendri,* cortex; *Cornus officinalis,* fructus; *Panax ginseng,* radix; *Citri reticulatae, pericarpium* fructus; *Pinellia ternate,* rhizome; *Amomum villosum,* fructus; *and Aucklandiae lappa,* radix. Extracts were manufactured by a Taiwan pharmaceutical company (Sun Ten Pharmaceutical Company, Taipei, Taiwan) certified in herbal Good Manufacturing Practice (GMP). The manufacturing procedure and formula, including the amount of excipients, have been documented in detail. Plants were extracted with hot water. The extraction was filtered and lyophilized, then transformed in specific ratio into granules. Granules were packed in aluminum foil packages and administered orally at a dose of 4 g, 3 times per day.

The identification of specific active principles is not part of this current research. However, to enable it at a future stage, high-performance liquid chromatography (HPLC) fingerprints were performed to identify substances in the final mixtures. This also ensured consistent quality of the product. No animal products, endangered species, or restricted herbal ingredients were used in this study. The pharmaceutical company simply supplied whole-batch TMN-1 and was not involved in sponsorship, study design, or monitoring of participants.

Participants

This multicenter, prospective, observational follow-up study was administered through a coordinating center at the National Taiwan University with enrollment done through four academic clinical research sites located in northern and

middle Taiwan. The institutional review boards at each site and at the coordinating center approved the study protocol. After receiving written and verbal instructions about the type, importance, implications, and duration of the study, as well as information about alternative therapies, all willing participants were requested to sign the informed consent.

Women were recruited from the general population through newspaper advertising, flyers posted in clinics, and health fairs. Participants were enrolled between July 2003 and December 2004. Eligible participants between the ages of 45 and 55 years had hot flashes with such severity that they sought therapeutic intervention. Postmenopausal women were defined as being $\geq$1 year without menstruation, and other women fitting the participant qualifications were defined as perimenopausal. To be eligible, women could not have participated in any other medical trial for at least 3 months before enrollment. Any current medications had to have been discontinued before screening: 2 weeks for herbal or Chinese medicinal mixtures that did not contain any herbs in TMN-1; and 12 weeks for estrogens, progestational agents, tamoxifen, raloxifene, or aromatase inhibitors, isoflavone, and antidepressants.

Women were excluded from the study if they presented with any sign of cancer or were receiving either chemotherapy or radiation therapy. Other criteria for exclusion were as follows: having evidence of renal or liver dysfunction, as defined by a level of at least 1.5 times the upper limit of reference (serum creatinine: 1.3 mg/dL, blood urea nitrogen: 22 mg/dL, serum aspartate–aminotransferase (AST): 25 international units [IU]/L, alanine-aminotransferase (ALT): 29 IU/L); uncontrolled hypertension; diabetes; or undiagnosed vaginal bleeding.

Study design and procedures

All study nurses at the four clinical sites attended a standardized 4-month training organized by the coordination center. This ensured consistent high quality and fulfilled requirements for good clinical practice in the study protocol. Participant eligibility, according to the selection criteria previously described, was assessed during the first two clinic visits. At the first visit, nurses measured each woman's weight, height, pulse, and blood pressure. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in meters). Information on demographic characteristics, reproductive history, smoking, and alcohol consumption were collected by self-administered questionnaire and verified by a study nurse. After the initial screening visit, participants entered a run-in phase to obtain baseline data. These consisted of symptoms, quality of life, physical examination, complete blood count, and tests of biochemical function and hormones. These data were collected to ensure the minimum eligibility criteria for each woman and to screen out respondents with potential poor compliance. After the run-in phase, every participant received sufficient TMN-1 to begin treatment of 4 g, 3 times per day, after meals for the 12-week treatment phase (Fig. 1). Study visits were scheduled for the following 1, 2, 3, 4, 6, 8, 10, and 12 weeks. Both menopausal symptoms and adverse events were assessed at each visit. At weeks 4 and 12, the participants had full evaluations including physical examination and blood tests. The following hormones were determined for the evaluation of endocrine changes: serum estradiol (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Participants were contacted by telephone 1–2 days before each visit to encourage compliance. Left-over package count was conducted throughout the study to monitor participant compliance.

Treatment efficacy and tolerability

The primary outcome measure of the 12-week TMN-1 treatment was the Kupperman Index (KI). The KI consists of 11 items that were rated on a four-point scale (0 = none to 3 = severe) that predominantly quantifies the incidence or severity of hot flashes, sweat, sleep disturbance, and nervousness.[30] Weightings were introduced to add the 11 items together in a total-sum score.[30] Useful categories for describing clinical relevance of the index were: >20 (moderate and severe complaints), 15–20 (mild complaints),[31] and 1–14 (very mild complaints). Participants were considered to have an improvement response when their KI severity status decreased at least from severe and moderate to mild or mild-to-very-mild; all other participants were classified as having no response. However, to distinguish one symptom from another, both total sum score and hot flashes were separately analyzed. Hot flashes measured at a given time point were treated as indicating an improvement response when

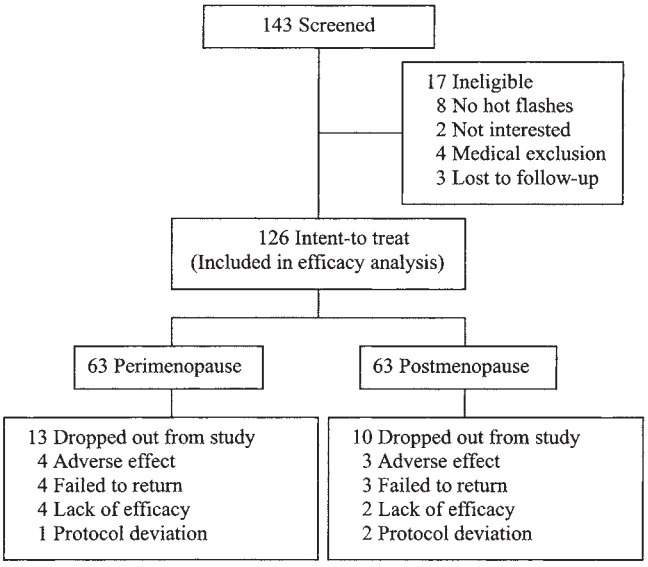

FIG. 1. Numbers of participants in TMN-1 herb study stages.

the score was at least 1 point reduction of the baseline severity scale; the subjects were classified as having no response (no improvement response with regard to hot flashes).

The Taiwan version of the World Health Organization (WHO) questionnaire on Quality of Life, Short Form (WHOQOL-BREF), was used as the secondary efficacy measure. It has previously been validated with other medical populations.[32,33] The WHOQOL-BREF Taiwan version contained 26 items, including one item (G1) for general quality of life, one item (G4) for health-related quality of life, and 24 items pertaining to four domains (physical, psychologic, social, and environmental), with higher scores indicating a superior quality of life.[34]

Safety assessment

Routine hematology, biochemistry, and physiology data were collected at weeks 0 (baseline), 4, and 12. The study nurse also actively monitored adverse events (AE) and recorded any unexpected signs, symptoms, and feelings (that had not occurred prior to the trial) during the treatment period. To prevent loss of information, we designed a questionnaire in the case report form to be filled out at each clinic visit, which contained the following symptoms: abdominal pain; abdominal fullness; diarrhea, vomiting; nausea; skin rash or urticaria; itching; purpura; jaundice; skin vesicle or local reddish swelling; edema; hypotension (systolic blood pressure $<$100 mm Hg; diastolic blood pressure $<$60 mm Hg); bradycardia ($<$50 heartbeats per minute); dyspnea, fever (body temperature $>$38°C); cough, runny nose; sore throat; muscle cramping, or any other active symptom(s). Causality of any adverse event was scored using a 5-point relatedness scale (0 = definitely unrelated; and 1 = unlikely, 2 = possibly, 3 = probably, and 4 = definitely related). The clinician and a team of epidemiologists reviewed each event according to the process of conjecture and refutation[35] to clarify possible causal relationships.

Statistical analysis

Peri- and postmenopausal groups of women were compared using Wilcoxon rank sum test on scores of hot flashes and KI. The later was divided into three levels according to the severity (very mild: KI $\leq$14; mild: KI = 15–20; moderate and severe: KI $\geq$21). Further analyses were done for scores of hot flashes and KI after stratification by menopausal status. A two-tailed p value $<$0.05 was considered statistically significant.

The treatment effects were described as the probability of improvement at each visit among climacteric women. Estimates of odds on improvement with two-sided 95% confidence intervals were obtained from logistic regression models. With Y_{it} as a dichotomous random variable representing improvement status, the study investigators defined $Y_{it} = 1$ if subject i had improvement response at the t^{th} time point compared to baseline measurement at time 0, and $Y_{it} = 0$ if the subject did not. Exploratory data analyses showed that the probability of improvement might depend on items such as the subject's complaint status at baseline and menopausal status. The logistic regression model is given by

$$\ln\left[\frac{\Pr(Y_{it}=1)}{\Pr(Y_{it}=0)}\right] = \alpha_1 Z_{1i} + \alpha_2 Z_{2i} + \alpha_3 Z_{3i} + \beta_1 W_i + \beta_2 W_i \times Z_{3i} + \gamma X_i$$

where Z_{1i}, Z_{2i}, and Z_{3i} are dichotomous random variables indicating whether the i^{th} subject's baseline complaint was respectively very mild, mild, moderate, or severe. The indicator variable W_i is 1 if subject i is perimenopausal and 0 if she is postmenopausal. Other covariates such as BMI, E2, and FSH are represented by the vector X_i. The covariate to be included in the model each time depended on the AIC of the fitted model. Parameter estimates were obtained using the free statistical package R (Auckland, New Zealand; www.r-project.org). If no covariate was selected for the final model, the estimated probability of improvement for participants with baseline severe complaint and in peri- and post-menopause conditions would respectively be $\frac{\exp(\hat{\alpha}_3 + \hat{\beta}_1 + \hat{\beta}_2)}{1 + \exp(\hat{\alpha}_3 + \hat{\beta}_1 + \hat{\beta}_2)}$ and $\frac{\exp(\hat{\alpha}_3)}{1 + \exp(\hat{\alpha}_3)}$.

RESULTS

Study population

Among the 143 women screened at all four research clinics, 17 were ineligible. The principal reasons for ineligibility included lack of hot flashes (n = 8), no interest in participation (n = 2), presence of medical conditions and medications (n = 4), and failure to show up for further study (n = 3). In all, 103 (82%) of the initial 126 subjects participating on an intent-to-treat basis (ITT) completed the 12-week study without any major protocol violation. These were included in the per-protocol data set for safety and efficacy analyses. Reasons for the 23 withdrawals were: adverse effects (n = 7), failure to return (n = 7), lack of efficacy (n = 6), and deviation from protocol (n = 3) (Fig. 1). Demographic and clinical characteristics of the study subjects were stratified by peri- and postmenopausal status (Table 1). The proportion of women with moderate or severe symptom scores in KI and hot flashes were slightly higher in the peri- than in the postmenopausal group.

Treatment effect of hot flashes and QOL

Among those participating on an intent-to-treat basis, 38 of 126 women who originally had very mild symptoms (KI $<$15) had the same status at the end of the study except four subjects who reported mild symptoms. Of the remaining 88 women with KI $>$15, 60% began to show significant improvement of KI scores after 1 week of treatment, as depicted in Figure 2. Among the 103 subjects who completed the study (29 women originally had KI $<$15), 55% (22/40)

Table 1. Demographic and Clinical Characteristics at Baseline for 126 Participants

	Perimenopause		*Postmenopause*		
Variables	N	*Mean (SD)*	N	*Mean (SD)*	p-*value*[a]
Demographics					
Age (year)	63	49.8 (2.3)	63	51.1 (2.8)	0.01
Height (cm)	63	157.0 (5.4)	63	154.8 (5.0)	0.02
Weight (kg)	63	55.6 (5.9)	63	56.2 (8.3)	0.64
BMI (kg^2/cm^2)	63	22.5 (2.3)	63	23.4 (3.4)	0.11
Serum hormonal level					
FSH (mIU/mL)	63	47.1 (31.8)	63	77.0 (30.9)	<0.001
LH (mIU/mL)	63	26.8 (18.0)	63	36.5 (15.6)	<0.01
E2 (pg/mL)	63	93.5 (69.7)	63	62.2 (61.2)	0.01
DHEA (pg/mL)	63	126.5 (67.4)	63	111.6 (52.3)	0.17
Hematology					
WBC (10e3/uL)	63	5.1 (1.2)	63	5.0 (1.3)	0.52
RBC (10e6/uL)	63	4.5 (0.5)	63	4.4 (0.4)	0.48
Hgb (g/dL)	63	12.9 (1.2)	63	13.3 (0.8)	0.04
Hct (%)	63	38.6 (3.0)	63	39.4 (2.3)	0.10
Endpoint (scores)	63	5.1 (1.2)	63	5.0 (1.3)	0.52
Kupperman Index at baseline					
Very mild (1–14)	20	11.3 (2.0)	18	12.6 (1.5)	0.22
Mild (5–20)	19	17.3 (1.6)	28	18.0 (1.6)	
Moderate and severe (≥21)	24	24.9 (3.0)	17	25.6 (4.3)	
Severity of hot flashes at baseline[b]					
Mild	34	1 (0)	42	1 (0)	0.20
Moderate and severe	29	2.2 (0.4)	21	2.1 (0.4)	
Domains of QOL					
Physical	63	14.1 (1.9)	63	14.4 (2.1)	0.39
Psychologic	63	12.7 (2.1)	63	12.9 (2.7)	0.58
Social	63	13.3 (2.2)	63	14.1 (2.4)	0.05
Environmental	63	14.1 (1.9)	63	14.3 (2.6)	0.77

SD, standard deviation; BMI, body–mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, serum estradiol; DHEA, dehydroepiandrosterone; WBC, white blood cell; RBC, red blood cell; Hgb, hemoglobin; Hct, hematocrit; QOL, quality of life.

[a]*p*-values are calculated for the comparison of difference between peri- and postmenopausal groups by *t*-test.

[b]Severity of hot flashes is an item of Kupperman Index rated on a 4-point scale: 0 is no hot flashes; mild (=1) is perception of daily hot flashes less than 3 times; moderate (=2) and severe (=3) perceive 3–9 and >9 times of hot flashes per day.

of postmenopausal women and 76% (26/34) of perimenopausal women with KI >15 had improved significantly by the end of the study.

In addition, the proportions of hot flash improvement were higher in the perimenopausal group than in the postmenopausal group (52% versus 33%) among the 103 women who completed the study. Logistic regression analyses showed that perimenopausal women with hot flashes had sevenfold (95% confidence interval [CI] 1.8–28.0) odds of improvement with treatment as assessed by KI score; if assessed based on hot flashes, the odds of improvement increased to 8.6 (95% CI 2.2–33.7). However, the improvements were insignificant in the postmenopausal group (odds 1.5, 95% CI 0.5 to 4.2 versus odds 1.2, 95% CI 0.5 to 3.0, respectively). This effect was same pronounced in peri- than in postmenopausal women based on the Wilcoxon rank sum test and using scores of hot flashes and KI (Table 2). Further analyses based on the severity levels (very mild: KI ≤14; mild: KI = 15–20; moderate and severe: KI ≥21) showed that TMN-1 produced a superior benefit in women with severe menopausal symptoms compared with women with mild menopausal symptoms. The treatment significantly improved symptoms of insomnia, nervousness, melancholia, and palpitation in perimenopausal women (Fig. 2).

Hormonal changes

There were no significant changes in DHEA and LH throughout the study (Table 3). Although estradiol levels seemed to rise in some peri-menopausal women, these women did not complain of any vaginal bleeding, breast tenderness, or bloating throughout the treatment. There was no report of vaginal spotting or breast tenderness or of venous thrombosis, pulmonary embolism, myocardinal infarction, stroke, fracture, or gallbladder disease throughout the trials for these 126 participants. There were significant differences in levels of FSH and E2 between the peri- and postmenopausal groups (Table 3).

Safety issues

There were five adverse drug reactions that were judged to be probably related to the treatment. These were single

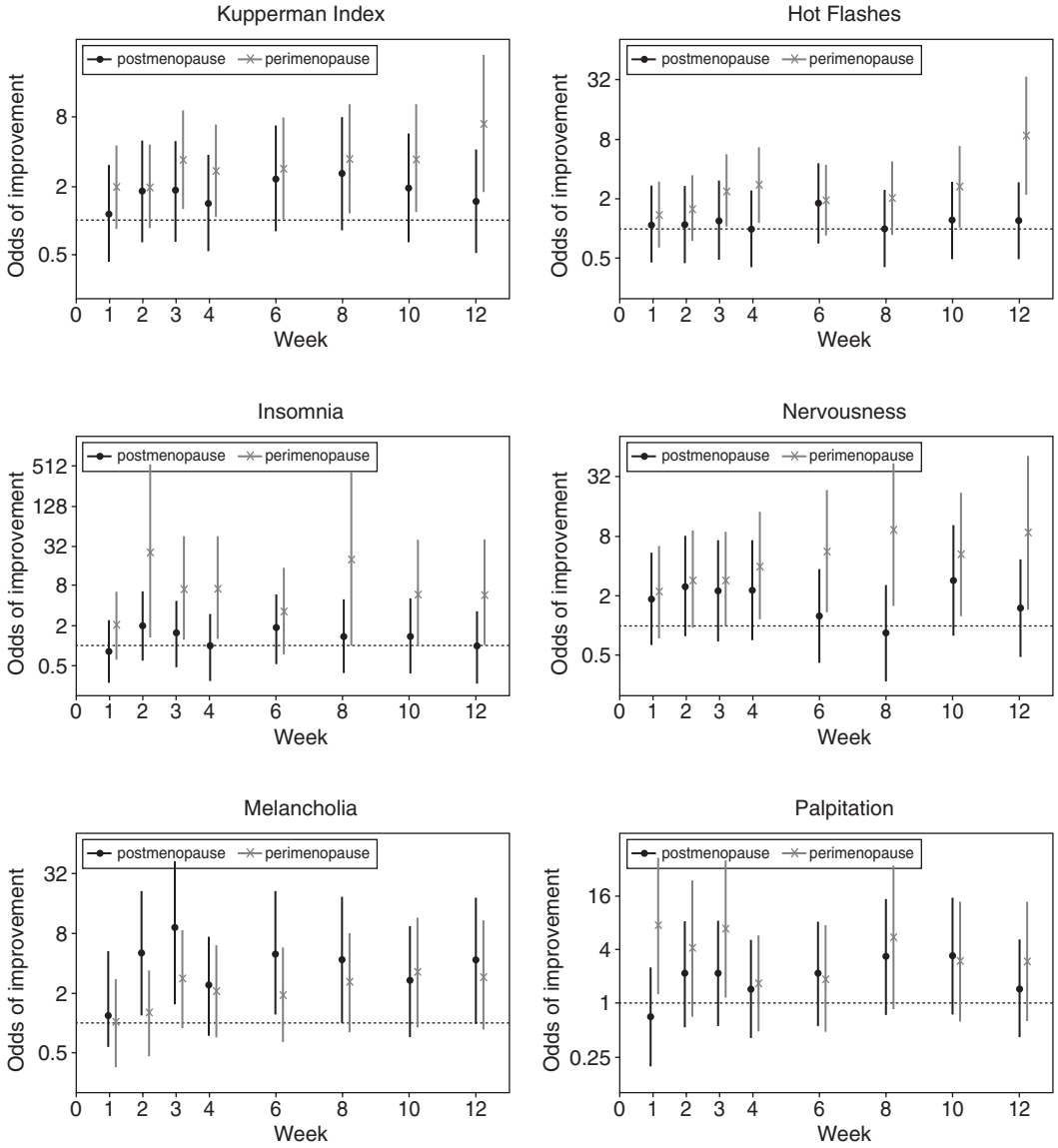

FIG. 2. Odds and 95% confidence interval of improvement for Kupperman Index and selected menopausal symptoms at each visit among post- and perimenopausal women based on intention to treat.

events of nausea, abdominal pain, abdominal fullness, and two events of diarrhea. One participant withdrew from the trial because of abdominal fullness. All others had reactions at mild and tolerable levels of severity, and causality was assessed as either "doubtful" or "possible" in relation to the treatment. Although there were slight reductions in serum cholesterol, hemoglobin, and blood pressure in perimenopausal women, the magnitudes were relatively small and indicating no major adverse effects (Table 3).

DISCUSSION

The study results demonstrate a significant improvement of hot flashes and other menopausal symptoms in climacteric women after 12 weeks of TMN-1 treatment. Although self-comparison was used to rule out potential confounding by BMI, smoking, exercise, and socioeconomic status,[36] the possibility of a placebo effect might still exist. Thus a more restrictive definition of improvement in total KI scores was applied and the data were stratified into those for peri- and postmenopausal groups. A similar severity pattern in hot flashes and total KI scores was found at the baseline examination for these two groups (Table 1). However, more pronounced improvements were found in perimenopausal women at both weeks 4 and 12 for KI, hot flashes, insomnia, nervousness, melancholia, and palpitation (Fig. 2).

In the postmenopausal group, total KI scores were improved on average by 4.6 points at the end of the study and 18% of the participants who completed the treatment perceived no hot flashes at least for the last 2 weeks. Although head-to-head comparisons were not available, these results

Table 2. Median of Difference of Self-Comparisons as Assessed at Weeks 4 and 12[a]

Severity of hot flashes[b] (N)	*Baseline*		*Week 4*		*Week 12*	
	Median	p-*value*	*Median*	p-*value*	*Median*	p-*value*
All participants						
Peri (63)	1	0.13	−1	0.00	−1	0.00
Post (63)	1		0		0	
Initial KI score[c] (N)						
Very mild (1–14)						
Peri (20)	1	0.17	−0.5	0.14	−1	0.33
Post (18)	1		0		0	
Mild (15–20)						
Peri (19)	1	0.43	−1	0.08	−1	0.07
Post (28)	1		0		0	
Moderate and severe (≥21)						
Peri (20)	2	0.79	−1	0.21	−1	0.03
Post (18)	2		0		0	

[a]Stratified by menopause status. Wilcoxon rank sum tests were performed to determine significant difference (p-values < 0.05) of measurements between the two groups (peri- and postmenopause).

[b]Severity of hot flashes is an item of Kupperman Index rated on a 4-point scale: 0 is no hot flashes; mild (=1) is perception of daily hot flashes <3 times; moderate (=2); and severe (=3) perceive 3–9 and >9 times of hot flashes per day. Reduction from baseline score represents an improvement.

[c]The Kupperman Index (KI) includes 11 items rated on a 4-point scale for which 0 is no perception of any symptom and 3 is the most severe. Reduction from baseline score represents an improvement.

compared favorably with the historical placebo groups in previous studies,[14,37] suggesting that the hot flashes and menopausal symptoms of postmenopausal women did not become worse during treatment. Although there was no placebo group or randomization in this study, the significant difference in improvement of hot flashes and KI scores indicated a positive effect of TMN-1 treatment in perimenopausal women. Further stratification of KI severity at baseline suggested that the potential TMN-1 effect was more pronounced in perimenopausal women with moderate or severe menopausal symptoms (Table 2).

The consistent trend of decline in E2 levels in postmenopausal women during the study implied that the medication did not contain any estrogen itself. Moreover, had TMN-1 followed an estrogenic pathway, a marked decrease of LH and FSH levels because of the negative feedback mechanism would have been found.[38,39] As the TMN-1 was tolerated well and there was no major adverse drug reaction after 3 months of TMN-1 treatment (Table 3), it can be concluded that TMN-1 has potential utility in the treatment for hot flashes and other menopausal symptoms in climacteric women.

The parameters in both physical and psychologic domains did not show any beneficial effect from TMN-1 throughout the regular assessment using WHOQOL-BREF. Further item analysis showed statistically significant improvements in "negative feelings" and "quality of sleep" in self-comparison for both the peri- and postmenopausal groups. There was no significant difference in quality of life between the two groups. The results are consistent with those from other studies that reported that improvements in hot flashes or menopausal symptoms were not associated the change of quality of life.[13,14,40–42] A major reason for this result is that mean scores of the WHOQOL-BREF at baseline were comparatively high. Consequently it may be unrealistic to expect a further marked increase in such scores. Another explanation was that because of its generic nature, the WHOQOL-BREF domain scores are not sensitive or responsive enough to detect changes.

A major limitation of this study is its observational nature or lack of a randomized placebo group. Therefore a claim of efficacy associated with TMN-1 might be not as valid as from a randomized clinical trial. Future studies of randomized placebo-controlled trials are still needed to document unequivocally the efficacy of this treatment. Moreover because the subjects in this study were all climacteric women with hot flashes, the results were not applicable to women without hot flashes. However TMN-1 seemed to have a more pronounced effect on menopausal symptoms in peri- than in postmenopausal women. As Asian women are known to exhibit less severe menopausal symptoms (particularly vasomotor symptoms) than women in other ethnic groups,[37,43,44] it would be interesting to compare treatment responses among different ethnic groups in future studies.

CONCLUSIONS

In conclusion TMN-1 appears to be a well-tolerated and valuable, short-term alternative therapeutic option for the treatment of hot flashes in climacteric women, especially those in the perimenopausal stage experiencing palpitations, emotional disturbance, and insomnia.

Table 3. Summary of Major Variables Measured at Baseline and Weeks 4 and 12, and Stratified by Status of Menopause[a]

	Baseline	*Week 4*	*Paired* t *test*		*Week 12*	*Paired* t *test*	
	Mean (SD)	*Mean (SD)*	*Mean difference*	*(95% CI)*	*Mean (SD)*	*Mean difference*	*(95% CI)*
Kupperman Index[b]							
Peri	18.3 (6.2)	12.9 (6.0)	−5.2	(−6.3, −4.1)[c]	11.7 (5.8)	−6.7	(−8.2, −5.2)[c]
Post	18.5 (5.6)	14.6 (6.0)	−4.0	(−5.3, −2.6)[c]	14.2 (7.4)	−4.6	(−6.3, −2.9)[c]
FSH (mIU/mL)							
Peri	47.1 (31.8)	41.3 (30.5)	−5.3	(−11.0, 0.5)	36.4 (30.0)	−8.7	(−15.3, −2.1)[d]
Post	77.0 (30.9)	75.4 (30.9)	−0.7	(−4.4, 3.0)	72.7 (28.9)	−2.6	(−6.0, 0.9)
LH (mIU/mL)							
Peri	26.8 (18.0)	23.7 (16.3)	−2.8	(−7.2, 1.6)	20.7 (16.0)	−5.3	(−9.5, −1.1)[d]
Post	36.5 (15.6)	35.9 (14.7)	−0.8	(−2.8, 1.2)	34.0 (14.2)	−2.9	(−5.6, −0.2)[d]
E2 (pg/mL)							
Peri	93.5 (69.7)	102.4 (86.3)	8.6	(−15.3, 32.5)	115.8 (87.7)	13.6	(−12.5, 39.7)
Post	62.3 (61.2)	51.1 (35.1)	−11.9	(−28.8, 4.9)	49.2 (25.6)	−16.0	(−31.7, −0.2)[d]
DHEA (pg/mL)							
Peri	126.5 (67.4)	121.0 (56.1)	−6.4	(−17.3, 4.5)	125.3 (59.2)	−5.1	(−19.4, 9.2)
Post	111.6 (52.3)	116.2 (54.5)	3.0	(−2.6, 8.5)	110.5 (52.5)	−3.3	(−9.5, 2.9)
CHOL (mg/dL)							
Peri	205.4 (32.7)	199.7 (34.6)	−6.9	(−11.2, 2.6)[d]	198.6 (37.9)	−7.7	(−12.8, −2.6)[d]
Post	207.0 (28.6)	203.9 (34.3)	−2.3	(−7.5, 2.8)	207.2 (37.3)	−1.7	(−8.0, 4.6)
TG (mg/dL)							
Peri	95.8 (75.7)	81.0 (33.9)	−13.8	(−30.6, 10.7)	85.0 (36.5)	−10.6	(−30.58, 9.5)
Post	90.7 (46.4)	96.0 (60.0)	6.1	(−1.9, 14.2)	102.5 (57.0)	9.9	(1.4, 18.3)[d]
Hgb (g/dL)							
Peri	12.9 (1.2)	12.8 (1.2)	−0.1	(−0.2, 0.0)	12.7 (1.2)	−0.3	(−0.4, −0.1)
Post	13.3 (0.8)	13.1 (0.9)	−0.2	(−0.3, −0.0)	12.9 (1.0)	−0.4	(−0.6, −0.3)[c]
Systolic BP (mm Hg)							
Peri	114.0 (11.0)	109.9 (8.3)	−4.2	(−6.8, −1.7)[d]	111.8 (8.9)	−2.8	(−5.3, −0.2)[d]
Post	113.0 (11.2)	111.9 (11.4)	−1.3	(−3.4, 1.0)	112.5 (8.8)	−0.9	(−3.5, 1.7)
Diastolic BP (mm Hg)							
Peri	72.6 (8.4)	70.4 (7.2)	−2.4	(−4.5, 0.3)[d]	70.3 (6.9)	−2.1	(−4.3, 0.0)[d]
Post	72.9 (7.5)	72.4 (7.9)	−0.6	(−2.6, 1.5)	70.4 (7.8)	−2.6	(−4.8, −0.4)[d]

CI, confidence interval; SD, standard deviation; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, serum estradiol; DHEA, dehydroepiandrosterone; CHOL, cholesterol; TG, triglyceride; Hgb, hemoglobin; BP, blood pressure.

[a]Self-comparisons of the measurements between weeks 4 and 12 and baseline are summarized as mean difference with a 95% confidence interval.

[b]The Kupperman Index includes 11 items rated on a 4-point scale for which 0 is no perception of any symptom and 3 is the most severe. Reduction from baseline score represents an improvement.

[c]$p < 0.001$ by paired t test compared to baseline.

[d]$p < 0.05$ by paired t test compared to baseline.

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