J Chin Med Assoc

ORIGINAL ARTICLE

Effect of tibolone vs hormone replacement therapy on climacteric symptoms and psychological distress

Sheng-Mou Hsiao[a,b,c,*], Shih-Cheng Liao[d]

[a]Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, New Taipei City, Taiwan, ROC; [b]Graduate School of Biotechnology and Bioengineering, Yuan Ze University, Taoyuan, Taiwan, ROC; [c]Department of Obstetrics and Gynecology, National Taiwan University College of Medicine, National Taiwan University Hospital, Taipei, Taiwan, ROC; [d]Department of Psychiatry, National Taiwan University College of Medicine, National Taiwan University Hospital, Taipei, Taiwan, ROC

Abstract

Background: The objective was to elucidate the effect of tibolone vs hormone replacement therapy (HRT) on climacteric symptoms and psychological distress.

Methods: All consecutive women with climacteric symptoms were allocated to receive tibolone (2.5 mg) or estradiol valerate (1 mg) plus medroxyprogesterone acetate (2.5 mg).

Results: The improvement in "feeling dizzy or faint" after tibolone treatment was more prominent than that after HRT (–0.7 ± 0.8 vs –0.0 ± 0.9, $p = 0.004$). In addition, other climacteric symptoms, including anxiety, depression, somatic symptoms, and vasomotor symptoms, and sexual function improved after tibolone and HRT, but there were no between-group differences. Psychological distress assessment demonstrated that somatic complaints, obsessive-compulsive symptoms, depressive symptoms, hostility, additional symptoms, and the General Symptom Index improved after tibolone treatment and HRT, but there were no between-group differences. Personality traits assessment revealed that neuroticism improved after tibolone treatment.

Conclusion: Tibolone seems more beneficial than HRT in treating symptoms of dizziness and faintness. Both tibolone and HRT could improve psychological distress.

Keywords: Menopause; Personality; Psychological distress

1. INTRODUCTION

Psychological distress, such as anxiety and depression, is common in women with climacteric symptoms.[1–3] Hormone replacement therapy (HRT) or tibolone is frequently prescribed for women with climacteric symptoms.[4–6] HRT was reported to have a beneficial effect on psychological distress in addition to climacteric symptoms.[7–9] In addition, HRT could facilitate the efficacy of antidepressants.[10] Nonetheless, Stephens and Ross[11] reported that there was no relationship between HRT use and psychological symptoms.

Tibolone is converted to three active metabolites after oral ingestion, and two metabolites have estrogenic effects on the bones, vagina, and climacteric symptoms.[12] Thus, tibolone has a therapeutic effect on climacteric symptoms. In addition, tibolone seems to have a beneficial effect on mood due to an increased plasma beta-endorphin levels.[13,14] Egarter et al[9] found that tibolone had a greater effect on depression and mood disorders than HRT.

Understanding the between-group differences in the effects on climacteric symptoms and psychological distress should be helpful in choosing a suitable medication for climacteric symptoms. Thus, the primary objective of this study was to compare the effect of tibolone vs HRT on climacteric symptoms and psychological distress. The secondary objectives aimed to compare the impact of tibolone vs HRT on personality traits and familial support.

2. METHODS

Between December 2012 and March 2021, all consecutive women with climacteric symptoms, who visited the outpatient gynecologic clinic of a tertiary referral center for HRT, were invited to participate in this study. Women who were treated with HRT or tibolone at the time of enrollment or within the month before enrollment were excluded. The study design was prospective and nonrandomized. Informed consent was obtained from each patient. All experimental protocols were approved by the Research Ethics Review Committee of the hospital (Approval number: 101080-F). This study has been registered with ClinicalTrial.gov (Identifier: NCT01822288). All methods in this study were carried out in accordance with relevant guidelines and regulations.

The initial screening (visit 1) included medical history, physical and gynecological examinations, gynecologic sonography, and mammography if not performed during the previous 24

* *Address correspondence. Dr. Sheng-Mou Hsiao, Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, 21, Section 2, Nanya South Road, Banqiao District, New Taipei City, Taiwan, ROC. E-mail address: smhsiao2@gmail.com (S.-M. Hsiao).*

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2024) 87: 189-195.

Received April 30, 2023; accepted August 26, 2023.

doi: 10.1097/JCMA.0000000000001012

months. Women were excluded if they had a history of hysterectomy, breast cancer, estrogen-dependent malignant tumor, untreated endometrial hyperplasia, a history of venous/arterial thromboembolism, or acute or chronic liver disease. Patients were allocated into two groups according to their preference. Tibolone (2.5 mg per day) was prescribed to patients who were willing to pay the extra fee, which is not covered by the National Health Insurance in Taiwan; otherwise, HRT with 1 mg estradiol valerate and 2.5 mg medroxyprogesterone acetate per day was prescribed. Patients were followed up at week 4 (visit 2) and week 12 (visit 3).

At visit 1, visit 2, and visit 3, all enrolled women were asked to complete a modified Greene Climacteric Scale,[15] Brief Symptom Rating Scale (BSRS),[16,17] Maudsley Personality Inventory,[18] and Adaptability, Partnership, Growth, Affection, and Resolve (APGAR) questionnaire.[19]

A modified Greene Climacteric Scale questionnaire was used to assess the efficacy of treatment on climacteric symptoms.[15] In the modified Greene Climacteric Scale questionnaire, each dimension is assessed by one or several questions on a four-point Likert scale (0-3 points). Each question is rated by circling 0, 1, 2, or 3, which are defined as not at all, a little, quite a bit, and extremely, respectively. A total of five dimensions are assessed, including anxiety, depression, somatic symptoms, vasomotor symptoms, and sexual function. The anxiety score is the sum of the scores for "feeling nervous" and "difficulty in sleeping." The depression score is the sum of the scores for "feeling tired," "feeling depressed," and "irritability." The somatic symptoms score is the sum of the scores for "feeling dizzy or faint," "headache," "joint pain," and "muscle pain." The vasomotor symptoms score is the score for "hot flush." The sexual function score is the score for "loss of interest in sex."

The BSRS includes the following dimensions of psychopathology: somatic symptoms, obsessive-compulsive symptoms, interpersonal sensitivity, depressive symptoms, anxiety symptoms, hostility, phobic-anxiety, and paranoid tendency. Additional symptoms include vegetative and other clinical indicators.[16,17] The BSRS is composed of 30 items rated based on the degree of distress caused by that item over the past week.[17] Each dimension is assessed by several questions scored on a five-point Likert scale (0-4 points). The severity of a psychopathological factor is expressed with an index calculated as the sum of the scores divided by the number of questions in that specific dimension. The General Symptoms Index, a mean score of all BSRS items, represents the global severity of psychological distress, and a higher General Symptoms Index indicates more severe psychological distress. The BSRS has been reported to be a reliable and valid psychiatric self-rating scale for use in psychosomatic research[20] and has been used for assessing women with overactive bladder syndrome.[21]

The shortened version of the Maudsley Personality Inventory (30 items) is used to assess personality traits and to measure the neuroticism stability and extraversion-introversion dimensions.[18] The psychometric properties of the Chinese version of the Maudsley Personality Inventory have been reported.[22] A higher score on this inventory indicates a higher level of neuroticism or extraversion.

The APGAR score (five items) is used to measure perceived family support in the domains of adaptation, partnership, growth, affection, and resolve.[18] Each item is designed to describe the frequency of feeling satisfied with one domain of family functioning, and a higher score indicates better family support.

One of the main hypotheses of this study was that the effect on psychological distress in the tibolone group would differ from that in the HRT group. Based on a previous similar study, which compared the psychological effects between tibolone and HRT,[8] it was suggested that at least 18 subjects in both groups were required to test the above hypothesis of the difference in the effect on psychological distress.

Stata v.11 software (StataCorp, College Station, TX) was used for statistical analyses. Women who had at least one follow-up visit were included in the statistical analysis. The Shapiro-Wilk test was used to assess normality. If data were normally distributed, parametric analytical methods (such as two-sample *t* test) were used; otherwise, nonparametric analyses were used instead. The Skillings-Mack test, chi-square test, Fisher exact test, Wilcoxon rank-sum test, and two-sample *t* test were used as the statistical methods when appropriate. p value of <0.05 was considered statistically significant.

3. RESULTS

There were 196 women who received tibolone or HRT for the treatment of climacteric symptoms. However, only 123 women visited our outpatient clinic after 4 weeks of treatment, and 58 women visited our clinic after 12 weeks of treatment (Fig. 1). The loss to follow-up rates did not differ at week 4 (37.0% [34/92] vs 37.5% [39/104], $p = 0.95$) and week 12 (44.8% [26/58] vs 60.5% [39/65], $p = 0.09$) between the HRT and tibolone groups.

Except for parity and extraversion-introversion, there was no between-group difference in baseline characteristics (Tables 1 and 2).

All dimensions, including the anxiety, depression, somatic symptoms, vasomotor symptoms, and sexual function dimensions, improved after HRT and tibolone treatment (Table 1).

Somatic complaints, obsessive-compulsive symptoms, interpersonal sensitivity, depressive symptoms, hostility, additional symptoms, and the General Symptom Index improved after HRT (Table 2). Similarly, somatic complaints, obsessive-compulsive symptoms, depressive symptoms, anxiety symptoms, hostility, additional symptoms, and the General Symptom Index improved after tibolone treatment (Table 2).

In addition, neuroticism improved after tibolone treatment (Table 2). However, the family APGAR score did not change after HRT or tibolone treatment (Table 2).

The change in "feeling dizzy or faint" after 12 weeks of tibolone treatment was more prominent than that after HRT (-0.7 ± 0.8 vs -0.0 ± 0.9, $p = 0.004$, Fig. 2, Table 3). The between-group difference in "feeling dizzy or faint" remained statistically significant even after adjusting for parity (coefficient of tibolone = –0.66, 95% CI, –1.10 to –0.21, $p = 0.004$, linear regression analysis). Nonetheless, the changes in other climacteric symptoms, psychological distress, personality traits, and familiar APGAR scores did not differ between the HRT and tibolone groups (Tables 3 and 4).

4. DISCUSSION

In this study, compared with HRT, tibolone was found to have a greater effect on reducing symptoms of dizziness and faintness (Fig. 2, Table 3). The feelings of dizziness and vertigo are similar. Similarly, Egarter et al[9] found that vertigo improved after tibolone treatment, but not HRT. A direct estrogenic effect of tibolone on the receptors of arterial smooth muscle cells in the vertebrobasilar area, leading to relaxation and consequently to an increase in vestibular blood circulation, may explain the finding of alleviated dizziness/faintness symptoms after tibolone treatment.[9,23]

Except for feelings of dizziness or faintness, the changes in the other climacteric symptoms from baseline did not differ between the two groups (Table 3). Similarly, Hammar et al[24] reported

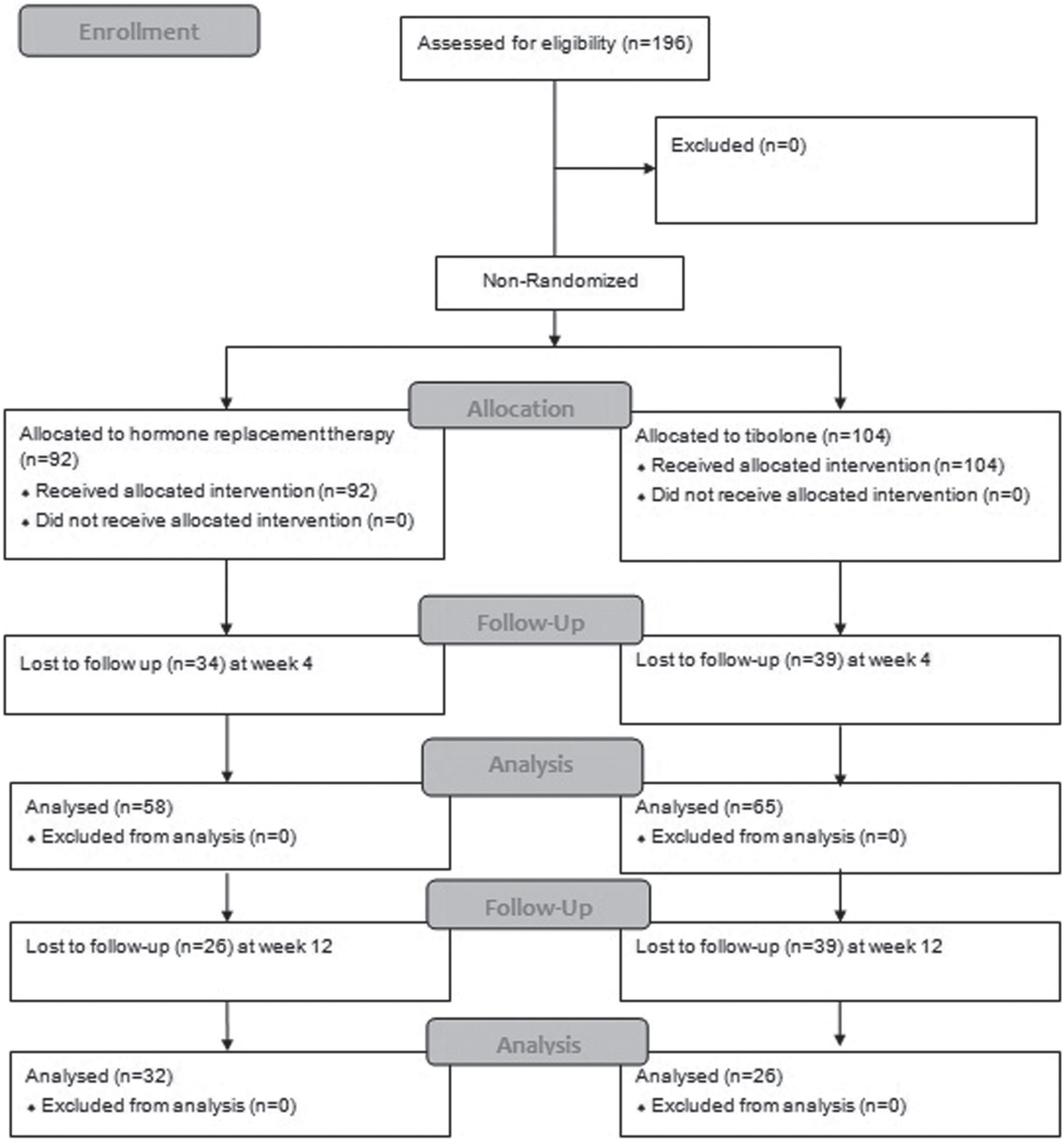

Fig. 1 Flowchart of participants with climacteric symptoms.

that tibolone reduces climacteric symptoms to a similar extent as conventional low-dose continuous combined HRT. However, tibolone was reported to be less effective than HRT in reducing vasomotor symptoms,[25,26] but tibolone has a greater effect than HRT on improving sexual function.[26]

In this study, psychological distress improved after HRT and tibolone treatment (Table 2). Khoo et al[7] also reported that HRT had beneficial effects on psychological distress, including the overall rating score, feelings of inadequacy, and depression. Boyle and Murrihy[27] found that HRT users had lower scores on the dimensions of anxiety, insomnia, and somatic symptoms than nonusers. However, Stephens and Ross[11] reported that there was no effect of HRT on psychological distress.

Few studies have mentioned the detailed impact of tibolone on psychological distress.[8,9] Our study revealed an improvement in somatic complaints, obsessive-compulsive symptoms, depression, anxiety, hostility, additional symptoms, and the General Symptom Index after tibolone treatment (Table 2). In addition, the effects on psychological distress were similar between tibolone and HRT (Tables 2 and 4). The above findings support the use of tibolone and HRT in women with climacteric symptoms and psychological distress. Similarly, Ross et al[8] reported that both tibolone and HRT had similar effects on vasomotor symptoms and psychological

Table 1

Baseline data and follow-up data of climacteric symptoms between the HRT and tibolone groups

Variables	HRT				Tibolone				
	Baseline (a) (n = 58)	4 wk[a] (n = 58)	12 wk[a] (n = 32)	p^b	Baseline (b) (n = 65)	4 wk[a] (n = 65)	12 wk[a] (n = 26)	p^b	a vs b, p^c
Age, y	53.4 ± 6.6 (range: 39-69)	-	-	-	52.5 ± 4.6 (range: 42-68)	-	-	-	0.61
BMI, kg/m^2	23.7 ± 3.3	-	-	-	23.0 ± 2.6	-	-	-	0.22
Parity	2.4 ± 1.2	-	-	-	2.0 ± 1.0	-	-	-	0.04
FSH, mIU/mL	50.9 ± 33.3	-	-	-	46.2 ± 34.9	-	-	-	0.48
Estradiol, pg/mL	40.7 ± 57.5	-	-	-	42.7 ± 75.9	-	-	-	0.88
Feeling nervous	1.5 ± 1.1	1.0 ± 0.8**	0.6 ± 0.7**	<0.001	1.4 ± 1.1	1.0 ± 1.0**	0.9 ± 0.9*	0.001	0.52
Difficulty in sleeping	1.9 ± 1.1	1.3 ± 1.1**	1.2 ± 1.1*	<0.001	2.0 ± 1.1	1.3 ± 1.1**	1.1 ± 1.1	<0.001	0.59
Feeling tired	1.6 ± 1.1	1.2 ± 1.0**	1.1 ± 1.0*	0.01	1.4 ± 1.0	0.9 ± 0.9**	0.9 ± 0.9*	0.005	0.19
Feeling depressed	1.5 ± 1.0	0.9 ± 0.9**	0.8 ± 0.9**	<0.001	1.4 ± 1.1	0.8 ± 0.8**	0.5 ± 0.8*	<0.001	0.27
Irritability	1.3 ± 1.0	0.6 ± 0.8**	0.5 ± 0.9**	<0.001	1.0 ± 1.0	0.4 ± 0.7**	0.4 ± 0.7**	<0.001	0.10
Feeling dizzy or faint	0.9 ± 0.9	0.7 ± 0.8	0.9 ± 0.9	0.13	1.0 ± 1.0	0.6 ± 0.8**	0.4 ± 0.7**	<0.001	0.91
Headache	0.8 ± 0.9	0.6 ± 0.8	0.8 ± 0.8	0.30	0.9 ± 1.0	0.6 ± 0.9	0.7 ± 0.9	0.06	0.70
Joint pain	1.4 ± 1.0	1.1 ± 1.0**	0.9 ± 0.9*	0.002	1.4 ± 1.0	0.9 ± 0.9**	0.9 ± 1.0	<0.001	0.75
Muscle pain	1.4 ± 1.1	1.3 ± 1.0	1.2 ± 1.0	0.16	1.5 ± 1.0	1.1 ± 1.0**	1.0 ± 0.9	0.002	0.78
Hot flushes	1.9 ± 1.1	1.1 ± 0.9**	0.5 ± 0.7**	<0.001	1.7 ± 1.2	0.8 ± 0.9**	0.6 ± 0.7**	<0.001	0.43
Loss of interest in sex	1.8 ± 1.2	1.3 ± 1.2**	1.3 ± 1.20	0.02	1.6 ± 1.1	1.2 ± 1.0*	1.0 ± 1.0**	0.002	0.26
Five dimensions									
Anxiety	3.4 ± 1.6	2.3 ± 1.5**	1.8 ± 1.4**	<0.001	3.4 ± 1.8	2.2 ± 1.8**	2.0 ± 1.5**	<0.001	1.00
Depression	4.4 ± 2.2	2.7 ± 2.2**	2.4 ± 2.4**	<0.001	3.7 ± 2.4	2.1 ± 1.8**	1.8 ± 1.9**	<0.001	0.09
Somatic	4.5 ± 2.4	3.7 ± 2.4**	3.9 ± 2.5**	0.008	4.7 ± 2.8	3.1 ± 2.7**	3.0 ± 2.8**	<0.001	0.66
Vasomotor	1.9 ± 1.1	1.1 ± 0.9**	0.5 ± 0.7**	<0.001	1.7 ± 1.2	0.8 ± 0.9**	0.6 ± 0.7**	<0.001	0.43
Sexual function	1.8 ± 1.2	1.3 ± 1.2**	1.3 ± 1.20	0.02	1.6 ± 1.1	1.2 ± 1.0*	1.0 ± 1.0**	0.002	0.26

Data were presented with mean ± SD or n (percentage).

BMI = body mass index; FSH = follicle stimulation hormone; HRT = hormone replacement therapy.

[a]Post-hoc analysis was performed by the Wilcoxon signed-rank test to compare the follow-up and baseline data.

[b]The Skillings-Mack test.

[c]Wilcoxon rank-sum test.

*$p < 0.05$;

**$p < 0.01$.

Table 2

Baseline data and follow-up data of psychological distress, personality traits, and family APGAR scores between the HRT and tibolone groups

Variables	HRT				Tibolone				
	Baseline (a) (n = 58)	4 wk[a] (n = 58)	12 wk[a] (n = 32)	p^b	Baseline (b) (n = 65)	4 wk[a] (n = 65)	12 wk[a] (n = 26)	p^b	a vs b, p^c
Somatic complaints	1.3 ± 0.9	1.0 ± 0.8**	0.8 ± 0.7**	<0.001	1.3 ± 1.0	0.8 ± 0.7**	0.7 ± 0.6*	<0.001	0.96
OBS	0.9 ± 0.9	0.6 ± 0.8**	0.5 ± 0.6*	0.002	1.0 ± 1.0	0.6 ± 0.8**	0.4 ± 0.5	0.003	1.00
Interpersonal sensitivity	0.5 ± 0.8	0.3 ± 0.5*	0.1 ± 0.2**	0.003	0.5 ± 1.0	0.3 ± 0.5	0.2 ± 0.5	0.27	0.84
Depressive symptoms	0.8 ± 0.9	0.5 ± 0.7**	0.5 ± 0.8**	<0.001	0.9 ± 1.0	0.4 ± 0.6**	0.4 ± 0.5	<0.001	0.59
Anxiety symptoms	0.8 ± 1.0	0.4 ± 0.6	0.3 ± 0.4	0.13	0.9 ± 1.1	0.5 ± 0.7**	0.4 ± 0.5	0.001	0.25
Hostility	0.5 ± 0.6	0.3 ± 0.5*	0.2 ± 0.4**	0.006	0.5 ± 0.7	0.2 ± 0.3**	0.2 ± 0.3	<0.001	0.50
Phobic-anxiety	0.5 ± 0.8	0.3 ± 0.5	0.1 ± 0.2	0.09	0.6 ± 1.0	0.4 ± 0.8	0.2 ± 0.3	0.12	0.51
Paranoid tendency	0.4 ± 0.8	0.3 ± 0.6	0.2 ± 0.5	0.13	0.5 ± 0.9	0.3 ± 0.6	0.3 ± 0.6	0.13	0.69
Additional symptoms	1.5 ± 1.0	1.0 ± 0.9**	0.7 ± 0.7**	<0.001	1.6 ± 1.1	0.9 ± 0.9**	0.6 ± 0.5**	<0.001	0.34
GSI	0.8 ± 0.7	0.5 ± 0.5**	0.4 ± 0.4**	<0.001	0.9 ± 0.8	0.5 ± 0.5**	0.4 ± 0.4*	<0.001	0.57
Lie	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.3	0.56	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	0.54	0.76
Neuroticism	0.6 ± 0.6	0.6 ± 0.6	0.5 ± 0.6	0.12	0.8 ± 0.6	0.6 ± 0.6	0.4 ± 0.5**	0.01	0.14
Extraversion-introversion	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	0.95	1.1 ± 0.3	1.0 ± 0.3	1.1 ± 0.2	0.97	0.04
Family APGAR	12.7 ± 4.3	12.9 ± 4.5	13.8 ± 4.7	0.33	13.4 ± 3.9	14.5 ± 4.2	14.0 ± 4.1	0.12	0.35

Data were presented with mean ± SD or n (percentage).

APGAR = Adaptability, Partnership, Growth, Affection, and Resolve; GSI = General Symptom Index; HRT = hormone replacement therapy; OBS = obsessive-compulsive symptoms.

[a]Post-hoc analysis was performed by the Wilcoxon signed-rank test to compare the follow-up and baseline data.

[b]The Skillings-Mack test.

[c]Wilcoxon rank-sum test.

*$p < 0.05$;

**$p < 0.01$.

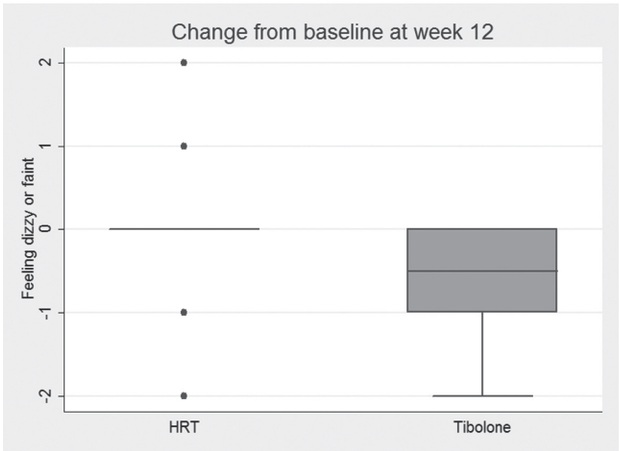

Fig. 2 The changes from baseline of "feeling dizzy or faint" between HRT and tibolone. HRT = hormone replacement therapy.

symptoms and suggested that improvements in vasomotor symptoms occurred first and were followed by changes in psychological symptoms over time. Egarter et al[9] also found that both tibolone and HRT improved depression. Menopause is associated with a decrease in endorphin levels, and this is believed to be associated with the pathogenesis of psychological disorders.[13] An increase in plasma endorphin levels was observed after tibolone treatment, and which might explain the effect of tibolone on psychological distress.[9,13]

In our study, we also noted that the severity of neuroticism improved after tibolone treatment (Table 2). To our knowledge, no literature has mentioned about the effect of tibolone on personality traits. Our findings support the use of tibolone in women with climacteric symptoms and neuroticism.

Thakur et al[28] reported that the hot flush scores of the perimenopausal and postmenopausal women in the general population were 1.16 ± 0.90 and 0.34 ± 0.47, respectively. In our study, the average hot flush score was 1.76 ± 1.16, which was similar to another Taiwanese study and one Italian study. The average hot flush score was 1.82 in another Taiwanese study,[29] and that in an Italian study was 1.97[30]; their drop-out rates were 9.2% (24/260) and 13.2% (20/151), respectively.[29,30]

However, one Austrian study reported a higher hot flush score (ie, 2.59 ± 0.66 in the soy group and 2.58 ± 0.65 in the placebo group),[31] and the drop-out rate was only 6.3% (12/192). Thus, our high drop-out rate might be associated with less severe symptoms in our enrolled patients.

Contrary to the high prevalence of hot flushes, "feeling dizzy or faint" is a less common climacteric symptom. In our study, the score for "feeling dizzy or faint" was less than that for most climacteric symptoms at baseline (Table 1). Benshushan et al[32] also reported that 43% (10/23) of climacteric symptoms were more common than the symptom of "feeling dizzy or faint" (prevalence of 28.8%). Thakur et al[28] reported that the average "feeling dizzy or faint" scores were only 0.35 ± 0.47 and 0.34 ± 0.54 in perimenopausal and postmenopausal women in the general population, respectively.

In this study, the average "feeling dizzy or faint" score was 0.98 ± 0.96, which was similar to another Taiwanese study and one Austrian study. The average "feeling dizzy or faint" score was 0.96 in the Taiwanese study,[29] and 1.07 ± 0.86 and 0.87 ± 0.94 in the soy and placebo groups, respectively, in the Austrian study.[31]

Our study had limitations, including long enrollment time intervals, a high drop-out rate, and a nonrandomized design. However, the high drop-out rate seems to represent the real-world scenario in which women with climacteric symptoms are reluctant to receive tibolone or HRT, probably related to the findings of the significant association of breast cancer with HRT in the Women's Health Initiative study.[33,34] In addition, less

Table 3

Comparison of the changes from baseline of climacteric symptoms after 4 and 12 wk treatment between the HRT and tibolone groups

Variables	4 wk			12 wk		
	HRT (n = 58)	Tibolone (n = 65)	p^a	HRT (n = 32)	Tibolone (n = 26)	p^a
Feeling nervous	−0.5 ± 1.1	−0.4 ± 1.0	0.66	−0.8 ± 1.2	−0.4 ± 1.1	0.16
Difficulty in sleeping	−0.6 ± 1.0	−0.8 ± 1.2	0.37	−0.6 ± 1.3	−0.7 ± 1.5	0.70
Feeling tired	−0.5 ± 1.0	−0.4 ± 1.1	0.78	−0.5 ± 1.1	−0.4 ± 0.9	0.67
Feeling depressed	−0.7 ± 1.1	−0.6 ± 1.0	0.56	−0.7 ± 1.1	−0.5 ± 0.9	0.60
Irritability	−0.6 ± 1.1	−0.6 ± 1.0	0.71	−0.9 ± 1.2	−0.7 ± 1.1	0.35
Feeling dizzy or faint[b]	−0.2 ± 0.8	−0.4 ± 0.9	0.20	−0.0 ± 0.9	−0.7 ± 0.8*	0.004
Headache	−0.2 ± 0.9	−0.3 ± 0.9	0.49	−0.1 ± 1.0	−0.2 ± 1.0	0.53
Joint pain	−0.3 ± 1.0	−0.5 ± 1.1	0.26	−0.4 ± 1.1	−0.3 ± 1.0	0.81
Muscle pain	−0.2 ± 1.2	−0.4 ± 1.1	0.25	−0.3 ± 1.1	−0.3 ± 1.1	0.95
Hot flushes	−0.9 ± 1.2	−0.9 ± 1.2	0.82	−1.3 ± 1.2	−1.0 ± 1.1	0.29
Loss of interest in sex	−0.4 ± 1.2	−0.4 ± 1.2	0.95	−0.5 ± 1.3	−0.9 ± 1.3	0.22
Five dimensions						
Anxiety	−1.1 ± 1.4	−1.2 ± 1.9	0.70	−1.4 ± 1.8	−1.1 ± 2.0	0.57
Depression	−1.9 ± 2.6	−1.6 ± 2.4	0.61	−2.1 ± 2.8	−1.6 ± 2.1	0.44
Somatic	−0.9 ± 2.4	−1.7 ± 2.7	0.09	−0.7 ± 2.8	−1.5 ± 2.9	0.31
Vasomotor	−0.9 ± 1.2	−0.9 ± 1.2	0.82	−1.3 ± 1.2	−1.0 ± 1.1	0.29
Sexual function	−0.4 ± 1.2	−0.4 ± 1.2	0.95	−0.5 ± 1.3	−0.9 ± 1.3	0.22

Data were presented with mean ± SD.

HRT = hormone replacement therapy.

[a]Two-sample *t* test.

[b]Within-group comparison was performed by the Wilcoxon signed-rank test to compare the follow-up and baseline data only in the between-group comparison with significant difference.

*$p < 0.01$.

Table 4

Comparison of the changes from baseline of psychological distress, personality traits, and family APGAR scores after 4 and 12 wk treatment between the HRT and tibolone groups

Variables	4 wk			12 wk		
	HRT (n = 58)	Tibolone (n = 65)	p^a	HRT (n = 32)	Tibolone (n = 26)	p^a
Somatic complaints	−0.5 ± 0.9	−0.6 ± 0.9	0.35	−0.6 ± 0.9	−0.3 ± 0.6	0.15
OBS	−0.3 ± 0.9	−0.4 ± 0.9	0.44	−0.4 ± 1.0	−0.2 ± 0.8	0.40
Interpersonal sensitivity	−0.2 ± 0.7	−0.2 ± 0.9	0.87	−0.3 ± 0.7	−0.1 ± 0.7	0.33
Depressive symptoms	−0.3 ± 0.8	−0.5 ± 0.8	0.11	−0.3 ± 0.9	−0.2 ± 0.7	0.61
Anxiety symptoms	−0.4 ± 0.9	−0.4 ± 0.9	0.63	−0.4 ± 0.9	−0.2 ± 0.8	0.54
Hostility	−0.2 ± 0.7	−0.3 ± 06	0.55	−0.4 ± 0.8	−0.2 ± 0.6	0.54
Phobic-anxiety	−0.2 ± 0.9	−0.2 ± 0.8	0.91	−0.3 ± 0.8	−0.3 ± 0.7	0.92
Paranoid tendency	−0.1 ± 0.8	−0.2 ± 0.7	0.35	−0.3 ± 0.7	−0.1 ± 0.6	0.43
Additional symptoms	−1.1 ± 1.2	−1.4 ± 1.2	0.46	−0.7 ± 1.1	−0.7 ± 1.0	0.77
GSI	−0.3 ± 0.7	−0.4 ± 0.6	0.31	−0.4 ± 0.7	−0.3 ± 0.6	0.44
Lie	−0.0 ± 0.4	−0.0 ± 0.4	0.74	−0.0 ± 0.4	−0.1 ± 0.4	0.37
Neuroticism	0.0 ± 0.6	−0.1 ± 0.5	0.14	−0.1 ± 0.6	−0.3 ± 0.5	0.20
Extraversion-introversion	−0.0 ± 0.3	−0.0 ± 0.3	0.88	−0.0 ± 0.3	−0.0 ± 0.3	0.88
Family APGAR	0.3 ± 4.1	1.1 ± 3.3	0.24	0.8 ± 3.9	1.2 ± 3.6	0.75

Data were presented with mean ± SD.

APGAR = Adaptability, Partnership, Growth, Affection, and Resolve; GSI = General Symptom Index; HRT = hormone replacement therapy; OBS = obsessive-compulsive symptoms.

[a]Two-sample *t* test.

severe symptoms in our study might be associated with the poor compliance and high drop-out rate.

In conclusion, tibolone seems to have a greater effect on dizziness and faintness symptoms than HRT. Both tibolone and HRT could improve psychological distress.

ACKNOWLEDGMENTS

This study was supported by Far Eastern Memorial Hospital (FEMH-2013-D-015).

REFERENCES

1. Ali AM, Ahmed AH, Smail L. Psychological climacteric symptoms and attitudes toward menopause among Emirati women. *Int J Environ Res Public Health* 2020;17:5028.
2. Muslić L, Jokić-Begić N. The experience of perimenopausal distress: examining the role of anxiety and anxiety sensitivity. *J Psychosom Obstet Gynaecol* 2016;37:26–33.
3. Kuh D, Hardy R, Rodgers B, Wadsworth ME. Lifetime risk factors for women's psychological distress in midlife. *Soc Sci Med* 2002;55:1957–73.
4. Tucker PE, Bulsara MK, Salfinger SG, Tan JJ, Green H, Cohen PA. The effects of pre-operative menopausal status and hormone replacement therapy (HRT) on sexuality and quality of life after risk-reducing salpingo-oophorectomy. *Maturitas* 2016;85:42–8.
5. Brockie J. Managing menopausal symptoms: hot flushes and night sweats. *Nurs Stand* 2013;28:48–53.
6. Nijland EA, Weijmar Schultz WC, Nathorst-Boös J, Helmond FA, Van Lunsen RH, Palacios S, et al; LISA Study Investigators. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. *J Sex Med* 2008;5:646–56.
7. Khoo SK, Coglan M, Battistutta D, Tippett V, Raphael B. Hormonal treatment and psychological function during the menopausal transition: an evaluation of the effects of conjugated estrogens/cyclic medroxyprogesterone acetate. *Climacteric* 1998;1:55–62.
8. Ross LA, Alder EM, Cawood EH, Brown J, Gebbie AE. Psychological effects of hormone replacement therapy: a comparison of tibolone and a sequential estrogen therapy. *J Psychosom Obstet Gynaecol* 1999;20:88–96.
9. Egarter C, Huber J, Leikermoser R, Haidbauer R, Pusch H, Fischl F, et al. Tibolone versus conjugated estrogens and sequential progestogen in the treatment of climacteric complaints. *Maturitas* 1996;23:55–62.
10. Miller KJ. The other side of estrogen replacement therapy: outcome study results of mood improvement in estrogen users and nonusers. *Curr Psychiatry Rep* 2003;5:439–44.
11. Stephens C, Ross N. The relationship between hormone replacement therapy use and psychological symptoms: no effects found in a New Zealand sample. *Health Care Women Int* 2002;23:408–14.
12. Kenemans P, Speroff L; International Tibolone Consensus Group. Tibolone: clinical recommendations and practical guidelines. A report of the International Tibolone Consensus Group. *Maturitas* 2005;51:21–8.
13. Genazzani AR, Petraglia F, Facchinetti F, Genazzani AD, Bergamaschi M, Grasso A, et al. Effects of Org OD 14 on pituitary and peripheral β-endorphin in castrated rats and in postmenopausal women. *Maturitas* 1987;9:35–48.
14. Davis SR. The effects of tibolone on mood and libido. *Menopause* 2002;9:162–70.
15. Greene JG. Constructing a standard climacteric scale. *Maturitas* 2008;61:78–84.
16. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med* 1983;13:595–605.
17. Liao SC, Lee MB, Lee YJ, Huang TS. Hyperleptinemia in subjects with persistent partial posttraumatic stress disorder after a major earthquake. *Psychosom Med* 2004;66:23–8.
18. Wretmark G, Aström J, Eriksson M. The Maudsley Personality Inventory as a prognostic instrument. *Br J Psychiatry* 1970;116:21–6.
19. Sprusińska E. The Family APGAR Index: study on relationship between family function, social support, global stress and mental health perception in women. *Int J Occup Med Environ Health* 1994;7:23–32.
20. Lee MB, Lee YJ, Yen LL, Lin MH, Lue BH. Reliability and validity of using a Brief Psychiatric Symptom Rating Scale in clinical practice. *J Formos Med Assoc* 1990;89:1081–7.
21. Hsiao SM, Liao SC, Chen CH, Chang TC, Lin HH. Psychometric assessment of female overactive bladder syndrome and antimuscarinics-related effects. *Maturitas* 2014;79:428–34.
22. Lee MB, Rin H, Lin HN, Lee YJ. Personality as an effective predictor of outcome of neurotic disorders. *Chin Psychiatr* 1990;4:111–21.
23. Maguess RB, Rosenfeld CR. Local and systemic estradiol-17 beta: effects on uterine and systemic vasodilation. *Am J Physiol* 1989;256:E536–42.
24. Hammar ML, van de Weijer P, Franke HR, Pornel B, von Mauw EM, Nijland EA; TOTAL Study Investigators Group. Tibolone and low-dose continuous combined hormone treatment: vaginal bleeding pattern, efficacy and tolerability. *BJOG* 2007;114:1522–9.
25. Formoso G, Perrone E, Maltoni S, Balduzzi S, Wilkinson J, Basevi V, et al. Short-term and long-term effects of tibolone in postmenopausal women. *Cochrane Database Syst Rev* 2016;10:CD008536.

26. Polisseni AF, Andrade AT, Ribeiro LC, Castro IQ, Brandão M, Polisseni F, et al. Effects of a continuous-combined regimen of low-dose hormone therapy (oestradiol and norethindrone acetate) and tibolone on the quality of life in symptomatic postmenopausal women: a double-blind, randomised study. *Maturitas* 2013;74:172–8.
27. Boyle GJ, Murrihy R. A preliminary study of hormone replacement therapy and psychological mood states in perimenopausal women. *Psychol Rep* 2001;88:160–70.
28. Thakur M, Kaur M, Sinha AK. Assessment of menopausal symptoms in different transition phases using the Greene Climacteric Scale among rural women of North India. *Ann Hum Biol* 2019;46:46–55.
29. Chen FP, Chang CJ, Chao AS, Huang HY, Huang JP, Wu MH, et al. Efficacy of Femarelle for the treatment of climacteric syndrome in postmenopausal women: an open label trial. *Taiwan J Obstet Gynecol* 2016;55:336–40.
30. Quattrocchi T, Micali E, Gentile A, La Ferrera EG, Barbaro L, Ciarcià S, et al. Effects of a phyto complex on well-being of climacteric women. *J Obstet Gynaecol Res* 2015;41:1093–8.
31. Imhof M, Gocan A, Imhof M, Schmidt M. Soy germ extract alleviates menopausal hot flushes: placebo-controlled double-blind trial. *Eur J Clin Nutr* 2018;72:961–70.
32. Benshushan A, Rojansky N, Chaviv M, Arbel-Alon S, Benmeir A, Imbar T, et al. Climacteric symptoms in women undergoing risk-reducing bilateral salpingo-oophorectomy. *Climacteric* 2009;12:404–9.
33. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.
34. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al; WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243–53.