CHAPTER 7

Effects of tibolone versus low dose E_2/NETA on urogenital complaints, sexuality and quality of life in postmenopausul women: results of a randomized controlled clinical trial

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Abstract

Objective: To compare the effects of tibolone 2.5 mg versus E_2 1 mg plus NETA 0.5 mg on sexual function, urogenital complaints and quality of life in postmenopausal women.

Design: a multicenter, randomized, double blind, double dummy group comparative trial. Several questionnaires were used to measure response to therapy: the McCoy sexuality questionnaire for sexual function, the Women's Health Questionnaire (WHQ) for general quality of life and the Urogenital Complaints Scale (LUGCS).

Results: 572 postmenopausal women aged 45-65 years were randomized to the trial. After 48 weeks of treatment, tibolone significantly improved sexual function when compared to E_2/NETA ($p=0.038$). Both treatments resulted in statistically significant improvements from baseline on various urogenital symptoms such as dyspareunia, nocturia, and urgency. A clinically relevant improvement was found for 7 out of 9 WHQ domains in the tibolone treated women and for 5 out of 9 WHQ domains in the E_2/NETA treated women. A statistically significant difference in favor of the E_2/NETA group was found for the vasomotor symptom domain for all visits when compared to tibolone ($p<0.01$).

Conclusions: Tibolone and oral low dose E_2/NETA improve sexual well being by improving various aspects of sexual function and quality of life, the effect being more pronounced with tibolone when compared to low dose E_2/NETA.

Introduction

Tibolone 2.5 mg (Livial®) and low dose continuous combined 1 mg17β-estradiol plus 0.5 mg norethisterone (Activelle®) both registered for the treatment of climacteric symptoms, are currently two of the most prescribed menopausal therapies in Europe. Tibolone is known for its beneficial effects on mood and sexual well-being, vaginal atrophy, urogenital symptoms and bone loss and its endometrial safety and tolerability have been confirmed in large scale randomized controlled trials.[1-5]

A previous study comparing tibolone with continuous combined 2 mg 17β-estradiol (E_2) plus 1 mg norethisterone (NETA) (Kliogest®) indicated that both treatments had a positive effect on sexual well-being.[6] No statistical significant difference between treatment groups could be observed for the change from baseline of the McCoy sexuality questionnaire total score. However, in the same paper a post hoc separate item analysis of the McCoy sexuality questionnaire revealed a statistically significant larger improvement on items such as satisfaction, enjoyment and frequency of sexual activity in favor of the tibolone treated women.

Although tibolone relieves menopausal symptoms and has a favorable tolerability profile, its effects on quality of life (QoI) has not yet been fully established in large randomized controlled trials. In a small placebo controlled study, a trend towards an increased quality of life was found in the group treated with tibolone.[7] Huber et.al., compared tibolone with continuous combined conjugated estrogens combined with medroxyprogesterone acetate (0.625 mg CEE/5 mg MPA), an found an improved QoI for both treatments with no differences between the groups.[8]

Recently the primary efficacy results of the TOTAL trial have been reported including the effects of 2.5 mg tibolone and 1 mg E_2/0.5 mg NETA on vasomotor symptom relief and vaginal bleeding in healthy postmenopausal women.[9] Both treatments significantly reduced vasomotor symptoms and were well tolerated with a comparably low incidence of drug related adverse events. However, treatment with tibolone resulted in a significantly lower vaginal bleeding incidence when compared to E_2/NETA (18.3% versus 33.1% during the first 3 months of treatment $p<0.001$).

The aim of the present study was to assess the effects of tibolone and E_2/NETA in the TOTAL trial on sexual function, urogenital symptoms and quality of life.

Methods

Study participants

Women were eligible to participate if they were aged between 45 and 65 years, had undergone a natural menopause (last menstrual period between 1 and 15 years prior to study entry) and an intact uterus. Women were also required to be in general good health, have a normal mammogram and Papanicoulou smear and a body mass index (BMI) between 18 and 32 kg/m^2. Previous hormone therapy (HT) use was allowed following the applicable wash-out periods specified in the protocol (4 weeks for oral and transdermal HT and tibolone and 6 months for estrogen implants or progestin depot

preparations). Reasons for exclusion were the usual contraindications known for HT and listed in the patient brochure and use of medication expected to affect any of the study outcome parameters or known to interact with steroid metabolism.
The study was conducted in the following countries (number of sites): Norway (11), Sweden (7), Belgium (5), Finland (3), The Netherlands (3), Denmark (2), United Kingdom (1). The study was performed between November 2002 and March 2005.
Each center included between 10 and 25 women. The protocol was approved by the Ethics Committee of each participating study center and written informed consent was obtained from participants before study entry. The study was performed in compliance with the Declaration of Helsinki for Good Clinical Practice.

Study procedures

This double blind, double dummy randomized controlled trial consisted of a 48-week treatment period. After a screening visit at which all subjects underwent a physical examination, a transvaginal ultrasonography (TVUS) and a mammography if a recent (less than 6 months old) mammogram had not been performed, women were randomized in a 1:1 ratio into one of the two study groups via an automatically Interactive Voice Response System (IVRS) using a restricted block-wise randomization. Random permuted blocks were used within each center. The women were treated once daily with either 1 tablet containing 2.5 mg tibolone (Livial®, N.V. Organon, Oss, The Netherlands) or 1 tablet containing 1 mg estradiol plus 0.5 mg norethisterone acetate (Activelle®, Novo Nordisk A/S, Bagsvaerd, Denmark). To enable a double-blind design the double dummy method was applied, with placebo tablets identical in appearance to Livial® or Activelle® to be taken simultaneously with the active treatment. The investigators, study site personnel, and participants remained blinded until after the database was locked.
Study visits were performed at screening and baseline and after 12, 24 and 48 weeks of treatment (Visits 1-3). Non-compliance was defined as missing more than 4 days of medication during a treatment period of 28 days or missing more than 15% of tablets over the entire study period.

Efficacy measures

Sexual function was assessed by the McCoy Female Sexuality Questionnaire Short Form (MFSQ) at baseline and at each follow up visit. The MFSQ questionnaire consists of 9 items grouped into 4 domains: sexual interest, vaginal lubrication, orgasm and sexual partner. A global score is based on the sum of all 9 items and ranges from 9-63 in which a higher score means a better value.[10]
Health related QoL, assessed by the Women's Health Questionnaire (WHQ) was measured at baseline and each follow up visit. The WHQ is a self-administered questionnaire consisting of 36 items, which are divided into 9 subscales: somatic symptoms, depressed mood, memory/concentration, anxiety/fears, sexual behavior, vasomotor symptoms, sleep problems, menstrual symptoms and attractiveness. Changes from baseline in the various WHQ domains are expressed in terms of a clinically relevant change (predefined per separate item) when compared to pre-menopausal values, which is the

valid standard to analyze the WHQ and in which lower values correspond to an improvement of the specific domain.[11,12]

Urogenital complaints were assessed at baseline and each follow up visit with a Local Urogenital Complaints Rating Scale. This scale allows subjects to rate their urogenital discomfort felt in the past month. The vaginal symptoms evaluated by this scale are: pain, dyspareunia, itching, discharge and burning feeling. The urinary symptoms evaluated are: dysuria, frequency, urgency, nocturia, incontinence and urinary tract infection. The possible rating was in five categories: none, mild, moderate, severe and not applicable.

Serum endocrine concentrations of estradiol (E_2), bio-available testosterone (bio-T), total testosterone (total T) and sex-hormone binding globulin (SHBG) were determined for a subset of 200 subjects divided over the centers and the relationship between the total scores and the separate domain scores of the McCoy sexuality questionnaire was assessed as well as the relationship between the serum hormones and the sexual behaviour domain of the WHQ.

Statistical analysis

The analyses were based on the Intent-to-treat principle including all subjects who received at least one dose of study medication and had at least one post baseline assessment of one of the efficacy parameters.

At week 48, questionnaires were evaluated by an Observed Cases endpoint analysis. All statistical tests were performed two-sided and considered statistically significant if $p<0.05$. Post hoc separate item analysis and subgroup analyses were performed to further explore the outcomes of the McCoy sexuality questionnaire.

Sexual dysfunction or sexual problems were no entry criteria in this trial. In order to explore possible differences between women with a self-reported "sub-optimal" sex-life and women who did not report any sexual problem, we divided the data into two subsets. Subset I was the group of women who had reported at baseline a combination of two confirmative answers on the following WHQ items: "I am unsatisfied with my current sexual relationship" and "I have a lost interest in sexual activity" (n=329, for convenience reasons presented in this paper as subset I: women with sexual problems n=329) and women who had not reported a confirmative answer on these WHQ items (n=167, for convenience reasons in this paper presented as subset II: women without sexual problems n=167).

The change from baseline for the nine WHQ domains and the four McCoy domains was compared between the two groups using the Wilcoxon rank sum test.

Analysis of effects on urogenital complaints was done using McNemar's test (to detect changes over time for each treatment group, grouping none/mild and moderate/severe symptoms) and Fisher's exact test (to compare treatment groups).

The correlation between serum hormone levels and outcomes of the sexuality questionnaire were investigated in graphically.

Figure 1. Subject disposition

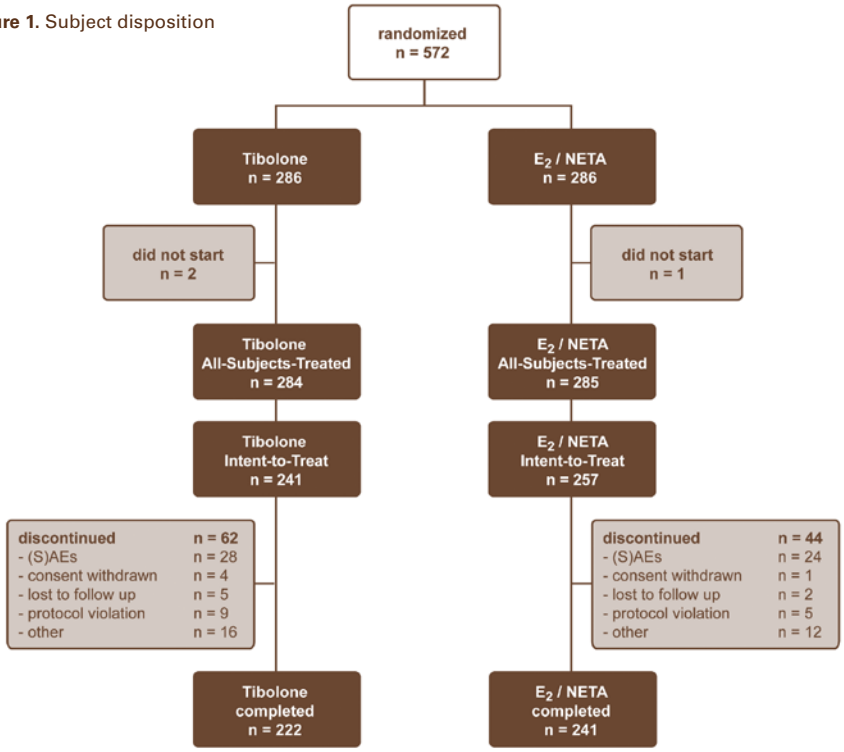
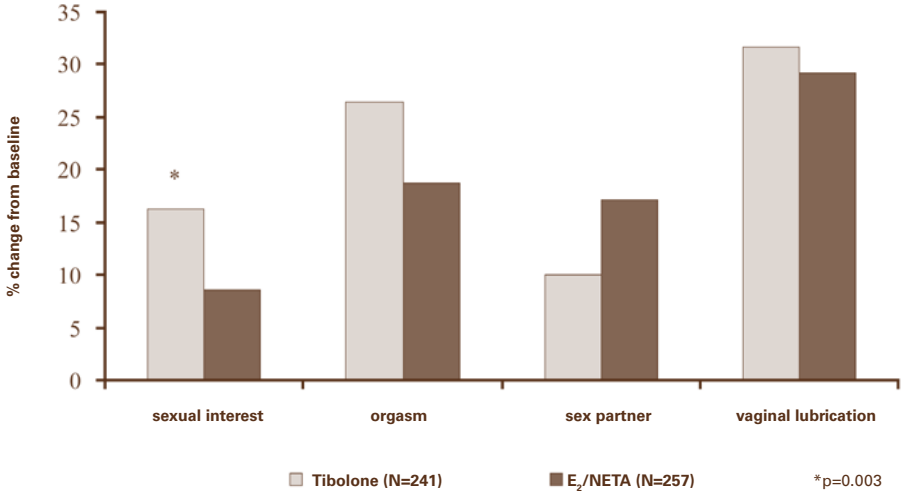


Figure 2. Changes from baseline per treatment group in the 4 domains of the McCoy sexuality questionnaire at week 48 (Intent-to-treat population, endpoint analysis)



Results

A total of 572 women were randomized, of whom 569 actually received treatment (284 in the tibolone group and 285 in the E_2/NETA group). The Intent-to-Treat group consisted of 498 subjects, 241 in the tibolone group and 257 in the E_2/NETA group, respectively. Ultimately, 222 subjects in the tibolone group and 241 in the E_2/NETA group completed the trial (Figure 1). For the baseline demographic data, which were comparable between groups, we refer to the previous report on the same study population.[9]

Sexual function

Both treatment groups showed an improvement from baseline in the separate domain scores as well as the total score of the McCoy sexuality questionnaire. At week 48, a statistically significant difference in favour of tibolone was observed between groups for the McCoy change from baseline total score (p=0.038). This was mainly due to the statistically significant larger increase in sexual interest domain at week 48 was found for the tibolone group when compared to the E_2/NETA group (p=0.003). See Figure 2.

At week 48, improvements from baseline were found for the following separate items (statistical significance marked with an asterix): lubrication (tibolone p<0.001*; E_2/NETA p<0.001*), pain (tibolone p<0.001*; E_2/NETA p<0.001*), frequency of aroused feeling during sex (tibolone p<0.001*; E_2/NETA p=0.165), frequency of orgasm (tibolone p=0.001*; E_2/NETA p=0.038), frequency of sexual thoughts/fantasies during sex (tibolone p=0.011*; E_2/NETA p=0.504), enjoyment of sexual activity (tibolone p<0.001*; E_2/NETA p=0.228), satisfaction with the frequency of sexual activity (tibolone <0.001*; E_2/NETA p=0.062), satisfaction with the partner as a friend (tibolone p=283; E_2/NETA p=0.977), satisfaction with the partner of a lover (tibolone p=0.506 en E_2/NETA 0.377). A significant difference between groups could only be determined for the item "frequency of sexual thoughts and fantasies"(p=0.035) at week 48. Figure 3.

Number of years since menopause significantly correlated with the total scores of the McCoy sexuality questionnaire (i.e. the higher the menopausal age the lower the scores p=0.007).

The change from baseline analyses for women with sexual problems at baseline (subset I) showed significant improvements at week 48 for 3 out of 4 domains (sexual interest, vaginal lubrication and orgasm) and the total McCoy score for both tibolone and E_2/NETA whereas in subset II (women without sexual problems at baseline) a significant improvement from baseline was only found for the vaginal lubrication domain in both treatment groups.

Serum hormone concentrations

The change from baseline in serum hormone concentrations are presented in Figure 4. In the tibolone group there was a decrease from baseline in SHBG and as a consequence an increase in bio-T whereas in the E_2/NETA group there was an increase in SHBG and a decrease in bio T at week 48. Total T decreased in both groups. Serum E_2 significantly increased from baseline in the E_2/NETA group whereas for tibolone no clinically meaningful changes could be observed.

Figure 3. McCoy separate item analysis. Change from baseline per treatment group at week 48 (Intent-to-treat population, endpoint analysis)

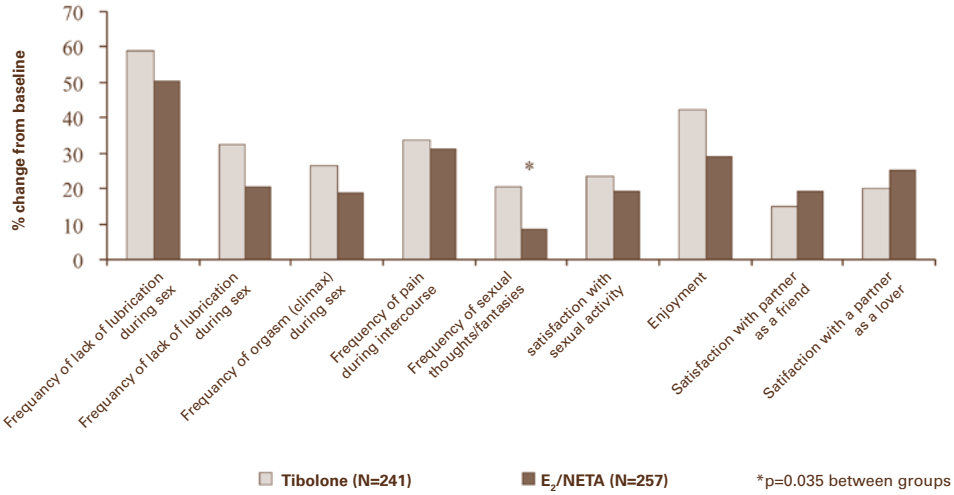
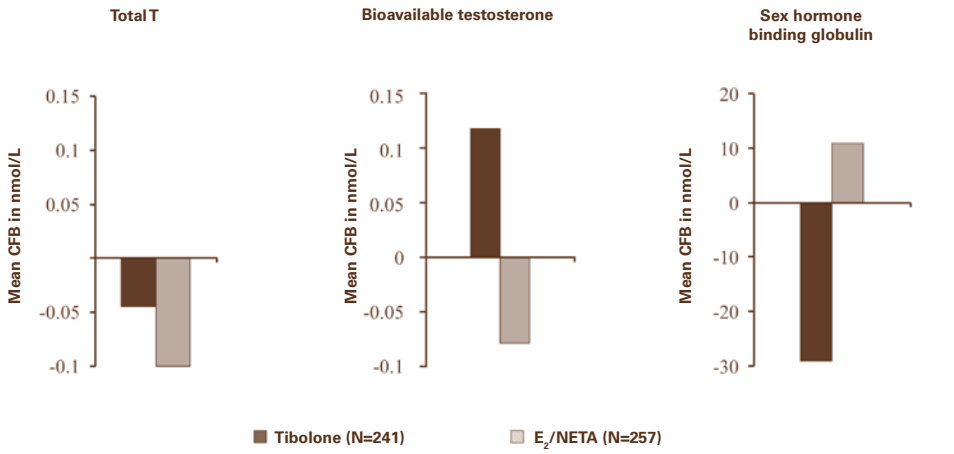


Figure 4. Changes from baseline in serum hormone levels at week 48



None of the individual serum hormone levels at baseline and at week 48 showed any clear correlation with any of the sexual function domains of the McCoy or the sexual behaviour domain of the WHQ.

Health related quality of life

Changes from baseline for each follow up visit in the separate domains of the WHQ are presented in Table 1. At week 48, a clinically relevant improvement was found for 7 out of 9 WHQ domains in the tibolone treated women (somatic symptoms, depressed mood, memory/concentration, anxiety fears, sexual function, vasomotor symptoms and sleep problems). For E_2/NETA a clinically relevant improvement was found for 5 out of 9 domains (somatic symptoms, depressed mood, memory/concentration, vasomotor symptoms and sleep problems) at week 48.

A statistically significant difference in favor of the E_2/NETA group was found for the vasomotor symptom domain for all visits when compared to tibolone ($p<0.01$ for all visits), at week 12 for the dimension "sleep problems" ($p=0.025$) and at week 48 for the dimension "memory/concentration" ($p=0.024$).

The percentage of missing answers on the sexual behavior domain of the WHQ was relatively high (17%). This is explained by the fact that women who were not sexually active did omit the answer on the following question: "As a result of vaginal dryness sexual intercourse has become uncomfortable." At baseline, 50% of the women equally divided over the two treatment groups reported to have lost interest in sexual activity and 25% of the women were not satisfied with their sexual relationship.

Urogenital complaints

The most frequently reported moderate to severe symptoms at baseline were: dyspareunia (10% in the tibolone group and 9% in the E_2/NETA group), frequency (8% in the tibolone group and 13% in the E_2/NETA group), nocturia (9% in the tibolone group and 8% in the E_2/NETA group) and urgency (7% in the tibolone group and 9% in the E_2/NETA group). There were no statistically significant differences between the two treatment groups with respect to efficacy on any of the urogenital complaints. A significant decrease in the number of women experiencing urogenital symptoms when compared to baseline was found for the following items: dyspareunia ($p<0.001$ for both tibolone and E_2/NETA), nocturia (tibolone $p<0.001$ and E_2/NETA $p=0.021$), urgency (tibolone: $p=0.039$ and E_2/NETA: $p=0.002$) and frequency (E_2/NETA: $p<0.001$) at week 48. Table 2.

Table 1. Changes from baseline in actual values of the various domains of the WHQ per treatment group (Intent-to-Treat population)

		Tibolone 2.5 mg (N = 241)	1 mg E_2/ 0.5 mg NETA (N=257)
Domain	**Actual visit**	**Mean (SD)**	**Mean (SD)**
Somatic symptoms (Norm value: 0.38) (Relevant change: 0.06)			
Baseline		0.373 (0.23)	0.385 (0.25)
Change from baseline	Week 12	-0.088 (0.219) #	-0.096 (0.192) #
	Week 24	-0.084 (0.225) #	-0.090 (0.208) #
	Week 48	-0.110 (0.221) #	-0.102 (0.219) #
Depressed mood (Norm value: 0.30) (Relevant change: 0.05)			
Baseline		0.222 (0.227)	0.225 (0.239)
Change from baseline	Week 12	-0.068 (0.212) #	-0.083 (0.212) #
	Week 24	-0.092 (0.207) #	-0.082 (0.213) #
	Week 48	-0.078 (0.201) #	-0.087 (0.233) #
Memory/concentration (Norm value: 0.37) (Relevant change: 0.10)			
Baseline		0.459 (0.381)	0.436 (0.391)
Change from baseline	Week 12	-0.140 (0.334) #	-0.136 (0.316) #
	Week 24	-0.132 (0.341) #	-0.140 (0.317) #
	Week 48	-0.110 (0.346) #	-0.170 (0.348) # *
Anxiety/fears (Norm value: 0.30) (Relevant change: 0.06)			
Baseline		0.234 (0.264)	0.214 (0.271)
Change from baseline	Week 12	-0.087 (0.240)#	-0.056 (0.228)
	Week 24	-0.088 (0.211)#	-0.055 (0.205)
	Week 48	-0.079 (0.243)#	-0.053 (0.226)
Sexual function (Norm value: 0.44) (Relevant change: 0.18)			
Baseline		0.405 (0.382)	0.416 (0.365)
Change from baseline	Week 12	-0.145 (0.361)	-0.138 (0.312)
	Week 24	-0.176 (0.340)	-0.156 (0.312)
	Week 48	-0.199 (0.343) #	-0.153 (0.316)
Vasomotor symptoms (Norm value: 0.47) (Relevant change: 0.20)			
Baseline		0.857 (0.305)	0.835 (0.330)
Change from baseline	Week 12	-0.515 (0.453) #	-0.693 (0.407) # *
	Week 24	-0.575 (0.459) #	-0.697 (0.421) # *
	Week 48	-0.589 (0.443) #	-0.697 (0.412) # *
Sleep problems (Norm value: 0.46) (Relevant change: 0.12)			
Baseline		0.562 (0.346)	0.535 (0.327)
Change from baseline	Week 12	-0.137 (0.316) #	-0.219 (0.333) #
	Week 24	-0.186 (0.356) #	-0.212 (0.351) #
	Week 48	-0.589 (0.443) #	-0.697 (0.412) #
Menstrual symptoms (Norm value: 0.25) (Relevant change: 0.08)			
Baseline		0.195 (0.230)	0.211 (0.261)
Change from baseline	Week 12	-0.005 (0.232)	-0.006 (0.272)
	Week 24	-0.050 (0.232)	-0.046 (0.268)
	Week 48	-0.062 (0.223)	-0.057 (0.263)
Attractiveness (Norm value: 0.58) (Relevant change: 0.07)			
Baseline		0.382 (0.378)	0.389 (0.359)
Change from baseline	Week 12	-0.011 (0.343)	0.034 (0.361)
	Week 24	-0.043 (0.293)	0.039 (0.350)
	Week 48	-0.051 (0.336)	0.023 (0.358)

Norm. value = Normative value of post-menopausal women
Relevant change = Difference in normative value between post- and pre-menopausal women
Clinically relevant change from baseline
* p-value < 0.05 between treatment groups in favour of E_2/NETA assessed by two-sided Wilcoxon rank sum test stratified by center for treatment differences on change from baseline.

Table 2. Results of the McNemar test on local urogenital complaints (symptoms versus no symptoms) for changes from baseline within groups at week 48

	Baseline				Week 48					
	Tibolone (N=237)		E_2/NETA (N=253)		Tibolone (N=229)			E_2/NETA (N=210)		
	n	%	n	%	n	%		n	%	
dyspareunia	24	10.1	23	9.1	1	0.5	p<0.001	4	1.7	p<0.001
nocturia	22	9.3	21	8.3	5	2.4	p<0.001	7	3.0	p=0.021
frequency	19	8.0	33	13.0	8	3.8	p=0.057	10	4.3	p<0.001
urgency	16	6.8	22	8.7	7	3.3	p=0.039	6	2.6	p=0.002

Discussion

The TOTAL study is the first randomized controlled comparative study between tibolone and low dose continuous combined 17β-estradiol plus norethisterone acetate investigating the effects on sexual function, health related quality of life and urogenital complaints in healthy postmenopausal women. Both treatments had an added benefit to healthy postmenopausal women treated for climacteric (mainly vasomotor) symptoms as both tibolone and E_2/NETA showed improvements in sexual function and urogenital complaints and a clinically relevant improvement in health related quality of life when compared to baseline.

Although women in our trial were not identified with sexual dysfunction per se, it seems reasonable, in view of the baseline answers reported at the WHQ and McCoy questionnaire, to assume that approximately half of them experienced mild to moderate sexual problems. Treatment with tibolone or E_2/NETA does not only improve sexual function, including sexual interest, an improved vaginal lubrication and a decrease in dyspareunia, but also several quality of life aspects which might indirectly influence sexuality such as improved sleep and mood as assessed by the WHQ. The total effect of treatment could thus be classified as an improvement in "sexual well-being".

Overall, tibolone had a more pronounced effect on sexuality than E_2/NETA and caused a statistically significant larger increase on the total score of the McCoy sexuality questionnaire and specifically on the sexual interest domain, when compared to low dose E_2/NETA. In addition, a clinically relevant improvement of the sexual behaviour domain of the WHQ (satisfaction with the sexual relationship) was seen in the tibolone treated women but not in the E_2/NETA group.

These findings are clinically relevant as a lack of sexual interest and a decreased satisfaction with the sexual relationship is a complaint, which is commonly reported by

postmenopausal women.[13] Moreover, the finding corresponds to findings from previous studies and might be contributed to the indirect effect of tibolone on androgen levels since these are reported to play a role in motivational aspects of sexuality.[1,6,14,15]

The effects of tibolone on sexual function have also been explored in two different subgroups: women with and without sexual problems at baseline as assessed by the WHQ sexual behaviour domain. It appears that the positive effect of tibolone on sexual function is more notable in the subgroup with sexual problems at baseline. Not sur-prisingly these subjects have lower McCoy total scores at baseline which also opens the possibly for more improvement and thus a larger treatment effect.

It is meanwhile known that no single endogenous hormone level corresponds to female sexual function.[16] We were unable to detect a relation between the improvement in sexual function assessed by the McCoy questionnaire and the circulating exogenous serum hormones as a result of treatment. As we used a valid approach to measure bio-T, employing sensitive non-commercial assays,[17] this negative finding confirms the current understanding that clinical outcome is difficult to predict from androgen blood levels, which probably do not reflect androgen action at the individual's tissue level. However, some of the recently published testosterone patch studies showed a relation between clinical outcome concerning sexual function and circulating testosterone.[18,19] So another reason for not being able to find a correlation might be that the measure of sexual function (McCoy questionnaire) is not sensitive enough to detect changes in sexual function which could be a result of hormonal fluctuations.

Various outcomes relating to health related quality of life (WHQ) showed a clinically relevant improvement in each of two treatment groups. For the domains such as "menstrual symptom" and "attractiveness" no clinically relevant improvement could be observed. This is probably due to the better (lower) baseline scores in these domains when compared to the norm values for postmenopausal women making it very hard if not impossible to find any improvement.

For similar reasons, it is likely that we did not find statistical improvements on some of the items of the urogenital complaint scale. Additional factors that might play a role are the small numbers of the women with symptoms and the skewness of the data.

A strength of this study is the relatively long follow up time as most HT comparative trials on efficacy and/or bleeding have a duration of 12 weeks.

A weakness of the trial is the lack of a placebo arm which ideally should have been included to measure the effect of HT and tibolone on quality of life and sexual function. However, for trial integrity reasons this was not possible as the trial would have been un-blinded by irregular vaginal bleeding in the active treatment arms. Another weakness is that the McCoy sexuality questionnaire may not be the most appropriate tool anymore to assess the treatment effect of HT on sexual function as the questionnaire does not cover the current definition and insights of female sexual dysfunction (FSD)[20] and addresses items which are not likely hormonal dependent such as sex with a partner and orgasm. Recently, Nappi et.al. published the first study in which women identified with FSD were treated with tibolone versus oral cc E_2/NETA.[21] In that trial both treatments increased clitoral circulation measured by Doppler ultrasonography and sexual function measured by the McCoy sexuality questionnaire the effect being significantly larger for

tibolone than for cc E_2/NETA. Interestingly, the mean baseline McCoy score in that trial were similar to those reported in our trial in spite that trial having included women with FSD, a population of which one would expect to correspond with lower baseline values at the McCoy sexuality questionnaire. Another weakness is that a partial placebo effect of both treatments on sexual function cannot be ruled out. However, at all follow up visits an increase from baseline of the McCoy questionnaire was seen which cannot be explained by a placebo effect only, as the trial duration was long enough to see a regression to the mean in case of a substantial placebo effect.

Conclusion: Tibolone and oral low dose E_2/NETA improve sexual well being by improving various aspects of sexual function and quality of life, the effect being more pronounced with tibolone when compared to low dose E_2/NETA.

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