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Improvement in sleep outcomes with a 17β-estradiol–progesterone oral capsule (TX-001HR) for postmenopausal women

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Abstract

Objective: The aim of the study was to evaluate the effects of TX-001HR, a single-capsule 17β-estradiol–progesterone on sleep parameters in postmenopausal women with vasomotor symptoms (VMS) using the Medical Outcomes Study (MOS)-Sleep scale questionnaire in the REPLENISH trial.

Methods: In the REPLENISH trial (NCT01942668), women were randomized to one of four doses of TX-001HR or placebo, and the 12-item MOS-Sleep questionnaire (secondary endpoint) was self-administered at baseline, week 12, and months 6 and 12. Changes from baseline in the MOS-Sleep total score and 7 subscale scores were analyzed for treatment groups versus placebo at all time points. Somnolence was also collected as an adverse event.

Results: Women (mean age 55 y) were randomized to TX-001HR (estradiol/ progesterone [E2/P4] [mg/mg]) doses: 1/100 ($n = 415$), 0.5/100 ($n = 424$), 0.5/50 ($n = 421$), 0.25/50 ($n = 424$), or placebo ($n = 151$). TX-001HR significantly improved MOS-Sleep total score, Sleep Problems Index II subscale, and sleep disturbance subscale versus placebo at all time points, except with 0.25 mg E2/50 mg P4 at week 12. Differences in LS mean changes between TX-001HR and placebo for MOS-Sleep total scores ranged from −6.5 to −7.6 at 12 months (all; $P \leq 0.001$). All doses of TX-001HR significantly improved the Sleep Problems Index I subscale at all time points. The sleep somnolence subscale significantly improved from baseline with 0.5 mg E2/100 mg P4 and 0.5 mg E2/50 mg P4 at month 12. The incidence of somnolence as a treatment-emergent adverse event ranged from 0.2% to 1.2% versus 0% with placebo.

Conclusion: TX-001HR significantly improved MOS-Sleep parameters from baseline to week 12, which was sustained for up to 12 months, and was associated with a very low incidence of somnolence.

Key Words: Estradiol – Hot flushes – Menopause – Progesterone – Sleep – Vasomotor symptoms.

Sleep disruption represents a symptom of menopause,[1] with postmenopausal women often reporting difficulties initiating and/or maintaining sleep with frequent nocturnal and early morning awakenings.[2] Vasomotor symptoms (VMS), which are often a hallmark of menopause, have been identified as a major risk factor for sleep disruption among postmenopausal women.[3,4] Declining estrogen levels may also be a contributing factor to sleep disruption in this population.[5]

Several studies over the last few decades have supported an association between VMS and sleep disruption.[4,6-10] The recent Midlife Women's Health study showed a significant negative impact of VMS on all sleep outcomes that were assessed.[4] In another study, which examined the effect of

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VMS intensity on insomnia and poor sleep quality in more than 6,000 women, sleep disturbances increased in parallel with increases in VMS intensity.[7] A smaller study specifically reported an association between hot flushes and poor sleep.[11] Chronic insomnia has been reported in approximately 50% to 55% of peri- and postmenopausal women versus approximately 35% of premenopausal women, with 81.3% of women with severe hot flushes experiencing symptoms of chronic insomnia.[6] Because VMS and associated symptoms, particularly sleep disruption, can lead to substantial physical and psychosocial impairment among postmenopausal women, addressing these symptoms is clinically important.[12]

TX-001HR (TherapeuticsMD, Boca Raton, FL) is a single, oral softgel capsule that contains hormones that are biologically identical to endogenous17β-estradiol (E2) and progesterone (P4).[13] This formulation was developed to treat moderate to severe VMS while protecting the endometrium from unopposed E2. Recently approved in October 2018, the 1 mg E2/100 mg P4 dose of TX-001HR (BijuvaTM) is the first FDA-approved, combined E2/P4 formulation for postmenopausal women, thereby providing these women with an alternative to combined hormone therapy (HT) using synthetic progestins or unapproved compounded E2/P4 formulations.[13] By treating VMS, TX-001HR could improve sleep quality and improve the related health status of symptomatic postmenopausal women.

In the REPLENISH study, TX-001HR provided significant improvements in frequency and severity of moderate to severe VMS at most time points from week 3 until week 12 with no endometrial hyperplasia (two highest doses meeting all coprimary endpoints).[13] Here, we present the results of a secondary outcome of the REPLENISH trial, which evaluated the effects of TX-001HR versus placebo on sleep parameters using the validated Medical Outcomes Study (MOS)-Sleep questionnaire.

METHODS

Study design

REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial conducted at 117 sites within the United States.[13] This trial assessed the incidence of endometrial hyperplasia at 12 months in all participants as its primary safety endpoint.[13] Changes in frequency and severity of VMS in women with moderate to severe hot flushes with TX-001HR versus placebo at weeks 4 and 12 were assessed using daily diaries as the coprimary efficacy endpoints.[13] The results for the primary safety and efficacy endpoints have been reported elsewhere.[13]

Women were randomized 1:1:1:1:1 to one of four oral doses of TX-001HR (1 mg E2/100 mg P4, 0.5 mg E2/100 mg P4, 0.5 mg E2/50 mg P4, or 0.25 mg E2/50 mg P4) or placebo for 12 months. To maintain study blinding, each dose was composed of two capsules because two different sizes were necessary to accommodate the different doses. The study was conducted in accordance with Good Clinical Practice guidelines of the FDA and the protocol was approved by an institutional review board.[13]

Participants

Healthy postmenopausal women with a uterus (40-65 y; BMI $\leq$34 kg/m^2; screening serum E2 level $\leq$50 pg/mL) seeking postmenopausal VMS treatment were eligible. Postmenopausal was defined as $\geq$12 months of spontaneous amenorrhea; at least 6 months of spontaneous amenorrhea with a screening serum FSH $>$ 40 mIU/mL; or $\geq$6 weeks after bilateral oophorectomy.

Women were excluded if they had contraindications or allergy to estrogens, progestins, or P4; a history of thromboembolic disorder, coronary artery or cerebrovascular disease, chronic kidney or liver disease, clotting disorder, estrogen-dependent neoplasia, diabetes, or other endocrine disease; malabsorption disorder, gallbladder dysfunction/disorders, endometrial hyperplasia, melanoma, or breast, uterine, or ovarian cancer; atypical ductal hyperplasia of the breast; undiagnosed vaginal bleeding; uterine fibroids diagnosed at screening; heavy smoking (15 cigarettes/d or greater), or a history of drug or alcohol abuse.

Women could not have used the following products within the stated duration before screening: vaginal nonsystemic hormonal products (rings, creams, tablets, gels) within 7 days; vaginal systemic products within 28 days; transdermal estrogen alone or estrogen/progestin products within 8 weeks; oral estrogen and/or progestin therapy and/or SERM within 8 weeks; progestational implants, estrogen or estrogen/progestational injectable drug therapy within 3 months; estrogen pellet therapy or progestational injectable drug therapy within 6 months; percutaneous estrogen lotions/gels within 8 weeks; and oral, topical, vaginal, patch, implantable or injectable androgen therapy within 8 weeks.

MOS-Sleep scale

The MOS-sleep questionnaire was administered at baseline, week 12, and months 6 and 12. The MOS-Sleep scale is a 12-item, self-reported questionnaire (Table 1) that addresses sleep initiation (time to fall asleep), sleep quantity (hours of sleep each night), sleep maintenance, respiratory problems, perceived sleep adequacy, and somnolence over the past 4 weeks.[14] Questions (except questions 1 and 2) are scored using a 6-point Likert scale ranging from ''All of the time'' to ''None of the time.'' Total scores for the 12-items can range from 12 to 71.[14] MOS-Sleep subscales are based on various combinations of the 12 questions as shown in Table 1; subscales included sleep disturbance, snoring, sleep shortness of breath or headache, sleep adequacy, sleep somnolence, Sleep Problems Index I (short form), and Sleep Problems Index II (long form) subscales. Subscale scores were linearly transformed to range from 0 to 100. The scoring method for each item and subscale was applied as reported by Spritzer and Hays.[15]

The effects of TX-001HR versus placebo on the outcomes of the validated MOS-Sleep questionnaire were analyzed in the modified intent-to-treat (MITT) population, defined as all participants who were randomized and took at least one dose (two capsules) of the investigational product, whereas the safety population included participants who were randomized

TABLE 1. *The Medical Outcomes Study (MOS)-Sleep Scale Questionnaire*[36]

Question no.	MOS questions	Subscales based on MOS questions						
		Sleep disturbance	Snoring	Sleep shortness of breath or headache	Sleep adequacy	Sleep somnolence	Sleep problems index I	Sleep problems Index II
1	How long did it usually take for you to fall asleep during the past 4 wk?	X						X
2	On average, how many hours did you sleep each night during the past 4 wk?							
How often during the past 4 wk did you…								
3	Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	X[a]						X[a]
4	Get enough sleep to feel rested upon waking in the morning?				X[a]		X	X
5	Awaken short of breath or with a headache?			X[a]			X[a]	X[a]
6	Feel drowsy or sleepy during the day?					X[a]		X[a]
7	Have trouble falling asleep?	X[a]					X[a]	X[a]
8	Awaken during your sleep time and have trouble falling asleep again?	X[a]					X[a]	X[a]
9	Have trouble staying awake during the day?					X[a]	X[a]	X[a]
10	Snore during your sleep?		X[a]					
11	Take naps (5 min or longer) during the day?					X[a]		
12	Get the amount of sleep you needed?				X[a]		X	X

[a]Scoring scale reversed when used for averaging.

and took at least one capsule of the investigational product. Change from baseline in total and subscale scores were assessed for each treatment compared with placebo at baseline, week 12, and months 6 and 12 for the MITT population using an ANCOVA model with treatment as factors and baseline as covariate. Results were statistically significant at $P < 0.05$.

RESULTS

Of a total of 1,845 women randomized to treatment, 1,835 women were included in the safety population and 1,833 were included in the MITT population. Demographics of the safety population are shown in Table 2. Mean age was 55 years and mean BMI was 27 kg/m^2; 65% of participants were white and 32% were African American.

Significant improvements ($P < 0.05$) were observed for the MOS-Sleep total score in the MITT population at week 12 with all doses, except for the lowest dose of 0.25 mg E2/50 mg P4. The MOS-Sleep total scores ranged from 43.2 to 48.1 at baseline and were 27.5 to 29.4 after TX-001HR and 37.4 with placebo at month 12 (Fig. 1A). Differences in LS mean changes between TX-001HR and placebo for MOS-Sleep

TABLE 2. *Participant demographics and baseline characteristics (safety population)*

Characteristic	Estradiol/Progesterone				Placebo
	1 mg/100 mg	0.5 mg/100 mg	0.5 mg/50 mg	0.25 mg/50 mg	
N	415	424	421	424	151
Age, y	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3
Race, *n* (%)					
White	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	100 (66.2)
African American	134 (32.3)	136 (32.1)	133 (31.6)	140 (33.0)	46 (30.5)
Other[a]	10 (2.4)	7 (1.6)	12 (2.8)	11 (2.6)	5 (3.3)
BMI, kg/m^2	26.8 ± 4.1	26.7 ± 4.3	26.7 ± 4.0	26.7 ± 4.0	26.6 ± 3.9
Time since menopause, y	5.8 ± 4.9	6.0 ± 5.1	5.7 ± 4.6	5.6 ± 4.9	6.0 ± 5.3
Baseline MOS-Sleep parameters					
Total	44.0 ± 18.7	43.2 ± 18.3	44.2 ± 19.0	45.4 ± 18.7	48.1 ± 19.0
Sleep Problems Index I	42.2 ± 18.6	41.3 ± 18.1	42.7 ± 19.0	44.2 ± 18.6	46.1 ± 18.6
Sleep Problems Index II	44.1 ± 18.8	43.1 ± 18.3	44.3 ± 19.0	45.4 ± 18.6	48.2 ± 19.0
Sleep Disturbance	48.8 ± 25.6	47.7 ± 24.9	48.7 ± 25.7	50.4 ± 24.8	53.5 ± 27.6
Sleep Somnolence	31.1 ± 22.0	30.9 ± 21.8	31.2 ± 20.6	32.6 ± 21.9	34.8 ± 21.5
Snoring	32.8 ± 31.1	38.7 ± 32.5	35.2 ± 31.9	34.6 ± 32.4	36.4 ± 32.7
Sleep adequacy	43.3 ± 24.8	44.1 ± 24.6	43.1 ± 24.4	41.1 ± 23.4	37.0 ± 23.7
Sleep Short of Breath or Headache	17.6 ± 25.6	17.1 ± 24.3	18.9 ± 27.8	17.9 ± 26.1	16.3 ± 25.6

Data shown as mean ± SD, unless stated otherwise.
BMI, body mass index; MOS, Medical Outcomes Study; SD, standard deviation.
[a]Other includes other ($n = 20$), Asian ($n = 12$), American Indian or Alaska Native ($n = 6$), Native Hawaiian or Pacific Islander ($n = 5$), and unknown ($n = 2$).

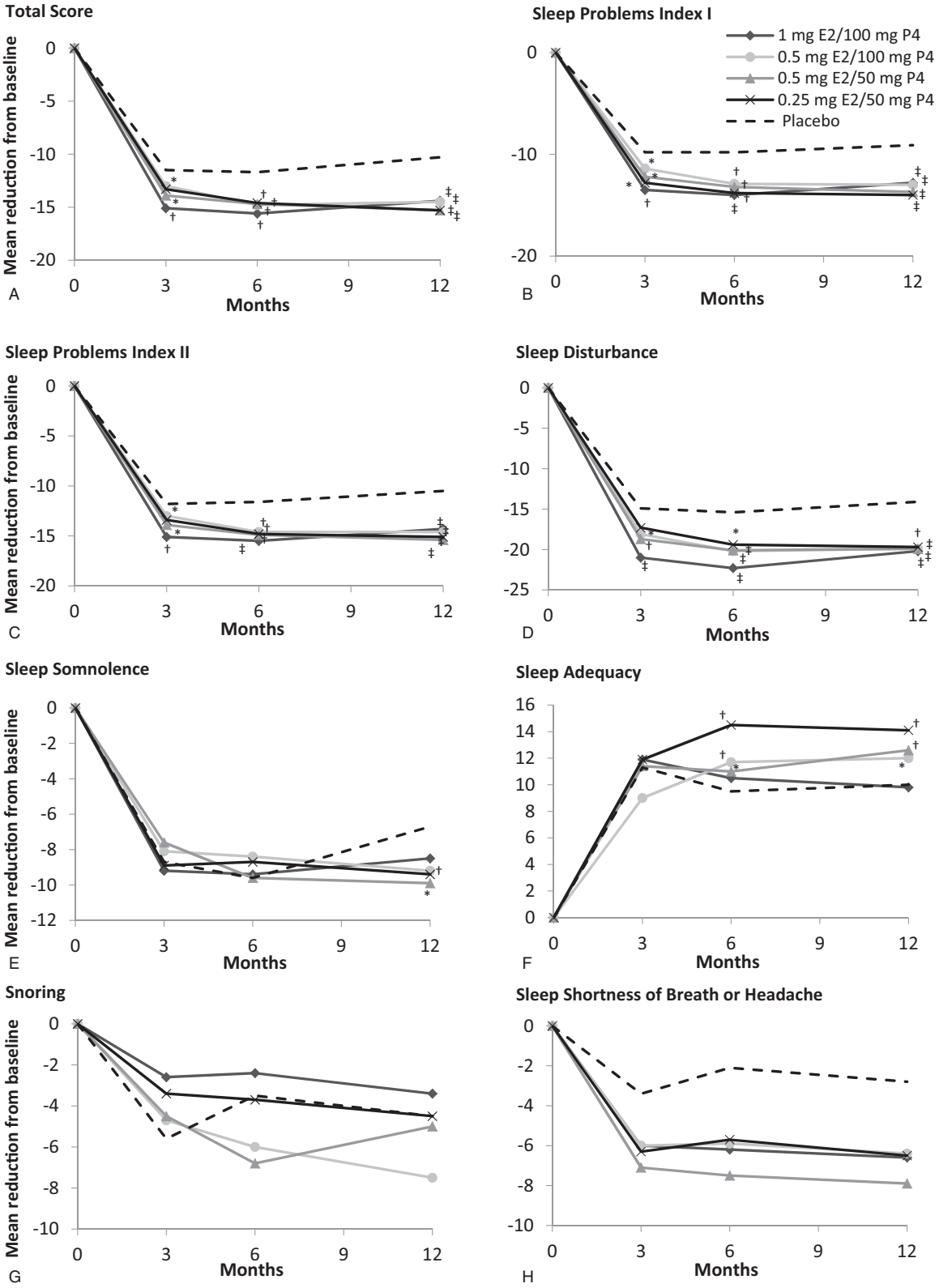

FIG. 1. Change from baseline at months 3, 6, and 12 with TX-001HR or placebo in (**A**) MOS-Sleep total score and MOS-Sleep subscales: (**B**) Sleep Problems Index I; (**C**) Sleep Problems Index II; (**D**) Sleep Disturbance; (**E**) Sleep Somnolence; (**F**) Sleep Adequacy; (**G**) Snoring; and (**H**) Sleep Shortness of Breath or Headache subscales. $^{*}P < 0.05$; $^{\dagger}P \leq 0.01$; $^{\ddagger}P \leq 0.001$ for TX-001HR versus placebo.

TABLE 3. *Differences in LS mean changes from baseline in MOS-Sleep parameters between TX-001HR and placebo in MITT population*

MOS-Sleep parameters	Estradiol/Progesterone			
	1 mg/100 mg	0.5 mg/100 mg	0.5 mg/50 mg	0.25 mg/50 mg
Total				
Week 12	-4.88 ± 1.6^{b}	-3.61 ± 1.6^{a}	-3.44 ± 1.6^{a}	-2.53 ± 1.6
Month 6	-5.39 ± 1.7^{b}	-5.39 ± 1.7^{b}	-4.88 ± 1.7^{b}	-4.42 ± 1.7^{b}
Month 12	-6.54 ± 1.9^{c}	-7.61 ± 1.8^{c}	-7.44 ± 1.8^{c}	-6.76 ± 1.9^{c}
Sleep Problems Index I				
Week 12	-4.92 ± 1.7^{b}	-3.79 ± 1.7^{a}	-3.28 ± 1.6^{a}	-3.41 ± 1.7^{a}
Month 6	-5.69 ± 1.7^{c}	-5.58 ± 1.7^{c}	-5.12 ± 1.7^{b}	-5.11 ± 1.7^{b}
Month 12	-6.01 ± 1.9^{c}	-7.22 ± 1.9^{c}	-6.92 ± 1.9^{c}	-6.42 ± 1.9^{c}
Sleep Problems Index II				
Week 12	-4.60 ± 1.6^{b}	-3.49 ± 1.6^{a}	-3.15 ± 1.6^{a}	-2.48 ± 1.6
Month 6	-5.44 ± 1.7^{c}	-5.53 ± 1.7^{c}	-5.12 ± 1.7^{b}	-4.64 ± 1.7^{b}
Month 12	-6.28 ± 1.8^{c}	-7.58 ± 1.8^{c}	-7.43 ± 1.8^{c}	-6.54 ± 1.9^{c}
Sleep Disturbance				
Week 12	-7.34 ± 2.1^{c}	-5.60 ± 2.1^{b}	-5.13 ± 2.1^{a}	-3.04 ± 2.1
Month 6	-8.38 ± 2.2^{c}	-7.52 ± 2.2^{c}	-7.32 ± 2.2^{c}	-5.60 ± 2.2^{a}
Month 12	-8.97 ± 2.4^{c}	-9.60 ± 2.4^{c}	-9.30 ± 2.4^{c}	-7.72 ± 2.4^{b}
Sleep Somnolence				
Week 12	-1.64 ± 1.7	-1.18 ± 1.7	0.14 ± 1.7	-0.68 ± 1.7
Month 6	-1.09 ± 1.9	-1.14 ± 1.9	-1.42 ± 1.9	-0.12 ± 1.9
Month 12	-3.36 ± 2.0	-5.34 ± 2.0^{b}	-4.94 ± 2.0^{a}	-3.88 ± 2.0
Sleep Adequacy				
Week 12	4.35 ± 2.5	2.61 ± 2.5	3.72 ± 2.5	3.48 ± 2.5
Month 6	5.11 ± 2.6	7.10 ± 2.6^{b}	5.90 ± 2.6^{a}	8.38 ± 2.6^{b}
Month 12	5.02 ± 2.9	7.56 ± 2.9^{b}	7.65 ± 2.9^{b}	7.89 ± 2.9^{b}
Snoring				
Week 12	2.02 ± 2.6	1.97 ± 2.6	1.50 ± 2.6	1.59 ± 2.6
Month 6	0.25 ± 2.7	-1.65 ± 2.7	-3.68 ± 2.7	-1.17 ± 2.7
Month 12	1.25 ± 2.9	-1.35 ± 2.8	-0.44 ± 2.8	-0.39 ± 2.9
Sleep Shortness of Breath or Headache				
Week 12	-0.44 ± 2.1	-0.64 ± 2.1	0.51 ± 2.0	$--0.46 \pm 2.0$
Month 6	-2.46 ± 2.2	-2.27 ± 2.1	-1.44 ± 2.1	-1.47 ± 2.2
Month 12	-1.96 ± 2.3	-2.43 ± 2.3	-1.51 ± 2.3	-1.68 ± 2.3

Data expressed as LS Mean ± SE.
LS, least square; MITT, modified intent-to-treat; SE, standard error.
[a] $P < 0.05$.
[b] $P \leq 0.01$.
[c] $P \leq 0.001$ vs placebo.

total scores ranged from −6.5 to −7.6 at 12 months (all; $P \leq 0.001$; Table 3). At months 6 and 12, MOS-Sleep total scores were also significantly improved in all active treatment groups compared with placebo ($P < 0.01$).

Compared with placebo, all doses of TX-001HR significantly improved the Sleep Problems Index I subscale from baseline at all time points (week 12, months 6 and 12; Fig. 1B). Similarly, TX-001HR also significantly improved the Sleep Problems Index II subscale from baseline at all time points versus placebo, except for the lowest dose (0.25 mg E2/50 mg P4) at week 12 (Fig. 1C).

The sleep disturbance subscale significantly improved from baseline with TX-001HR versus placebo across all time points, except for the lowest dose (0.25 mg E2/50 mg P4) group at week 12 (Fig. 1D). Sleep somnolence subscale significantly improved from baseline with the TX-001HR doses of 0.5 mg E2/100 mg P4 and 0.5 mg E2/50 mg P4 compared with placebo at month 12 (Fig. 1E). The sleep adequacy subscale also significantly improved with TX-001HR doses 0.5 mg E2/100 mg P4, 0.5 mg E2/50 mg P4, and 0.25 mg E2/50 mg P4 at 6 and 12 months (Fig. 1F). TX-001HR had no effects on the snoring and the sleep shortness of breath or headache subscales (Fig. 1G and H).

The incidence of self-reported somnolence as a treatment-emergent adverse event throughout the study was low, ranging from 0.2% to 1.2% of women in the TX-001HR groups compared with 0% in the placebo group for the safety population.

DISCUSSION

In the REPLENISH trial, TX-001HR consistently and significantly improved sleep parameters from baseline to week 12 and up to month 12 in postmenopausal women with VMS. These sleep parameters are characteristically impaired during menopause. Improvements with TX-001HR were observed using the MOS-Sleep scale, a validated and reliable scale covering multiple dimensions of sleep.[14] The MOS-Sleep scale is one of the most frequently used scales in clinical trials and is utilized in the assessment of multiple psychiatric and neurological conditions known to impact sleep.[16-19]

Improvements in the MOS-Sleep scale scores suggest that TX-001HR improves sleep quality based on its ability to reduce the frequency and severity of VMS, which was the primary endpoint of the REPLENISH trial. This association is consistent with a large body of literature that has observed a relationship between VMS and sleep disturbance.[7,10-12,20-22]

Most recently, Smith et al. found that the frequency of sleep disturbances and insomnia increased with increasing severity and frequency of VMS symptoms among women enrolled in the Midlife Women's Health Study.[4] As expected, the subscales measuring snoring and awakening with shortness of breath or with a headache were not significantly different from TX-001HR treatment as these phenomena are unlikely to be related to estrogen levels or VMS.

Sleep improvements with E2 were also reported in the 4-year KEEPS trial. Better sleep improvements were observed with the transdermal 50-μg E2 patch versus oral 0.45 mg conjugated equine estrogens (CEE), when both were taken with cyclic 200 mg P4.[23] For both treatments, Pittsburgh Sleep Quality Index global scores and sleep satisfaction and latency domains improved significantly from baseline when compared with placebo.[23] A significantly higher percentage of women with poor sleep quality at baseline had, however, improved sleep quality with E2 versus placebo, whereas percentages were similar with CEE versus placebo.[23] The sleep disturbance domain also significantly improved with E2 but not with CEE compared with placebo.[23] No changes in sleep efficiency, sleep duration, and daytime dysfunction were noted with either treatment.[23]

Changes in the MOS-Sleep scale may be clinically important for patients with neuropathic pain and fibromyalgia. In one study, an estimated minimal important difference or smallest relevant change in pain intensity corresponded to a 5.1-point change from baseline in the MOS-Sleep Problems Index II (scale 0-100), whereas a moderate change in pain corresponded to a 18.9-point change.[24] In another study, a clinically important difference in patients with fibromyalgia who were improved by one category on the Patient Global Impression of Change (PGIC) corresponded to a 7.9-point change from baseline in the MOS-Sleep disturbance subscale.[25] Although these clinically important differences were not reported in postmenopausal women with VMS, this analysis of the REPLENISH study found similar or greater changes from baseline with TX-001HR (∼15 points for Sleep Problems Index II and ∼20 points for Sleep disturbance subscales), suggesting that the changes observed in women treated with this E2/P4 formulation may be clinically meaningful.

Somnolence is a concern with P4 therapy,[26] and has been reported in approximately 2.7% of women taking a different formulation of micronized P4 (Prometrium, dose and regimen not specified), with the highest incidence in women aged 50 to 59 years.[27] In the REPLENISH trial, when P4 was given continuously (50 mg or 100 mg) the incidence of somnolence was, however, low and not clinically different than placebo. Moreover, we observed that TX-001HR did not negatively impact the MOS-Sleep somnolence subscale.

Allopregnanolone, a metabolite of P4, has been shown to induce GABAergic effects and promote sleep.[28] A small, 3-week study showed that 300 mg of P4 given orally at bed time to healthy postmenopausal women had no effect on undisturbed sleep but restored normal sleep when sleep was disturbed, with no effect on sleep architecture.[29] Another small study in postmenopausal women showed that 300 mg P4 alone for 21 days significantly increased rapid eye movement sleep in the first third of the night and reduced time spent awake compared with placebo.[30]

One study suggested that although P4- and medroxyprogesterone acetate (MPA)-containing HT are both effective for the treatment of menopausal symptoms, those containing P4 might be more effective at improving quality of sleep.[31] In one polysomnography study, postmenopausal women with VMS who were treated with 0.625 mg CEE plus cyclic 200 mg/d P4 or cyclic 5 mg/d MPA showed significant improvements in subjective sleep indices (questionnaires); however, sleep efficiency and time spent awake after sleep onset were only significantly improved in those taking CEE plus P4.[31] Similarly, significantly better sleep outcomes were observed with continuous 0.3 mg CEE/100 mg P4 compared with 0.3 mg CEE/2.5 mg MPA in another study.[32]

The main limitation of the current analysis is that although the MOS-Sleep subscale was an a priori endpoint, it was a secondary measure in the REPLENISH trial. Other limitations may include the 1 year duration that the study may have evaluated a population of women who may be healthier than the general population, and a discontinuation rate of 30%; all of which are typical characteristics of phase 3 efficacy and safety menopausal therapy trials, as previously noted.[13] Although the specific reason for why the placebo effect was so high in our study is not known, such a high placebo effect is consistent with other studies evaluating the effects of HT in postmenopausal women. The placebo response for vasomotor symptom improvement is known to be high, with reductions in VMS frequency ranging from 17% to 61% with placebo.[33-35]

CONCLUSIONS

In women with VMS, compared with placebo, TX-001HR caused significant improvements in sleep parameters from baseline to week 12, as measured with the MOS-Sleep scale, which were sustained up to 12 months. These improvements in sleep measures likely resulted from the clinically meaningful improvements in frequency and severity of VMS observed with all TX-001HR doses, and the beneficial CNS effect of P4.[13] The 1 mg/100 mg dose of TX-001HR is the first FDA-approved oral combination of bioidentical E2/P4 for treating VMS symptoms, with potential improvements in sleep outcomes.

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