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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☆

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ABSTRACT

Objective: This study compared the effects of a continuous-combined regimen of low-dose hormone therapy (LD-HT) versus tibolone and supplemental calcium/vitamin D3 (control) on quality of life (QoL) in symptomatic postmenopausal women.
Design: This study was a prospective, randomised, double-blind, comparative trial with a control group.
Setting: The study was conducted in a climacteric outpatient clinic in the University Hospital of Federal University of Juiz de Fora, Brazil.
Population: A total of 174 postmenopausal women under 60 years of age who attended the climacteric outpatient clinic between June 2009 and June 2011 were recruited. These women complained of moderate or intense vasomotor symptoms and exhibited no contraindications for the use of hormone therapy.
Interventions: The patients were randomised into three groups: (1) daily treatment with 2.5 mg tibolone ($n = 64$), (2) 50 mg calcium carbonate + 200 IU vitamin D3 (Ca/Vit D3, $n = 54$) or (3) 1 mg oestradiol + 0.5 mg norethindrone acetate (E2/NETA, $n = 56$) for 12 weeks.
Primary outcome measures: The primary outcome was the evaluation of QoL using the Women's Health Questionnaire (WHQ) in all subjects at baseline and after 4, 8 and 12 weeks of treatment.
Results: A total of 130 women in the following groups completed the study: tibolone ($n = 42$), Ca/Vit D3 ($n = 44$) and E2/NETA ($n = 44$). An improved QoL based on the WHQ was observed at T0 (80.12 ± 14.04, 77.73 ± 15.3, 77.45 ± 15.4) and T12 (57.0 ± 15.5, 55.7 ± 16.7, 58.4 ± 12.6) for the tibolone, E2 + NETA and Ca/Vit D3 groups, respectively (p values <0.05). The three groups exhibited significantly different scores at T12 for sexual behaviour and vasomotor symptoms. The tibolone group exhibited better sexual function compared with the E2/NETA and Ca/Vit D3 groups (4.2 ± 26, 5.6 ± 2.8, 5.4 ± 2.8, respectively, p values <0.05). LD-HT was superior to tibolone and Ca/Vit D3 treatment for improvements in vasomotor symptoms (3.2 ± 1.5, 4.0 ± 1.8, 4.3 ± 2.0, respectively, p values <0.05). Adverse effects were few and mild.
Conclusions: An improved QoL was observed in the three study groups. Tibolone primarily improved sexual function, and E2/NETA exhibited a superior response for vasomotor symptoms.

1. Introduction

Vasomotor symptoms, vaginal atrophy, sexual dysfunction, urinary symptoms, and increased risk for cardiovascular disease and osteoporosis are all consequences of the hypoestrogenism that occurs during perimenopause. These signs and symptoms may reduce the quality of life (QoL) of climacteric women [1–3]. The interest in studying QoL has increased in several fields because an increase in life expectancy should be accompanied by an improved QoL. The physical, social, psychological, and spiritual domains of

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QoL should be evaluated [4]. Several factors are related to the QoL in postmenopausal women, including education; marital status; paid work; family income; morbidities; lifestyle; and marital, family, social, and sexual difficulties [5]. The symptoms that arise at this stage result from hypoestrogenism and may reduce the QoL of these women [2,6]. Hormone therapy (HT) using oestrogen or other drugs, such as tibolone, has been recommended to improve these symptoms [6–9]. The issue of QoL has not been widely studied in Brazil, despite its importance. Many studies have been conducted in other countries, but these results may not be valid for the population in Brazil because of cultural and socio-economic differences [10]. The importance of HT in the improvement of menopausal symptoms is indisputable, but the impact of HT on the QoL of postmenopausal women is controversial [11–20]. Previous studies use different oestrogens and progestins, as well as varying drug regimens, doses and routes of administration, resulting in conflicting results. This study compared the effects of a combined, continuous, low-dose hormone therapy (LD-HT) with the effects of tibolone and a control group on the QoL in symptomatic postmenopausal women.

2. Methods

2.1. Study design and population

This prospective, randomised, double-blind study with control group was conducted at the University Hospital of Federal University of Juiz de Fora (HU-UFJF), Minas Gerais, Brazil, from June 2009 to June 2011. The study population included 174 postmenopausal women who were selected from a group of women who were treated at a climacteric outpatient clinic.

The Ethics Committee in Research of the University Hospital of Federal University of Juiz de Fora (Brazil) – CEP-HU/UFJF – approved this research (protocol number 0046/09), and each subject provided written informed consent prior to any study-related procedures. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable laws and regulations. The ethics committee's approval was obtained at each of the participating sites.

2.1.1. Eligibility criteria for participants

The selected participants were between 45 and 60 years in age and were in the postmenopausal phase with moderate or pronounced vasomotor symptoms and a Blatt–Kupperman menopausal index (BKMI) that was equal to or greater than 20 points. Women outside of this age range were excluded if they had no vasomotor symptoms or had mild symptoms; used hormone, non-hormone, herbal, or isoflavone therapy or soy-based foods in the last 6 months; underwent surgery for breast and/or endometrial cancer; had a history of myocardial infarction or coronary artery disease; had a history of thromboembolism, acute or severe liver disease, renal failure, coagulopathy, decompensated thyroid disease, or intestinal disorders that might interfere with drug absorption; or exhibited abnormal genital bleeding of unknown cause, porphyria or any other contraindication for the use of HT. The diagnosis of postmenopausal phase was primarily clinical and was based on the patient's age. Menopause was characterised by the absence of menstruation for at least 12 months and was confirmed by an increase in follicle-stimulating hormone (FSH) to levels greater than 40 mIU/mL.

2.2. Data collection procedures

Data collection from the women was performed during scheduled patient clinic visits to the postmenopausal outpatient clinic at the HU-UFJF on the occasion of their inclusion in the trial. Women with appointments at the clinic between June 2009 and June 2011 who met the eligibility criteria and agreed to participate were included in the study. The purpose of this research and study participation was explained to each participant. Interviews were used to collect patient data. Participants answered questions on sociodemographic characteristics and clinical and life habits. The Blatt–Kupperman menopausal index (BKMI) and the Women's Health Questionnaire (WHQ) were applied. The same investigator administered all of the questionnaires. Complementary exams were requested after the clinical and gynaecological examinations, according to the protocol. A computer-generated list of random numbers was used to allocate the participants. The participants were randomly assigned to one of the three treatment groups using simple randomisation procedures: group 1 received Formula 1 capsules (2.5 mg tibolone); control group 2 received Formula 2 capsules (50 mg calcium carbonate and 200 UI vitamin D3) and group 3 received Formula 3 capsules (1 mg oestradiol + 0.5 mg norethindrone acetate). The Cavalieri Dispensing Chemists, Ltd. (Juiz de Fora – MG) was responsible for the handling and dispensing of the medications. Quality control was conducted of the raw material, the supplier and the finished product to ensure the uniform content of the hormones. All capsules appeared identical, which made distinguishing the contents impossible. The capsules were prepacked in identical boxes and consecutively numbered for each woman according to the randomisation schedule. The composition of the capsules was unknown to the researcher and the research participant. Only the pharmacist responsible for the handling of the capsules and Cavalieri Dispensing Chemists, Ltd., knew the capsule contents. The participants were instructed to take one capsule daily in the morning for a period of 4 weeks, take notes of any symptoms that occurred, communicate with the investigator when necessary, and return for scheduled evaluations. The BKMI and WHQ were administered after 4, 8 and 12 weeks of medication use.

2.2.1. Efficacy assessment

This study compared the effects of tibolone and LD-HT on the overall QoL in each study group from baseline to 12 weeks of treatment.

The secondary efficacy analysis compared the effect of these drugs in each WHQ domain in each group and between group pairs, from baseline to 12 weeks of treatment. The group pairs that exhibited a significant difference at the end of treatment were compared.

2.2.1.1. Women's Health Questionnaire. QoL was evaluated using the WHQ that was developed by Hunter [21] and modified by Dias [22] for the Portuguese language. The WHQ analyses physical changes and changes in the well-being of postmenopausal phase women.

The WHQ includes 36 questions that offer four possible alternatives responses. The questions are divided into nine groups, or domains, that assess the following categories of symptoms: depressed mood (questions 3, 5, 7, 8, 10, 12, 25), somatic symptoms (questions 14, 15, 16, 18, 23, 30, 35), cognitive difficulties (questions 20, 33, 36), vasomotor symptoms (questions 19, 27), anxiety (questions 2, 4, 6, 9), sexual behaviour (questions 24, 31, 34); sleep problems (questions 1, 11, 29), menstrual symptoms (questions 17, 22, 26, 28), and attractiveness (questions 13, 21, 32) [21].

Survey responses were interpreted according to a score that related to symptom severity [21,23].

The following scores were assigned for each of the possible answers: (1) no, not at all; (2) rarely; (3) yes, sometimes; and (4) yes, definitely. Thirty questions refer to an unfavourable issue, and 6 questions refer to a favourable issue. This study evaluated 32 questions of the WHQ. An improvement in the unfavourable WHQ items was noted as a lower score. An improvement in the favourable items was noted as a higher score. Symptom clusters (WHQ domains) and

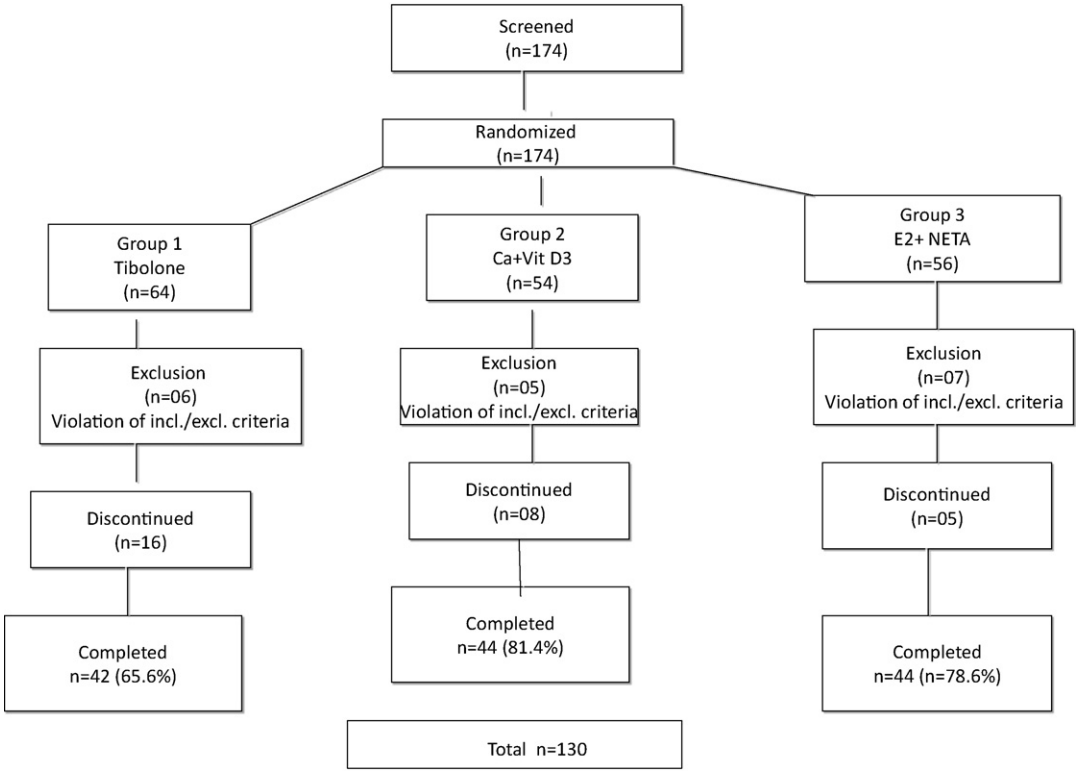

Fig. 1. Subject disposition.

the overall evaluation of the WHQ were standardised by reversing the favourable question scores so that all issues exhibited a higher initial score, which decreased with improved QoL [22].

2.3. Statistical analysis

The sample size was calculated using GraphPad StateMate version 2 using the following parameters: $\alpha = 5\%$, $\beta = 20\%$ (80% of power) and a magnitude of intergroup difference = 30%. The calculation results indicated a total of 120 subjects, which corresponded to 40 subjects per group.

Inferential analysis determined the data distribution, which was assessed relative to its normality (Kolmogorov–Smirnov test) and scedasticity (Levene's test). Inferences were performed using non-parametric statistics.

The Wilcoxon signed-rank test assessed the significance of the overall QoL in each domain for each group [24]. Comparisons between groups at all times for overall QoL for each domain were performed using the Kruskal–Wallis test [24]. Group pairs that exhibited significant differences were compared using the Kruskal–Wallis test and the Mann–Whitney test at the end of treatment [24]. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 14). A value of $p < 0.05$ was considered significant.

3. Results

3.1. Subject disposition and baseline characteristics

Subject dispositions are displayed in Fig. 1. Of the 174 women in group 1 ($n = 64$) who used tibolone, six were excluded for violations of the inclusion and exclusion criteria: measurements of follicle-stimulating hormone (FSH) <40 mIU/mL ($n = 3$, 1.8%), the Blatt–Kupperman menopausal index (BKMI) <20 ($n = 1$, 0.6%), age <45 years ($n = 1$, 0.6%), or vasomotor symptoms of mild intensity ($n = 1$, 0.6%). We had 16 trial participants who discontinued the study. Six patients (3.6%) discontinued because of adverse effects [abdominal pain ($n = 2$, 1.2%), insomnia ($n = 1$, 0.6%), muscle pain ($n = 2$, 1.2%), or bleeding ($n = 1$, 0.6%)] and ten patients discontinued due to drug inefficacy ($n = 1$, 0.6%), family problems ($n = 3$, 1.8%), and the failure to attend follow-up examinations ($n = 6$, 3.6%). Amongst the 54 women in group 2 (control group), five were excluded for violations of the inclusion and exclusion criteria: measurements of FSH <40 mIU/mL ($n = 3$, 1.5%), BKMI <20 ($n = 1$, 0.5%), or vasomotor symptoms of mild intensity ($n = 1$, 0.5%). An additional five participants discontinued the study because of family problems ($n = 3$, 1.5%) and the failure to attend follow-up examinations ($n = 2$, 1.0%). Of the 56 women in group 3 (E2/NETA), seven were excluded for violations of the inclusion and exclusion criteria: measurement of FSH <40 mIU/mL ($n = 4$, 2.4%), BKMI <20 ($n = 2$, 1.2%), and a mammography BI-RADS category of 4 ($n = 1$, 0.6%). Five participants (3.0%) discontinued the study due to breast tenderness ($n = 1$, 0.6%), drug inefficacy ($n = 1$, 0.6%), family problems ($n = 2$, 1.2%), or failure to attend follow-up examinations ($n = 1$, 0.6%). Adverse effects were few and mild and were most prevalent in the group of women taking tibolone.

A total of 130 women completed the study. Group 1 ($n = 42$) received a daily capsule containing 2.5 mg tibolone, group 2 ($n = 44$) received 50 mg calcium carbonate + 200 IU vitamin D3 daily (control) and group 3 ($n = 42$) received 1 mg oestradiol + 0.5 mg norethindrone acetate daily.

No significant differences in the time of menopause ($p = 0.441$) or QoL ($p = 0.666$) were observed between the groups at baseline (T0). The demographic and baseline clinical characteristics of the three groups are presented in Table 1.

3.2. Primary efficacy analysis

The primary efficacy endpoint compared the effects of a combined, continuous, LD-HT with those of treatment with tibolone

Table 1
Demography and baseline clinics characteristics.

Variables	Tibolone ($n=42$)	Ca + Vit D3 ($n=44$)	E2 + NETA ($n=44$)
Age, years	51.24 ± 3.48	53.18 ± 4.06	52.98 ± 3.39
FSH	59.86 ± 16.73	74.42 ± 24.82	65.90 ± 19.68
YSM	4.28 ± 4.15	4.17 ± 3.07	5.12 ± 3.76
QoL	80.12 ± 14.04	77.45 ± 15.42	77.73 ± 15.32
Marital status			
Married	22 (52.4%)	35 (79.5%)	34 (77.3%)
Single/others	20 (47.6%)	09 (20.5%)	10 (22.7%)
Race			
White	24 (57.1%)	28 (63.6%)	24 (54.5%)
Other	18 (42.9%)	16 (36.4%)	20 (45.5%)
School education			
Uneducated	0	0	01 (0.8%)
1–8 years	26 (61.9%)	32 (72.7%)	24 (54.5%)
9–13 years	13 (30.9%)	05 (11.4%)	17 (38.7%)
>13 years	03 (7.2%)	07 (15.9%)	02 (4.5%)

FSH: follicle stimulating hormone; YSM: years since menopause.

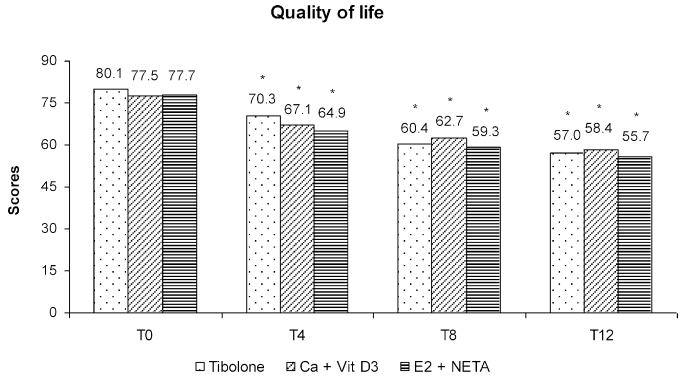

Fig. 2. Overall quality of life. Average score on the WHQ at baseline (T0) and 4 (T4), 8 (T8), and 12 (T12) weeks after treatment in groups of postmenopausal women treated with tibolone ($n=42$), Ca + Vit D3 ($n=44$), and E2 + NETA ($n=44$). *$p<0.05$ vs. corresponding baseline value for the group.

and a control group on overall QoL in symptomatic postmenopausal women.

3.2.1. Assessment of overall QoL between groups

A significant decrease ($p<0.05$) in the average WHQ scores of the three groups was observed from baseline to T12 (Fig. 2 and Table 2):

Table 2
Means and standard deviations of each domain of the WHQ at baseline (T0) and T12 in groups 1, 2, and 3.

	Domains	Tibolone	Ca + Vit D3	E2 + NETA
T0	Depressed mood	15.52 ± 4.46	14.89 ± 5.49	15.16 ± 4.99
	Somatic symptoms	18.17 ± 4.12	17.36 ± 4.51	17.23 ± 4.61
	Cognitive difficulties	8.62 ± 2.26	8.41 ± 2.39	8.32 ± 2.33
	Vasomotor symptoms	7.17 ± 1.17	6.80 ± 1.34	6.77 ± 1.27
	Anxiety	10.05 ± 2.95	8.68 ± 3.00	8.82 ± 3.27
	Sexual behaviour	5.38 ± 3.72	7.02 ± 2.78	7.18 ± 3.00
	Sleep problems	8.05 ± 1.96	7.52 ± 2.04	7.95 ± 2.15
	Attractiveness	7.17 ± 2.36	6.77 ± 2.70	6.30 ± 2.40
	QoL	80.12 ± 14.04	77.45 ± 15.42	77.73 ± 15.32
T12	Depressed mood	11.40 ± 3.83	11.82 ± 4.66	11.39 ± 4.81
	Somatic symptoms	14.33 ± 5.03	13.41 ± 3.51	12.70 ± 3.91
	Cognitive difficulties	6.57 ± 2.25	6.80 ± 2.42	6.61 ± 2.79
	Vasomotor symptoms	3.98 ± 1.80	4.30 ± 2.00	3.20 ± 1.50
	Anxiety	6.76 ± 2.53	6.70 ± 2.55	6.66 ± 2.95
	Sexual behaviour	4.17 ± 2.59	5.39 ± 2.85	5.59 ± 2.82
	Sleep problems	5.83 ± 1.79	5.84 ± 1.93	5.91 ± 2.13
	Attractiveness	5.9 ± 2.28	5.77 ± 2.41	5.14 ± 2.10
	QoL	57.00 ± 15.50	5839 ± 12.60	55.70 ± 16.67

tibolone (80.12 ± 14.04 and 57.0 ± 15.5), E2/NETA (77.73 ± 15.3 and 55.7 ± 16.7), and Ca/Vit D3 (77.45 ± 15.4 and 58.4 ± 12.6).

3.2.2. Assessment of the overall QoL in group pairs

No significant differences between group pairs were observed over time (T4, T8 and T12, Fig. 2).

Assessments of the overall QoL in group pairs over time demonstrated that the E2/NETA group exhibited the best QoL at the end of treatment (T12), with an average WHQ score of 55.7 ± 16.7. However, no statistically significant difference between the groups was observed. This result suggests an improved QoL in the groups treated with tibolone, E2/NETA, and supplemental Ca/Vit D3 (control) groups (Fig. 2 and Table 2).

3.3. Secondary efficacy analysis

The separate analysis of the eight WHQ domains revealed a significant reduction in scores for all three groups at the end of treatment (T12, Figs. 3 and 4 and Table 2). This response was observed in the fourth week of treatment for most WHQ domains.

The intensity of depressed mood decreased considerably between T0 and T12 of treatment, from 15.5 ± 4.46 to 11.4 ± 3.83 in the tibolone group, 14.89 ± 5.49 to 11.82 ± 4.66 in the control group, and 15.16 ± 4.99 to 11.39 ± 4.81 in the E2/NETA group ($p<0.05$).

The course of somatic symptoms is displayed in Table 2 and Fig. 3. All three groups exhibited statistically significant decreases in somatic symptoms (i.e., improvement). The intensity of cognitive difficulties and anxiety decreased considerably after 12 weeks of treatment (Table 2 and Figs. 3 and 4).

The tibolone group exhibited a significant decrease in the intensity of vasomotor symptoms (Table 2 and Fig. 3) after 12 weeks of treatment, from 7.2 to 4.0 (7.17 ± 1.17–3.98 ± 1.80); the control group decreased from 6.8 to 4.3 (6.80 ± 1.34–4.30 ± 2.00); and the E2/NETA group decreased from 6.8 to 3.2 (6.77 ± 1.27–3.20 ± 1.50).

The tibolone group exhibited a significant decrease in the intensity of sexual behaviour complaints after 12 weeks of treatment, from 5.4 to 4.2; the control group, 7.0 to 5.4; and the E2/NETA group, 7.2 to 5.6 (Table 2 and Fig. 4).

The intensity of sleep problems and attractiveness symptoms also decreased, as demonstrated in Table 2 and Fig. 4.

3.3.1. Assessment of QoL in group pairs in the different domains of the WHQ

The three groups exhibited significantly different scores for only sexual behaviour and vasomotor symptoms at T12. The tibolone-treated group exhibited a better response than the E2/NETA and supplementary Ca/Vit D3 groups to sexual function issues (4.2 ± 2.6, 5.6 ± 2.8, 5.4 ± 2.8, respectively, $p<0.05$). The LD-HT group exhibited better vasomotor symptom scores than the tibolone and Ca/Vit D3 groups (3.2 ± 1.5, 4.0 ± 1.8, 4.3 ± 2.0, respectively, $p<0.05$; Table 3 and Figs. 3 and 4).

4. Discussion

The importance of HT in the QoL for postmenopausal women has been widely questioned. This study compared the effects of a continuous combined LD-HT regimen to those of tibolone and supplemental calcium/vitamin D3 on the QoL of postmenopausal women. The present data indicated that LD-HT and tibolone improved the QoL of the study participants in a short period of time. Gambacciani et al. [11] demonstrated a significant improvement in the QoL of postmenopausal women using low doses of E2/NETA (LD-HT) in a comparative study in Italy. Other studies have demonstrated similar results [25,26]. Eviö et al. [20] observed no change in the QoL between HT users and non-users. The average

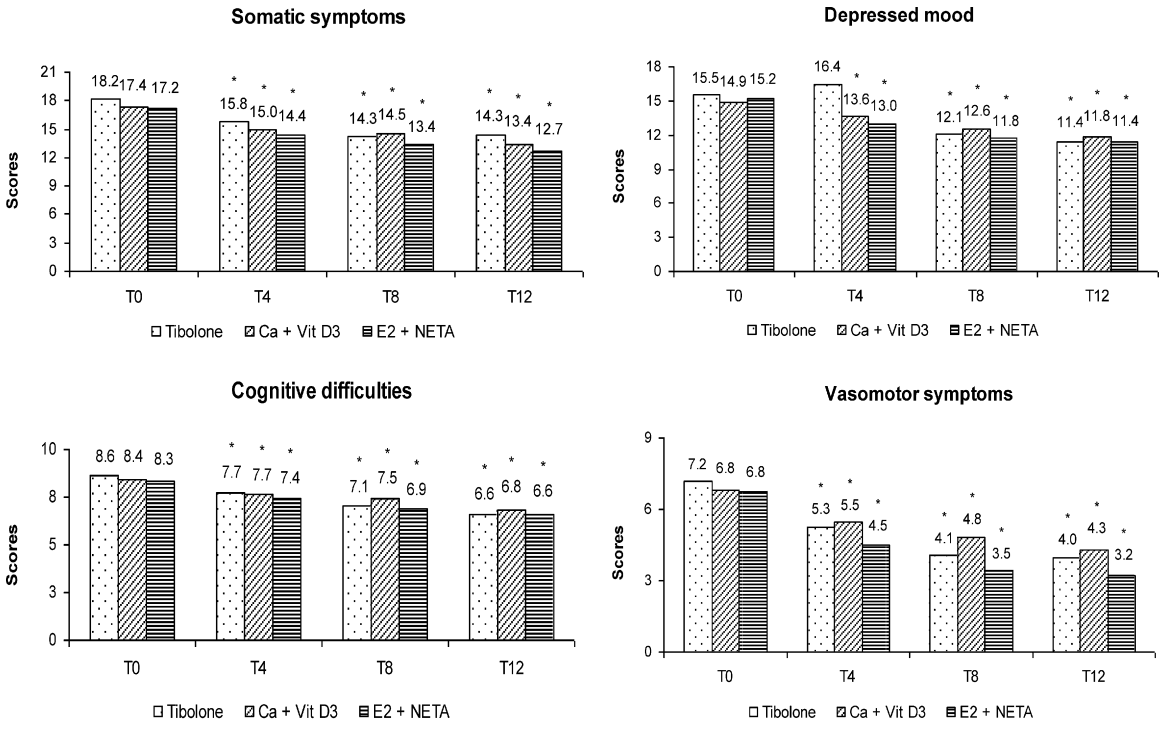

Fig. 3. Somatic symptoms, depressed mood, cognitive difficulties, and vasomotor symptoms. Average scores of the domains of the Women's Health Questionnaire (WHQ) at baseline (T0) and after treatment at 4 (T4), 8 (T8), and 12 (T12) weeks in groups of postmenopausal women using tibolone ($n = 42$), Ca + Vit D3 ($n = 44$), and E2 + NETA ($n = 44$). $^{*}p < 0.05$ vs. corresponding baseline value for the group.

ages of the HT users and non-users in this Finnish study were 67.5 years and 68.9 years, respectively. The use of HT in this age group is inconsistent with the literature and does not correspond to the target age of the present research, which may explain the differences in results. Most of the participants in the Eviö et al. study exhibited comorbidities and used other medications, which may have adversely affected their QoL.

The present results demonstrated that the eight domains of the WHQ were significantly improved in all three groups at the end of treatment, which suggests an improved QoL even in the control

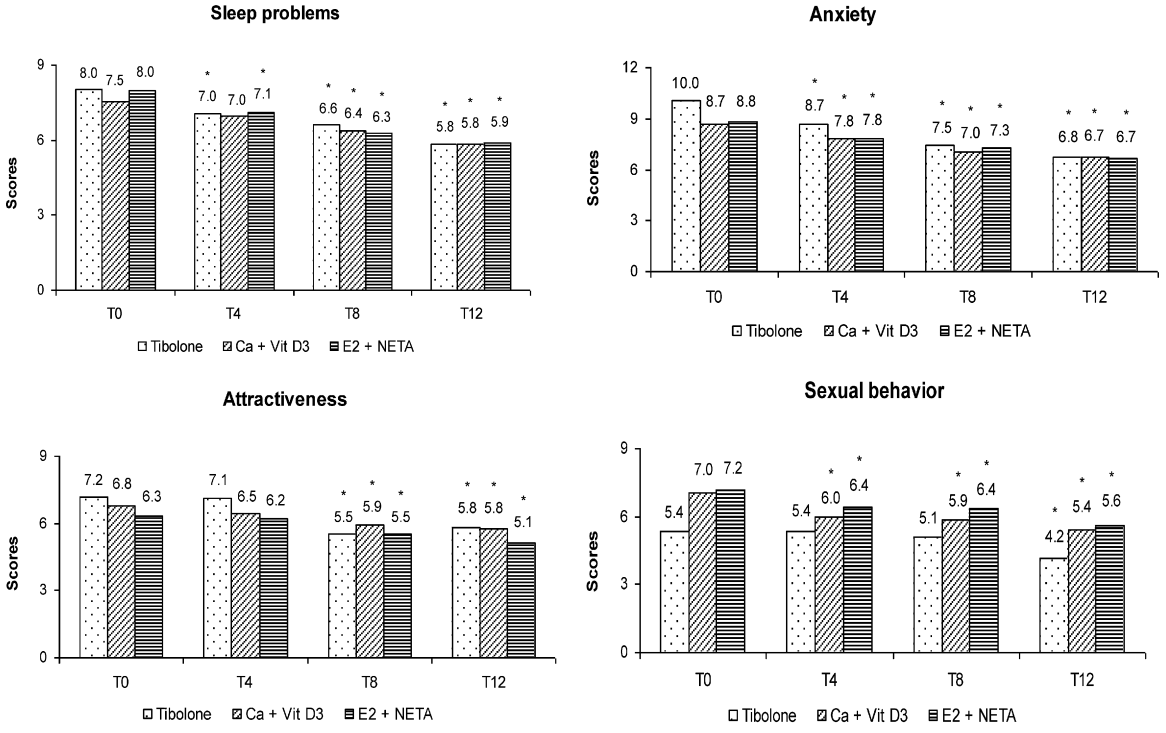

Fig. 4. Sleep problems, anxiety, attractiveness and sexual behaviour. Average scores of the domains of the Women's Health Questionnaire (WHQ) at baseline (T0) and after treatment at 4 (T4), 8 (T8), and 12 (T12) weeks in groups of postmenopausal women using tibolone ($n = 42$), Ca + Vit D3 ($n = 44$), and E2 + NETA ($n = 44$). $^{*}p < 0.05$ vs. the corresponding baseline value for the group.

Table 3
Comparisons between groups in the domains of the WHQ that exhibited significant differences in *p*-values by the Kruskal–Wallis test at the end of treatment (T12).

Groups	Mean ± std. deviation	*p* value
Vasomotor symptoms		
Tibolone × Ca + Vit D3	4.0 ± 1.8 × 4.3 ± 2.0	0.531
Tibolone × E2 + NETA	4.0 ± 1.8 × 3.2 ± 1.5	0.036
Ca + Vit D3 × E2 + NETA	4.3 ± 2.0 × 3.2 ± 1.5	0.007
Sexual behaviour		
Tibolone × Ca + Vit D3	4.2 ± 2.6 × 5.4 ± 2.8	0.034
Tibolone × E2 + NETA	4.2 ± 2.6 × 5.6 ± 2.8	0.018
Ca + Vit D3 × E2 + NETA	5.4 ± 2.8 × 5.6 ± 2.8	0.987

Ca + Vit D3: calcium carbonate/vitamin D3; E2 + NETA: oestradiol/norethindrone acetate.

group. Mameri Filho et al. [27] compared the QoL of three groups of randomly distributed women who used placebo, conjugated oestrogens, and conjugated oestrogens/methyltestosterone. An improved QoL was observed at the end of all the treatments, even in the placebo group. However, the reduction in the WHQ score was significant in only three domains for the placebo group and seven domains for the oestrogen and oestrogen–androgen combination groups.

The LD-HT scheme was more effective than tibolone for the treatment of vasomotor symptoms. The primary indication for systemic oestrogen HT is the treatment of these symptoms. Oestrogen also improves other symptoms. Hedrick et al. [28] demonstrated an improvement in vasomotor symptoms using a transdermal oestradiol gel in symptomatic postmenopausal women in a multicentre study of 488 patients in the United States and Canada. These results have been confirmed in subsequent studies [19,25,29–31].

The results of the present study demonstrated that tibolone was more effective than the LD-HT scheme for the improvement of sexual function. Kamenov et al. [26] compared the effects of tibolone and placebo on menopausal symptoms and sexual function in two groups of postmenopausal women in a prospective study. Tibolone treatment exhibited beneficial effects on the climacteric symptoms and sexual functions related to desire, arousal, lubrication, and pain. The importance of tibolone in the improvement of sexuality and QoL in postmenopausal women has been demonstrated previously [32–36]. Tibolone administration to postmenopausal women is associated with significant decreases in the levels of sex hormone binding globulin (SHBG) and an increase in free testosterone and the testosterone/SHBG ratio [32–36].

The performance of the study in a public university hospital likely inspired confidence in the researcher, and the systematic and frequent monitoring likely motivated the participants in the treatment, which generated favourable expectations in treatment outcome and may explain the results in the control group.

The use of vitamin D in the control group may have affected the QoL because vitamin D prevents osteoporosis, cardiovascular disease, diabetes, cancer, infections, and neurodegenerative diseases [37–39]. However, previous studies used much larger doses of vitamin D in older patients. Further studies to corroborate the effect of vitamin D are required.

Some methodological limitations should be mentioned, such as the subjective nature of QoL, the multidimensional aspects and influence of factors related to education, and economical and sociocultural aspects [5,40–42]. The sample size may have compromised potential statistical associations, but important information on this subject was obtained.

5. Conclusion

Improvements in QoL were observed in the three study groups. Tibolone positively impacted the QoL in postmenopausal women, and this compound exerted a better effect on sexual function than the oestrogen–progesterone combination and Ca/Vit D3 supplement. The oestrogen–progesterone combination (LD-HT) effectively improved the QoL in these women, and LD-HT exhibited a significantly stronger effect on vasomotor symptoms than Ca/Vit D3 and tibolone. The choice of the drug according to the primary symptom, the individualisation of the prescription, and the medication dose are fundamental factors for an effective therapeutic response. Future studies should assess QoL using clinical and laboratory data to evaluate the efficacy of HT.

Contributors

Alvaro Fernando Polisseni: author of the study; Amaury Teixeira Leite Andrade: participated in the data analysis and revision of the study; Luiz Cláudio Ribeiro: participated in the statistical analysis of the study; Isabela Queirós Castro: participated in the statistical analysis of the study; Marcos Brandão: participated in the quality control of the medications used in the study; Fernanda Polisseni: participated in the data analysis and revision of the study; Martha de Oliveira Guerra: participated in the data analysis and revision of the study.

Competing interest

None. The researchers have no associations with the Farmácia de Manipulação Cavalieri Ltda. [Cavalieri Dispensing Chemists Ltd.], which provided the medication.

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