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ORIGINAL STUDY

Hormone therapy as a possible solution for postmenopausal women with nocturia: results of a pilot trial

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Abstract

Objective: To observe the impact of different hormonal treatment options on nocturia, its causative factors and bother in postmenopausal women.

Methods: This prospective study recruited 245 postmenopausal women and divided them into four treatment groups based on patient's choice: Estrogen + Progesterone (E+P), Estrogen-only in patients with a prior hysterectomy, tissue-selective estrogen complex (TSEC) and no treatment. Nocturia and its causative factors were observed using two standardized questionnaires before and after treatment: the International Consultation on Incontinence Questionnaire Nocturia Module and the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO). The results of the Targeting the individual's Aetiology of Nocturia to Guide Outcomes were divided in four influencing topics of which the sum score was calculated.

Results: A significant reduction in prevalence of nocturia $\geq$ twice per night was seen after treatment, as the prevalence decreased from 27.7% (59/213) to 16.4% (35/213). Specified per therapy, a significant reduction in nocturnal voiding frequency was observed in patients treated with E+P and TSEC ($P = 0.018$ and $P = 0.018$, respectively). This improvement could be explained by a significant reduction in SLEEP sum score in patients treated with E+P and TSEC ($P < 0.001$, $P = 0.013$, respectively). Estrogen-only led to a significant change in URINARY TRACT sum score, which is the result of a reduction in urgency prevalence ($P = 0.039$).

Conclusions: E+P and TSEC treatment led to a significant reduction in nocturia prevalence and bother in women with $\geq$ 2 nocturnal voids. This effect is mainly the result of improvement in sleep disorders, however an improvement in bladder disorders can be suggested as well. More research is necessary to confirm these findings.

Key Words: Hormonal treatment – Menopause – Nocturia – Nocturnal frequency.

Video Summary: http://links.lww.com/MENO/A710.

Nocturia, waking to pass urine during the main sleeping period,[1] is a common problem in older women as it tends to increase after menopause.[2-5] In the global population, nocturia has a multifactorial etiology, but is mostly the result of nocturnal polyuria.[6,7] The lack of endogenous estrogen in this postmenopausal population can influence the onset of nocturia through bladder dysfunction,[4,8] sleep disorders[9] (Obstructive Sleep Apnea Syndrome (OSAS) and hot flushes (HF)), increased oral dryness (OD)[10] and alternations in renal water and salt handling[11,12] resulting in a higher diuresis overnight.

In this regard, administration of estrogen through hormonal therapy (HT) can possibly have a positive impact on different causative factors of nocturia and thus potentially reduce nocturnal frequency. Today, different options for menopausal HT are available. However, in postmenopausal women without

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prior hysterectomy, systemic estrogen treatment should always be combined with progesterone to reduce the risk of endometrial hyperplasia. In patients with an intolerance or contra-indication for progesterone, treatment with a tissue-selective estrogen complex (TSEC) can be a plausible treatment option.[13] A TSEC is a combination of a Selective Estrogen Receptor Modulator (SERM) and a conjugated estrogen. Due to this composition, this treatment has specific characteristics with an antagonistic effect on the endometrium. Its use in the treatment of postmenopausal symptoms (including HF, osteoporosis etc.) has proven to be safe and effective.[14,15]

The literature specifically assessing the effect of HT on nocturia is limited. A systematic review observing the effect of vaginal estrogen in postmenopausal women suggested weak strength and very low quality of evidence for the treatment of nocturia.[16] Kok et al found a significant improvement of nocturnal frequency after intake of an oral estrogen in combination with oral progesterone.[17] However, nothing is known about the effect of other hormonal combinations and the newer TSEC's on nocturia.

It has been demonstrated that HT improves the causative factors of postmenopausal nocturia, as it has an effect on the most prevalent postmenopausal sleep disorders; OSAS and HF.[18-21] Moreover, OD is reported to improve after HT treatment,[22] whereas the effect of systemic and vaginal HT on bladder dysfunction tend to differ. Vaginal estrogens are reported as the most effective treatment for genitourinary syndrome of menopause.[16] Systemic treatment however, is reported to have variable results on lower urinary tract symptoms (LUTS), as a Cochrane systematic review observed improvement of urgency and a worsening of incontinence.[23] Lastly, an increased concentration of antidiuretic hormone (ADH) was observed in postmenopausal women after intake of exogenous estrogen.[11] This higher concentration of ADH can result in reduced overnight diuresis. However, an opposite effect of progesterone stimulation on ADH release has been reported.[24]

The aim of this study was twofold:

1. To explore the prevalence and impact of nocturia among postmenopausal women.
2. To explore the effect of HT on the prevalence, bother and underlying pathophysiological triggers of nocturia.

METHODS

Design and participants

In this prospective observational trial, all participants were recruited (March 2018 to January 2020) at the department of Gynecology of the Ghent University Hospital. Postmenopausal state was biochemically confirmed (low estrogen, high follicle-stimulating hormone). All women were 'early' postmenopausal stages +1a,+1b or +1c as defined by the Stages of Reproductive Aging Workshop (STRAW) criteria.[25]

All women admitted for a routine check-up to the menopausal clinic and suffering from menopausal symptoms (HF, night sweats, vaginal atrophy, osteoporosis,. . .) were asked to participate in this research. Women were not questioned about their nocturnal voiding pattern at the time of study enrollment, as nocturnal frequency was not an inclusion criteria of this study. Participants with the following comorbidities were excluded: thyroid dysfunction, use of antihypertensive agents, history of psychiatric or neurological disorders, and a history of alcohol or drug abuse. Lastly, women with a history of stroke or breast cancer were excluded from this study, as these women are contra-indicated for systemic hormonal treatment.

All participants were counseled about the benefits and potential side effects of HT. Based on participant's choice, women were divided into four treatment groups:

- Estrogen in combination with progesterone (E + P)
- Estrogen-only in participants with a prior hysterectomy
- Tissue-selective estrogen complex (TSEC)
- No treatment (NT)

In participants without prior hysterectomy, progesterone was administered using oral tablets or a progesterone containing intrauterine device (IUD) to diminish the risk of endometrial hyperplasia.[13]

Measurements

Baseline characteristics of all participants, including date of birth, parity, caffeine consumption, and smoking habit were collected. Subsequently, self-reported height and weight were obtained to calculate BMI. Intake of anticholinergic drugs or a beta-3-mimetica was questioned.

All women were asked to complete two standardized questionnaires before initiation and after 6 months of treatment: the International Consultation on Incontinence Questionnaire Nocturia Module (ICIQ-N) and the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO). The ICIQ-N assesses nocturia by answering the following question: 'How many times on average do you have to get up at night to urinate?' Nocturia was defined as ≥ 2 nocturnal voids. Additionally, bother linked with nocturia was rated on a VAS-scale from 0 to 10, with '0' having no bother and '10' having high bother.

Subsequently, all women completed the TANGO screening tool to observe underlying risk factors for nocturia divided into four specific influencing topics: cardio-metabolic, sleep, urinary tract and patient wellbeing. The following questions were asked: CARDIO: presence of edema, presence of orthostatic hypotension, intake of diuretics and known diagnosis of diabetes; SLEEP: sleep duration $\leq$ 5 hours/night, self-reported sleep quality, difficulties initiating sleep 'It takes me longer than 30 minutes to fall asleep', difficulties maintaining sleep 'I have difficulty of staying asleep', sleep apnea signs 'I have been told I snore loudly or stop breathing at night'; URINARY TRACT: urgency, urge-incontinence and straining. In our analysis 'awakening in the first 3 hours of the night to void' was not included in the URINARY TRACT sum score, as this question not only reflects bladder dysfunction but can reflect a high fluid intake during the evening or an impaired secretion of ADH resulting in an increased water diuresis overnight.

Lastly questions were asked about participant wellbeing: self-reported health status, history of falls, daytime sleepiness and loss of anticipation and enjoyment. The sum score of each of the 4 TANGO domains was calculated using 'Method 3' designed and approved by Rose et al, with the higher the sum score the more influence of the domain on the development of nocturia.[26-28] The maximum value of each domain is 25, to generate a possible sum score out of 100. Lastly, the difference in sum scores before and after treatment was calculated.

Statistical analysis

Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY). Descriptive statistics are presented as median (interquartile range) Chi-square tests were used for comparisons between bladder parameters (incontinence, urgency and nocturia) of each treatment group at baseline. Comparisons between nocturnal frequency and sleep disorders at baseline and after treatment were performed using the nonparametric Wilcoxon signed rank test. The McNemar test was used to observe differences in the specific questions of the TANGO between the situation before and after treatment. A univariate and multivariate linear regression analysis with the difference in nocturnal frequency as a dependent variable was done to observe the impact of each TANGO topic. A P value < 0.05 was considered statistically significant.

This study was approved by the local ethical committee (EC 2018/0315). The Declaration of Helsinki was followed and conducted in accordance to the legal regulations in Belgium. Written informed consent was obtained from all included participants.

RESULTS

In total, 245 women with a median (IQR) age of 53 (51-57) years completed the questionnaires at both test moments. The median follow-up time was 6 (5-6) months. Treatment was initiated in 213 postmenopausal women; 32 women declined. Participants were divided among the four therapeutic options (Figure 1). Baseline characteristics were similar between the different treatment groups and are reported in Table 1. None of the participants used anticholinergics or beta-3-mimmetica at enrollment.

At baseline, the general nocturia prevalence among this cohort was 26.1% (64/245), with prevalences of reported nocturia of 24.8% (33/133) for women who opted for treatment with E + P; 29.8% (14/47) in women choosing estrogen-only; and 36.4% (12/33) in women treated with TSEC.

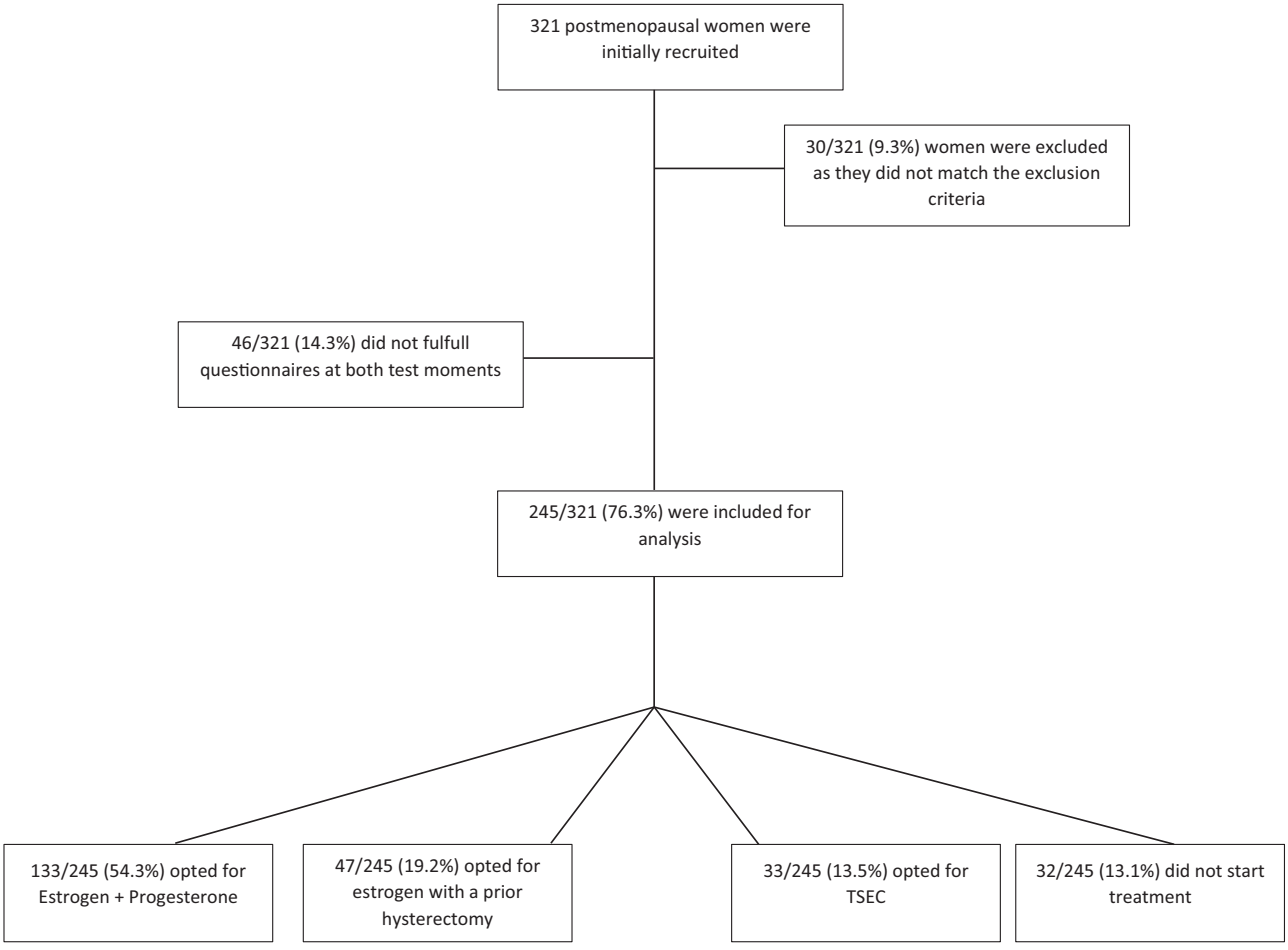

FIG. 1. Treatment allocation. TESC, tissue-selective estrogen complex.

TABLE 1. *Baseline characteristics*

	Oral estrogen + Oral progesterone $N=133$	Estrogen $N=47$	Tissue-selective estrogen complex $N=33$	No treatment $N=32$	Total $N=245$
Age (years; median (IQR))	52 (50-55)	54 (47-57)	55 (52-59)	54.5 (51.3-59.8)	53 (51-57)
Anthropometrics					
Height (cm)	165 (160-169)	165 (160-171)	165 (161-169)	164 (161-169)	165 (161-169)
Weight (kg)	66.0 (60.0-74.0)	66.5 (60.0-73.5)	64.5 (56.5-70.8)	66.3 (57.8-70.1)	66 (60-73)
BMI (kg/m^2)	24.2 (21.4-27.7)	23.8 (21.4-27.8)	23.4 (20.9-25.8)	24.4 (20.6-26.8)	23.9 (21.4-27.4)
Clinical History					
Parity (children)	2 (1-2)	2 (1-3)	1 (0.5-2)	2 (1-2)	2 (1-2)
Comorbidities–CARDIO items					
Lower leg edema (%)	21.8% (29/133)	31.9% (15/47)	24.2% (8/33)	9.4% (3/32)	22.4% (55/245)
Orthostatic hypotension (%)	20.3% (27/133)	25.5% (12/47)	21.2% (7/33)	12.5% (4/32)	20.4% (50/245)
Impaired glucose tolerance (%)	3.0% (4/133)	6.4% (3/47)	3.1% (1/33)	0% (0/33)	3.3% (8/244)
Intake of diuretics (%)	0.8% (1/133)	0% (0/47)	0% (0/33)	3.1% (1/32)	0.8% (2/245)
Lifestyle Factors					
Caffeine consumption (units; median (IQR))	3 (2-4)	2 (2-4)	2 (2-5)	3 (2-5)	3 (2-4)
Currently smoking (%)	14.3% (19/143)	12.8% (6/47)	18.8% (6/33)	18.8% (6/32)	15.1% (37/245)
Bladder parameters					
Nocturia ($\geq$ 2 nocturnal voids) (%)	24.8% (33/133)	29.8% (14/47)	36.4% (12/33)	15.6% (5/32)	26.1% (64/245)
Urgency (%)	19.5% (26/133)	36.2% (17/47)	24.2% (8/32)	12.5% (4/32)	22.4% (55/245)
Incontinence (%)	12.0% (16/133)	17% (8/47)	12.1% (4/33)	15.6% (5/32)	13.5% (33/245)

IQR, interquartile range.

Baseline urgency and incontinence are reported in Table 1. No significant differences among baseline bladder disorders were reported between the different treatment groups (nocturia, $P=0.2$; urgency, $P=0.055$; incontinence, $P=0.8$).

Impact of HT on nocturia prevalence

A significant reduction in nocturia prevalence was seen after 6 months of HT, as the ratio of women reporting $\geq$ 2 nocturnal voids decreased from 27.7% (59/213) to 16.4% (35/213; $P<0.001$). Moreover, a significant higher percentage of women reported either 1 nocturnal void or no nocturnal voids after treatment (one void: baseline 45.1% [96/213], after treatment 51.2% [109/213] $P<0.001$; no nocturnal voids: baseline 27.2% [58/213], after treatment 32.4% [69/213] [$P<0.001$]). At baseline 96 (45%) women who opted for therapy, reported one nocturnal void. In 67.7% (65/96) of those women, 6 months of HT did not change nocturnal frequency and in 8.3% (8/96) an increase of nocturnal frequency to 2 voids/night was seen. Lastly, 23 women (24%) with one nocturnal void at baseline experienced a decline to no nocturnal voids after treatment ($P<0.001$).

When looking at the effect of each separate treatment option, a significant reduction in nocturnal frequency could be observed in participants treated with E + P and in participants treated with TSEC ($P=0.018$ and $P=0.018$, respectively). In the E + P group, the prevalence of nocturia improved from 24.8% (33/133) at baseline to 12.8% (17/133) after treatment leading to a higher amount of women reporting one nocturnal void (baseline 43.6% [58/133]; after treatment 54.1% [72/133]). Equal observations were reported in the TSEC group. Among participants treated with estrogen alone, no general change in nocturnal frequency could be witnessed ($P=0.108$). However, participants presenting with nocturia at baseline and treated with estrogen alone, reported a significant improvement in nocturnal frequency, as the prevalence of nocturia decreased from 24.8% (14/47) to 21.3% (10/47) ($P=0.03$). Participants without treatment did not experience any change in nocturnal frequency (Figure 2).

Impact on causative factors of nocturia

A significant reduction in SLEEP sum score was seen among all treatment groups. Estrogen-only treatment was the only treatment leading to a significant reduction of the URINARY TRACT sum score, which can be explained by a significant improvement in urgency prevalence after treatment (baseline 36.2% [17/47], after treatment 19.1% [9/47], $P=0.039$; Table 2). Subsequently, this analysis was repeated in the population with $\geq$ 2 nocturnal voids at baseline. In women treated with E + P and TSEC a significant reduction in SLEEP items was observed ($P<0.001$, $P=0.013$ respectively), but no impact on the SLEEP item was witnessed in women treated with estrogen-only ($P=0.1$). Moreover, no significant change in URINARY TRACT score could be observed in women reporting two nocturnal voids at baseline (Figure 3).

When this analysis was performed in the general population with nocturia, that is, without stratification per therapy, a significant improvement of SLEEP sum score was observed, decreasing the score from 8.5 (5.1-11.5) to 5 (0.0-8.4) ($P<0.001$). Wellbeing improved after treatment (baseline: 7 [0.0-12.0], after treatment: 0.0 [0.0-5.0] $P<0.001$), but no changes in CARDIO sum score (baseline: 0 [0-4.5], after treatment 0.0 [0.0-3.5] $P=0.14$) and URINARY TRACT sum score were observed (baseline 4.2 [0-10], after treatment 0 [0.0-10]; $P=0.3$).

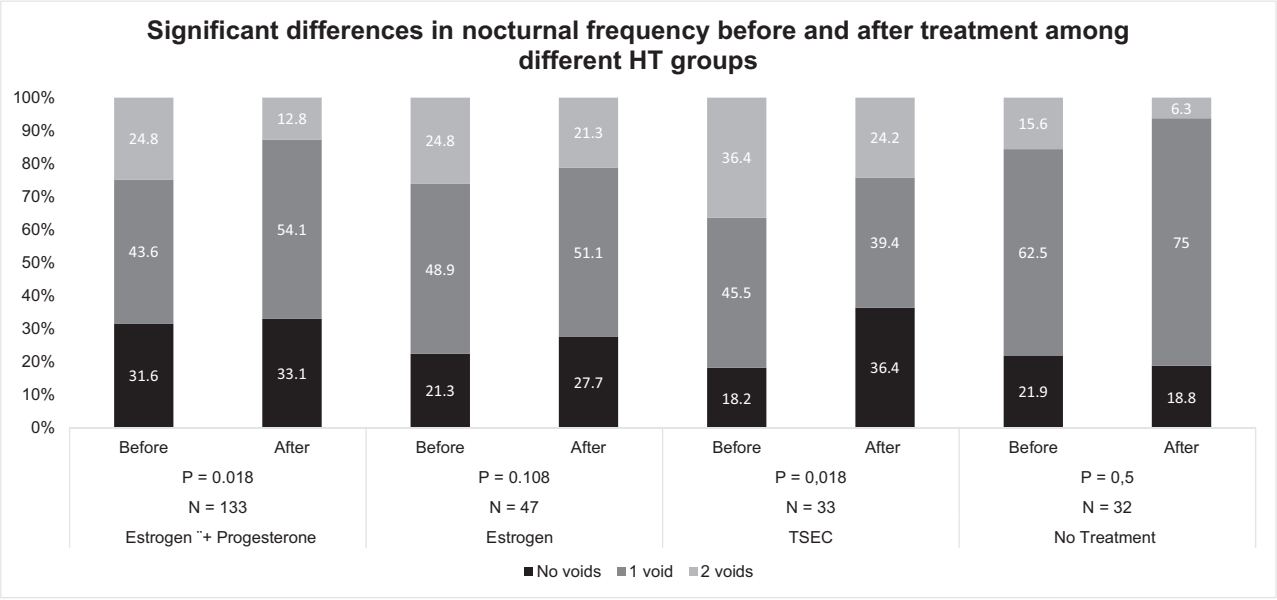

FIG. 2. Nocturnal frequency before and after treatment among different hormonal treatment groups. Each bar represents the ratio of participants within the treatment group reporting no, one or two nocturnal voids. Comparisons between situation at baseline and 6 months after treatment were made using Wilcoxon-signed-rank test. A *P*-value < 0.05 was considered statistically significant. TSEC, tissue-selective estrogen complex.

TABLE 2. *Overview of significant differences in TANGO items before and after treatment*

	Estrogen + progesteron $N = 133$			Estrogen-only $N = 47$			TSEC $N = 33$			No treatment $N = 32$		
	Baseline	After treatment	*P* value[a]	Baseline	After treatment	*P* value[a]	Baseline	After treatment	*P* value[a]	Baseline	After Treatment	*P* value[a]
CARDIO	0 (0-4)	0 (0-3.5)	0.051	3.5 (0-5.5)	0 (0-3.5)	**0.009**	0 (0-5)	0 (0-3.5)	0.113	0 (0-0)	0 (0-0)	0.9
SLEEP	5.5 (0.8-11.5)	0 (0-5)	**< 0.001**	9.5 (5.0-11.5)	5.0 (0-8.5)	**< 0.001**	10.0 (4.8-12.8)	4.5 (0.0-8.5)	**< 0.001**	4.8 (0.0-8.4)	3.0 (0.0-5.0)	0.1
URINARY TRACT	0 (0-9)	0.0 (0.0-0.0)	0.6	0 (0.0-10)	0.0 (0.0-9.0)	**0.02**	0 (0.0-9.5)	0.0 (0.0-9.5)	0.3	0.0 (0.0-0.0)	0.0 (0.0-7.0)	0.4
WELLBEING	0.0 (0.0-12.0)	0.0 (0.0-0.0)	**< 0.001**	3.5 (0.0-12.0)	0.0 (0.0-5.00)	**< 0.001**	0.0 (0.0-12.0)	0.0 (0.0-5.0)	**0.022**	0.0 (0.0-5.2)	0.0 (0.0-5.0)	0.4

Median (ICQ) of each separate item. Comparisons between situation at baseline and 6 months after treatment were made using Wilcoxon-signed-rank test. TSEC, tissue-selective estrogen complex.
[a]A *P* value < 0.05 was considered statistically significant and highlighted in bold.

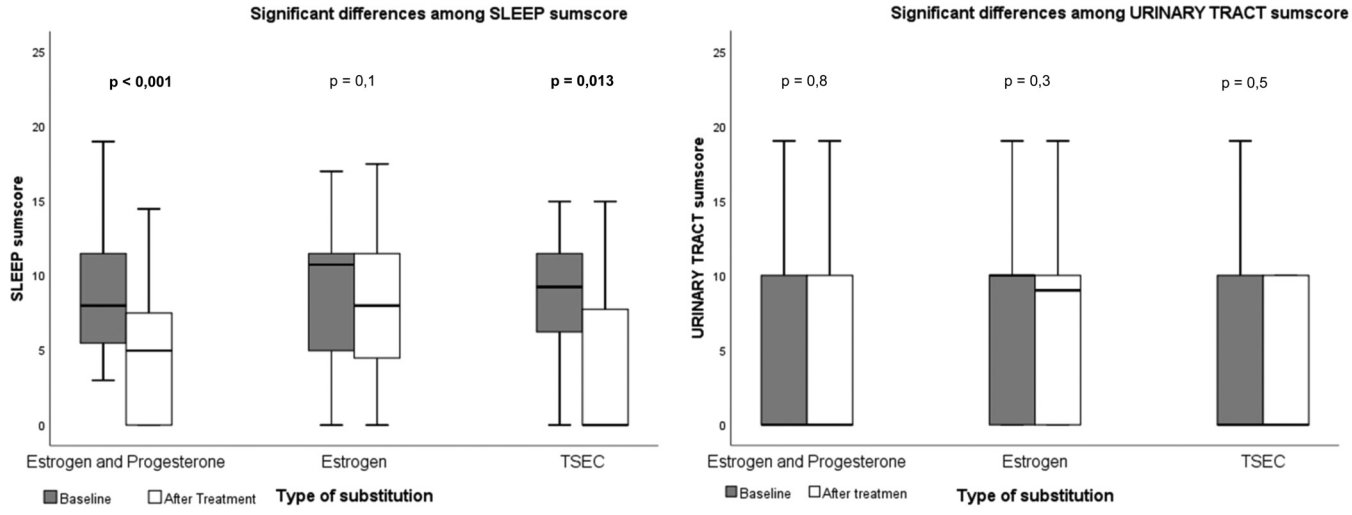

FIG. 3. SLEEP and URINARY TRACT sum score in participants with nocturia at baseline among different treatment groups. Estrogen and Progesterone N = 33, Estrogen-only N = 14 and TSEC N = 12. Comparisons between situation at baseline and 6 months for each treatment group was made using Wilcoxon-signed-rank test. A *P* value of < 0.05 was considered statistically significant and was highlighted in bold. TSEC, tissue-selective estrogen complex.

TABLE 3. *Impact of HT on SLEEP, URINARY TRACT and WELLBEING items assessed using the TANGO*

	1 nocturnal void at baseline $N=96$			≥ 2 nocturnal voids at baseline $N=59$		
	Baseline	After treatment	P value[a]	Baseline	After treatment	P value[a]
SLEEP item						
Bad sleep quality	54.2% (52/96)	22.9% (22/96)	**< 0.001**	55.9% (33/59)	27.1% (16/59)	**0.006**
Sleeping $\leq$ 5 h/night	30.2% (29/96)	17.7% (17/96)	**0.012**	27.1% (16/59)	10.2% (6/59)	**< 0.001**
Onset insomnia	40.6% (39/96)	13.5% (13/96)	**< 0.001**	52.5% (31/59)	25.4% (15/59)	**< 0.001**
Secondary insomnia	19.8% (19/96)	18.8% (18/96)	1	37.3% (22/59)	33.9% (20/59)	0.6
Sleep apnoea signs	24.0% (23/96)	19.8% (19/96)	0.5	32.2% (19/59)	16.9% (10/59)	**0.004**
URINARY TRACT item						
Urgency	25.0% (24/96)	15.6% (15/96)	0.061	40.6% (26/64)	32.8% (21/64)	**0.3**
Incontinence	13.5% (13/96)	10.4% (10/96)	0.4	20.3% (13/64)	21.9% (14/64)	**0.7**
Straining	6.3% (6/96)	2.1% (2/96)	0.2	4.7% (3/64)	4.7% (3/64)	**1**
WELLBEING ITEM						
Self reported sleep quality 'bad'	13.5% (13/96)	4.2% (4/96)	0.1	16.9% (10/59)	10.2% (6/59)	**0.046**
History of falls	10.4% (10/96)	7.3% (7/96)	0.8	5.1% (3/59)	6.8% (4/59)	0.7
Daytime sleepiness	12.5% (12/96)	4.2% (4/96)	**0.03**	11.9% (7/59)	8.5% (55/59)	0.5
Los of anticipation and enyoment	32.3% (31/96)	17.7% (17/96)	**0.011**	49.2% (29/59)	20.3% (12/59)	**< 0.001**

Comparisons between situation at baseline and 6 months after treatment were made using McNemar test.
HT, hormone therapy; TANGO, Targeting the individual's Aetiology of Nocturia to Guide Outcomes.
[a]A P value < 0.05 was considered statistically significant and highlighted in bold.

In participants with one nocturnal frequency at baseline an improvement in all 4 TANGO sum scores was observed (CARDIO: baseline 0.0 [0.0-5.5], after treatment 0.0 [0.0-3.5], $P = 0.023$; SLEEP: baseline 8.0 [3.0-12.0], after treatment 4.5 [0.0-6.0], $P < 0.001$; URINARY TRACT: baseline 0.0 [0.0-9.8], after treatment 0.0 [0.0-0.0], $P = 0.03$; WELLBEING: baseline 0.0 [0.0-12.0], after treatment 0.0 [0.0-5.0], $P < 0.001$).

The improvement in SLEEP sum score is the result of a significant improvement in sleep quality, sleep duration and insomnia for women with one ($P < 0.001$, $P = 0.012$, $P < 0.001$, respectively) and two nocturnal voids at baseline ($P = 0.006$, $P < 0.001$, and $P < 0.001$, respectively). Moreover, the presence of symptoms suggestive of sleep apnea decreased significantly in participants with two nocturnal voids ($P = 0.004$) (Table 3). The statement 'I have to wake in the first 3 hours of the night to void' was not included in the URINARY TRACT issue, however women with nocturia at baseline reported a significant improvement of early night-time awakening as the prevalence decreased from 67.2% (43/64) to 40.6% (26/64) ($P < 0.001$). In women with one nocturnal void at baseline, a trend towards improvement was observed (baseline 21.9% [21/96], after treatment 14.6% [21/96]; $P = 0.052$).

Subsequently, an uni- and multivariate regression analysis was performed in the general population, using the change in nocturnal frequency as a dependent variable. This analysis reported a significant higher reduction in nocturnal frequency linked with improvement of both SLEEP and URINARY TRACT items after adjusting for CARDIO and WELLBEING items (Table 4).

Impact on bother linked with nocturia

Firstly, bother linked with nocturia was analyzed in the total therapeutic group without specifying the HT method. Participants with nocturia at baseline reported a significant reduction of bother (baseline 5 [2-7]; after treatment 2 [0-4], $P < 0.001$). Equal observations were made in women with one nocturnal void (baseline (2 [0-5] to 0 [0-2], $P < 0.001$). Women without nocturnal voids at baseline where not bothered. Subsequently, impact of HT on bother was analyzed per treatment group. A significant improvement in attributable bother was seen in females suffering from nocturia at baseline and treated with E + P. In participants treated with estrogen alone and with TSEC no statistically significant change in bother scores were observed, although the bother scores tended to improve (Figure 4).

DISCUSSION

This pilot study demonstrated a significant reduction in nocturia and its associated bother when different HT options

TABLE 4. *Univariate and multivariate linear regression analysis with difference in nocturnal frequency between baseline measurements and the measurement after 6 months as dependent variable*

	Univariate			Multivariate		
TANGO item	B	95% CI around B	P value[a]	B	95% CI around B	P value[a]
Change in CARDIO between 0 and 6 mo	0.014	−0.022 to 0.042	0.5	0.014	−0.031 to 0.038	0.8
Change in SLEEP between 0 and 6 mo	0.031	0.014 to 0.048	**<0.001**	0.176	0.005 to 0.044	**0.014**
Change in URINARY TRACT between 0 and 6 mo	0.018	0.003 to 0.033	**0.02**	0.175	0.005 to 0.039	**0.01**
Change in WELLBEING between 0 and 6 mo	0.007	−0.00 to 0.016	0.6	−0.007	−0.017 to 0.011	0.7

The multivariate regression analysis has been adjusted for age and BMI.
BMI, body mass index; TANGO, Targeting the individual's Aetiology of Nocturia to Guideline Outcomes.
[a]A P value of < 0.05 was considered statistically significant and is highlighted in bold.

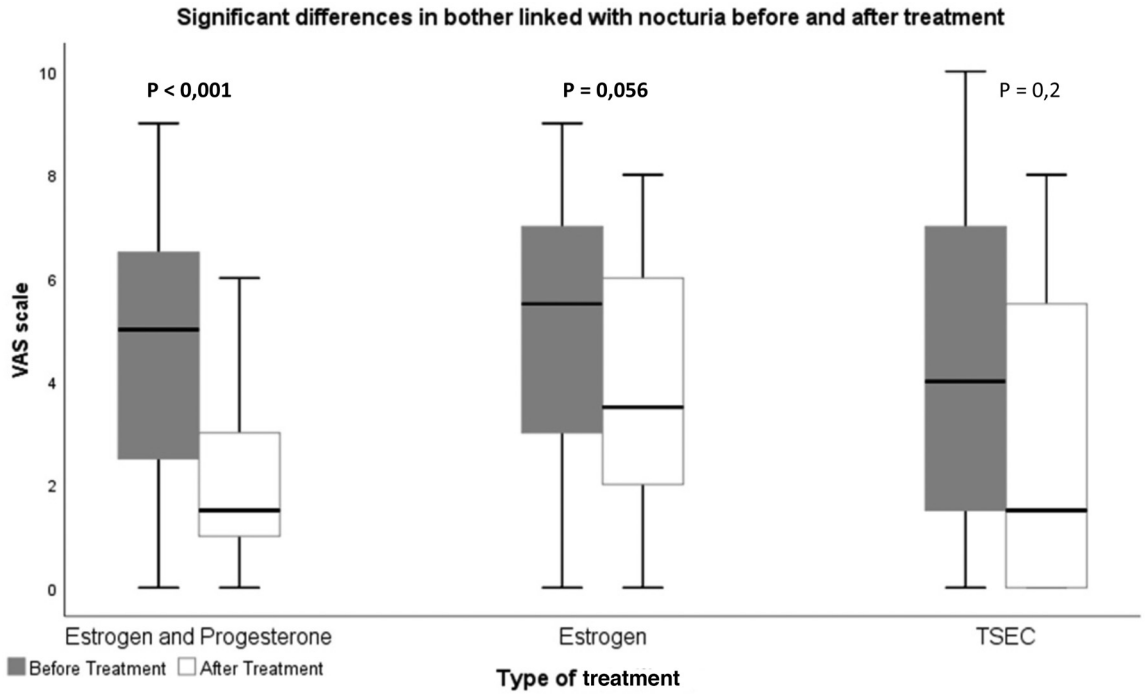

FIG. 4. Bother linked with nocturia among different treatment groups. Comparisons between situation at baseline and 6 months for each treatment group was made using Wilcoxon-signed-rank test. A P value of < 0.05 was considered statistically significant and was highlighted in bold. TSEC, tissue-selective estrogen complex.

were given for 6 months. This finding may relate to a significant improvement in sleep quality.

Initiation of HT resulted in a significant reduction of nocturia, with a higher amount of participants reporting one or no nocturnal voids after treatment. Analysis per treatment option indicated, improvement in participants treated with E + P and women treated with TSEC. The effect of E + P treatment was previously described by Kok et al as they observed a disappearance of nocturia in 65.4% of women who initially presented with nocturia.[17] Long et al[29] observed a significant reduction of nocturnal frequency after treatment with both oral and vaginal estrogen in hysterectomized postmenopausal women. Our analysis could not demonstrate a significant difference in nocturnal frequency for this type of treatment. However, a significant reduction in participants reporting ≥ 2 nocturnal voids was observed. The literature offers no comparison for TSEC treatment

Despite the variable effect on nocturnal frequency, a clear impact on bother linked with nocturia was observed in participants treated with E + P and estrogen alone. This finding is of utmost importance as this bother not only reflects the problem of getting up during the night, but also refers to the general quality of life and well-being of the patient.[30,31] Previously, it has been found that nighttime LUTS were more bothersome than daytime LUTS,[32] which can be explained by compromised sleep.[32,33]

The decrease in nocturnal frequency and the improvement of bother can mostly likely be explained by the positive impact of HT on sleep, as the SLEEP sum score decreased significantly after treatment with both E + P and TSEC. Moreover, univariate regression analysis showed a reduction in mean change in nocturnal frequency between both test moments by 0.017, whereas the change in SLEEP sum score improved by 1 point. Although it was not specifically investigated, these results may reflect change in HF, as perspiration and sweating during the night disturbs sleep. In a Cochrane meta-analysis MacLennan et al[19] observed a decreased prevalence and a 75% reduction of HF intensity after treatment with HT. Specific improvement of HF, insomnia or sleep quality due to HT has never been assessed in postmenopausal women with nocturia. Neither was this analysis done in postmenopausal women suffering from both nocturia and OSAS. However, a lower odds on OSAS was reported after HT.[19,20]

In this analysis, the causative factor URINARY TRACT was only affected in women with one nocturnal void at baseline, who are treated with estrogen-only, as daytime urgency improved significantly. No improvement concerning straining, urgency-incontinence or urgency was observed in other treatment groups. These observations are in line with reports of different effects of systemic HT on LUTS. In their meta-analysis Cody et al found a worsening of urge-incontinence and an improvement of urgency,[23] whereas other epidemiological studies reported an increased risk on developing urgency in women treated with systemic HT.[34,35] However, uni- and multivariate analysis showed a significant improvement of nocturnal frequency with each point of improvement of the URINARY TRACT item, which is demonstrated by improvement of urgency in one specific subgroup. For this reason, we hypothesize that the

improvement of nocturia and its bother is mainly explained by the improvement of SLEEP sum score, rather than the minimal change in the URINARY TRACT sum score.

A significant improvement on the statement 'I have to wake up during the first three hours of the night to void' was seen in women with nocturia at baseline. Since this finding also reflects evening fluid intake and renal fluid handling, a positive effect of HT on OD or renal fluid handling can be suggested but not confirmed. These hypotheses should be tested in further research including frequency volume charts and renal function profiles, as these tools quantify both bladder and kidney function.

To our knowledge, this study is the first to assess the relation between different menopausal HT options and nocturia. The findings of this study are important, as both the reduction of nocturia and the associated bother have implications on women's health and quality of life. This study supports a hypothesis to test in a future randomized study, namely that different systemic and vaginal estrogens will be more effective at reducing nocturia frequency than maintaining hormone depletion.

The limitation of this study is the lack of randomization since treatment allocation was based on participant choice. Moreover, treatment using vaginal estrogens was not included in this trial as prior research demonstrated only low systemic absorption of vaginal estrogens. We thought that for this reason vaginal estrogen would not influence ADH, leading to a suboptimal assessment of the effect on nocturia.[36] Selection bias may have occurred, as participants were recruited during a routine visit at a menopause clinic, and the cohort was potentially not a reflection of the general population of postmenopausal women. In addition, all participants included in this analysis were healthy women without comorbidities and not using medication. However, no information about earlier bladder or sling surgery was questioned. Lastly, the determination of nocturia was based on validated questionnaires rather than on voiding dairies or frequency volume charts. The accuracy of self-reporting nocturia and the participants interpretation of nocturia cannot be confirmed.

CONCLUSION

Treatment of postmenopausal women with systemic HT led to a significant reduction in nocturia prevalence and a significant improvement of bother in women with $\geq$ 2 nocturnal voids. This reduction in nocturia prevalence was observed in participants treated with E + P and TSEC. This effect can mainly be explained by an improvement in sleep quality. Improvement of bladder dysfunction may relate to reduced urgency but requires further investigation. Future work should involve data from frequency volume charts and renal function profiles.

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