Oral 17β-Estradiol/Progesterone (E2/P4) Improved Sleep Outcomes in the REPLENISH Trial

Andrew M Kaunitz, MD[1]; Risa Kagan, MD[2]; Shelli Graham, PhD[3]; Brian Bernick, MD[3]; Sebastian Mirkin, MD[3]

[1]University of Florida College of Medicine-*Jacksonville*, Jacksonville, FL; [2]University of California, San Francisco and Sutter East Bay Medical Foundation, Berkeley, CA; [3]TherapeuticsMD, Boca Raton, FL

Introduction

- Postmenopausal women often complain about having difficulty sleeping,[1-4] which has been associated with vasomotor symptoms (VMS)[5-8]
- Moderate to severe VMS can be effectively treated with approved hormone therapy (HT)
- The phase 3 REPLENISH trial in postmenopausal women with a uterus showed that the two highest daily doses of combined E2/P4 oral HT capsule reduced frequency and severity of VMS[9] and improved quality of life outcomes,[10] while protecting the endometrium[9]
  - In October 2018, the US Food and Drug Administration (FDA) approved combined bioidentical 1 mg E2/100 mg P4 capsules as Bijuva® (TherapeuticsMD, Boca Raton, FL) for the treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus

Objective

To review the effects of E2/P4 on sleep outcomes, including pertinent data from the Medical Outcomes Study (MOS)-Sleep and the Menopause-specific Quality of Life (MENQOL) questionnaires, and their correlations with VMS using mediation models

Methods

Study Design

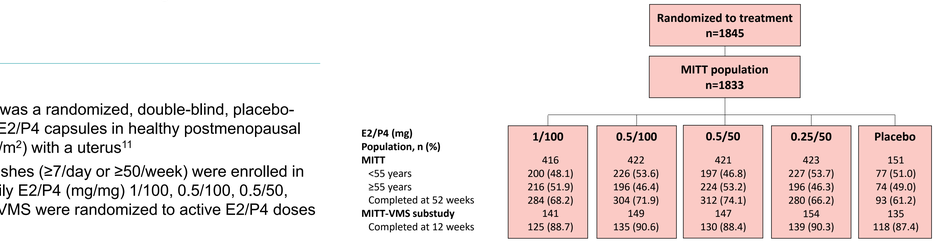
- The REPLENISH trial (NCT01942668) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of E2/P4 capsules in healthy postmenopausal women (aged 40-65 years; BMI ≤34 kg/m^2) with a uterus[11]
- Women with moderate to severe hot flushes (≥7/day or ≥50/week) were enrolled in a VMS substudy and randomized to daily E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo; women with fewer VMS were randomized to active E2/P4 doses only
- All subjects self-administered the MOS-Sleep[11] and MENQOL[10] questionnaires at baseline, week 12, and months 6 and 12
- MOS-Sleep is a 12-item questionnaire measuring 6 sleep dimensions in the past 4 weeks[11]
  - Items were scored using a 6-item Likert scale ranging from “All of the time” to “None of the time”
- MENQOL questionnaire included a question on difficulty sleeping (question #14)
  - The item was rated using a 7-item Likert scale ranging from “Not at all bothered” (score of 2) to “Extremely bothered” (score of 8) if difficulty sleeping was experienced; if not experienced, the score was set to 1
- Changes from baseline were analyzed for each treatment versus placebo at each timepoint in all women (MITT population) using an ANCOVA model; MENQOL data were also stratified by age (pre-specified FDA subgroup; <55 and ≥55)
- Somnolence was reported as a treatment-emergent adverse event[11]
- Mediation models were constructed using VMS substudy data to evaluate the effect of E2/P4 vs placebo on sleep disturbance from MOS-Sleep mediated through the MENQOL hot flush bother item (model 1) or VMS frequency and severity diary scores (model 2)[12]
  - One-month recall data from the MENQOL and MOS-SLEEP questionnaires were used from week 12; one month of daily VMS frequency and severity data were computed to cover the same observational window
  - Computed using the mediational structural equation modeling in STATA 15.1

Results

Study Disposition and Demographics

- A total of 1833 women were included in the MITT population and 726 were included in the MITT-VMS substudy (**Figure 1**)
- Mean age was 55 years (40-66 years) and mean BMI was 27 kg/m^2 for the MITT population; 65% were white and 32% were black

Figure 1. Patient disposition



MOS-Sleep Outcomes[11]

- Mean baseline scores ranged from 43.2–48.1 points and declined to 27.5–29.4 with TX-001HR and 37.4 with placebo at month 12
- All doses of TX-001HR significantly improved the MOS-Sleep total (**Figure 2A**), sleep problems index II subscale and sleep disturbance subscale scores compared with placebo at all timepoints (all, *P*<0.05), except those treated with 0.25/50 at week 12
- Better improvements were observed in the sleep problems index I subscale score for all E2/P4 doses versus placebo at all timepoints (**Figure 2B**)

MENQOL Difficulty Sleeping Item

- Mean baseline scores for “difficulty sleeping” ranged from 5.1 to 5.8 points, with similar ranges for women <55 years (5.3–5.8 points) and ≥55 years (5.1–5.8 points)
- The difficulty sleeping score significantly improved with the three highest E2/P4 doses compared with placebo at all timepoints (all, *P*<0.05), except for 0.5/50 at month 6
  - In women <55 years, significant improvements from baseline were observed with two E2/P4 doses (1/100 and 0.5/50) vs placebo at all timepoints (**Figure 3A**)
  - In women ≥55 years, significant improvements from baseline were observed with three E2/P4 doses (1/100, 0.5/100, 0.5/50) vs placebo at week 12 only (**Figure 3B**)

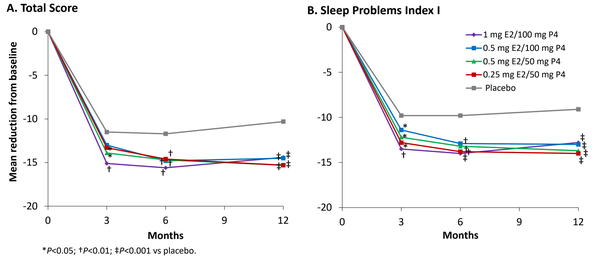
Somnolence Adverse Events[11]

- Incidence of somnolence was low (0.2%–1.2%) with E2/P4 versus 0% with placebo in the safety population (women who took at least one treatment capsule)

Mediation Models[12]

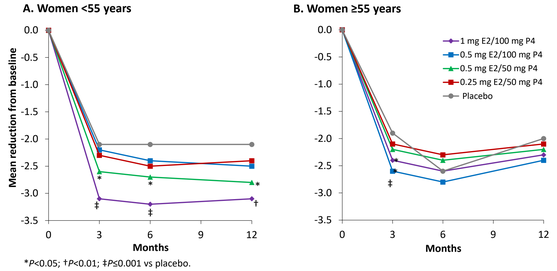
- Mediation models showed that E2/P4 had an indirect effect on sleep via VMS improvement
  - Model 1: E2/P4 directly affected the MENQOL hot flush bother item, which in turn directly affected the MOS-Sleep disturbance scale (**Figure 4**)
  - Model 2: E2/P4 directly affected both VMS frequency and severity scores, which also directly affected the MOS-Sleep disturbance scale (**Figure 4**)

Figure 2. Improvement in the MOS-Sleep total score in MITT population



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.

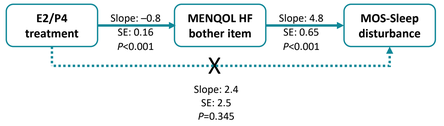
Figure 3. Mean changes from baseline and placebo in the MENQOL difficulty sleeping score for women (A) <55 years or (B) ≥55 years in MITT population



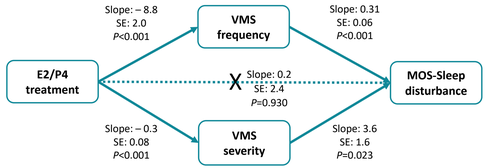
*P<0.05; †P<0.01; ‡P≤0.001 vs placebo.

Figure 4. Mediation sleep models using the MENQOL hot flush bother item (Model 1) and VMS frequency and severity (Model 2)

Model 1. MENQOL hot flush bother item (n=552)



Model 2. VMS frequency and severity (n=651)



E2: estradiol; HF: hot flushes; MENQOL: menopause-specific quality of life; MOS: medical outcomes study; P4: progesterone; SE: standard error.

Conclusions

- In REPLENISH, women with VMS treated with E2/P4 capsules experienced significant and sustained improvements in sleep parameters versus placebo
- Sleep mediation models showed that E2/P4 improved MOS-sleep disturbances indirectly through improvements in VMS
- In women taking oral E2/P4 capsules to treat moderate to severe VMS, E2/P4 may also improve sleep

References

1. Blumel JE, et al. *Menopause*. 2011;18:778-785. **2.** Hunter MS, et al. *BJOG*. 2012;119:40-50. **3.** Duffy OK, et al. *BJOG*. 2012;119:554-564. **4.** Blumel JE, et al. *Maturitas*. 2012;72: 359-366. **5.** Smith RL, et al. *Sleep Med*. 2018;45:98-105. **6.** Regestein Q, et al. *Maturitas*. 2015;81:449-455. **7.** de Zambotti M, et al. *Fertil Steril*. 2014;102:1708-1715.e1. **8.** Savolainen-Peltonen H, et al. *Menopause*. 2014;21:732-739. **9.** Lobo RA, et al. *Obstet Gynecol*. 2018;132:161-170. **10.** Simon JA, et al. *Menopause*. 2019;26:506-512. **11.** Kagan R, et al. *Menopause*. 2018;26:622-628. **12.** Mirkin S, et al. *Menopause*. 2019;26:637-642.

Disclosures

- AMK consults for or is on the advisory board of AMAG, Mithra, Pfizer, and Shionogi and has received research support (paid to the University of FL) from Bayer Healthcare, Endoceutics, and TherapeuticsMD. RK consults for Allergan, Cooper Surgical, Duchesnay, Lupin, Noven, Procter & Gamble, Radius Health, and TherapeuticsMD and is on the speaker’s bureau of AMAG, Cooper Surgical, and TherapeuticsMD. SG, BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
- TherapeuticsMD sponsored the study and supported the medical writing assistance provided by Dominique Verlaan, PhD (Precise Publications, LLC).