TOP SCORING ABSTRACT SESSION

S-11.

TX-001HR is Associated with a Clinically Meaningful Effect on Vasomotor Symptoms

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Objective: TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone (E2/P4; sometimes referred to as bio-identical hormones) in a single, oral softgel capsule, currently being developed for the treatment of vasomotor symptoms (VMS) in menopausal women with an intact uterus. A secondary objective of the REPLENISH trial was to determine the clinical meaningfulness of the effect of TX-001HR versus placebo for the treatment of moderate-to-severe VMS in menopausal women. **Design:** REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated TX-001HR in menopausal women (40-65 years) with an intact uterus. Women with hot flushes (≥7/day or ≥50/week) were included in the VMS substudy and were randomized 1:1:1:1:1 to daily E2/P4 of 1.0 mg/100 mg (n=141), 0.5 mg/100 mg (n=149), 0.5 mg/50 mg (n=147), 0.25 mg/50 mg (n=154), or placebo (n=135); others were randomized 1:1:1:1 to active E2/P4 doses as part of the primary safety endpoint analysis of endometrial hyperplasia. Participants assessed their VMS using the anchor-based Clinical Global Impression (CGI) score with a 7-level response scale ranging from "very much improved" to "very much worse," which were further categorized into a clinically meaningful response (CGI ratings of "much improved" or "very much improved"), minimally improved response (rating of "minimally improved"), and no change or worse (ratings of "no change" to "very much worse"). Response thresholds were determined by nonparametric discriminant analyses to define clinical responders. TX-001HR effects on quality of life using the menopause quality of life (MENQOL) questionnaire were also assessed (reported elsewhere). Results: Women enrolled in the VMS substudy (n=726) had a mean age of 55 years, a mean BMI of 27 kg/m2; 67% were white and 31% were black. As assessed by the CGI, significantly more women experienced a clinically meaningful response to TX-001HR (50-63%) compared with placebo (33%; all, P<0.01) at week 4. Similarly, significant results in clinically meaningful responders were observed for TX-001HR versus placebo at week 12 (73-82% vs 53%; all, P<0.01). Based on the nonparametric discriminant analyses, clinical responders were determined by response thresholds of weekly reductions in frequency of ≥36 moderate-to-severe VMS at week 4 and ≥39 at week 12. Overall, significantly more clinical responders were found with all 4 doses of TX-001HR (46-59%) than with placebo (33%; all, P<0.05) at week 4, and at week 12 (68-73% vs 52%; all, P<0.05). Conclusion: These REPLENISH data demonstrate that TX-001HR provides clinically meaningful improvements in VMS frequency in menopausal women. A consistency of effect of TX-001HR was observed with statistically significant improvements in the frequency of VMS, as well as in the vasomotor domain of the MENQOL questionnaire. TX-001HR may provide a new oral option, as a single estradiol/progesterone capsule, for the treatment of VMS in menopausal women with an intact uterus, including those women taking unapproved and inadequately studied compounded bio-identical hormone therapy.

Sources of Funding: TherapeuticsMD

S-12.

Effects of Cognitive Behavioral Therapy for Menopausal Insomnia on Depressive Symptoms

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Objective: Given the high prevalence rates of insomnia (30-60%) and depressive symptoms (25-40%) in peri- and postmenopausal women, interventions which improve both conditions would be particularly beneficial. Cognitive behavioral therapy for insomnia (CBTI) is an efficacious, first-line treatment for insomnia. There is some preliminary evidence suggesting CBTI is also effective in ameliorating depressive symptoms in the general population. This pilot study is the first to examine the effects of cognitive behavioral therapy for menopausal insomnia (CBTMI) on depressive symptoms among midlife women and comparing high and low depression severity groups on improvement of insomnia severity pre-post treatment. **Design:** Forty women (mean age= 55±6.2) self-described as peri- or postmenopausal who met diagnostic criteria for insomnia disorder and reported ≥ 1 nocturnal hot flash/night were randomized CBTMI or menopause education control (MEC). Participants were not excluded if they had a comorbid diagnosis of major depression. Based on structured clinical interview, four participants met DSM-5 criteria for present major depressive episode. CBTMI included four individual 50-minute sessions over eight weeks focused on the treatment of insomnia and hot flashes, delivered by social workers or psychologists in gynecology clinics. MEC included a 1-hour meeting to discuss menopausal symptoms and sleep hygiene; and provide educational pamphlets and a non-directive suggestion to "make any behavioral changes as desired." Pre- and posttreatment measures included: Insomnia Severity Index (ISI), Center for Epidemiologic Studies Depression Scale (CES-D), and Hamilton Depression Rating Scale (HDRS). Comparisons of high and low depression severity were examined based cut-off scores of 8 on the CES-D and 16 on the HDRS. **Results:** Mixed models revealed a significant time x treatment arm interaction for subjective complaint of depression (p=0.019) and objective rating of depression (p=0.01), and significant main effects for time (p's < 0.001). Women receiving CBTMI had significantly greater reductions in depressive symptomology from pre to post treatment on the CES-D score (16 ± 9 to 8 ± 7) and HDRS score (11 ± 7 to 2 ± 3) compared to women receiving MEC [pre to post treatment changes for MEC group: CES-D score (15 ± 11 to 13 ± 9), HDRS score (9 ± 6 to 6 ± 4)]. Improvements in insomnia severity did not differ by high or low depression (p >.05). Pre and post-treatment ISI scores for treatment arms were: Low CES-D (14 ± 3 to 6 ± 5) vs. High CES-D (18 ± 4 to 10 ± 6) and Low HDRS (14 ± 3 to 6 ± 5) vs. High HDRS (17 ± 4 to 7 ± 6). **Conclusion:** For midlife women experiencing insomnia and nocturnal hot flashes, a 4-session CBT intervention targeting both insomnia and hot flashes led to clinically meaningful improvements in depressive symptoms. Results also suggest that pre- to post CBTMI improvements in insomnia symptoms were similar among patients with and without elevation in depressive symptom severity. Thus, the benefits of CBTMI extend beyond insomnia and include improvements in depressive symptom severity; and are equally beneficial to women, including those experiencing more severe depressive symptoms.

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S-13.

The relationship between migraine, cardiovascular disease (CVD) and hormone therapy (HT) in postmenopausal women in the Women's Health Initiative Study (WHI)

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Objective: The evidence for the relationship between migraine and cardiovascular disease has been conflicting, depending on aura status, age of the population and CVD outcomes examined.The association between exogenous estrogen use and increased risk of stroke in women who have migraine with aura, has led to the recommendation that combined oral contraceptives (COCs) shall be avoided in migraine with aura and used with caution in migraine without aura. In comparison with COCs, the effect of hormone therapy (HT) on migraine and subsequent cardiovascular disease (CVD) risk, has not been extensively studied. The objective of the study was to further examine the relationship of migraine with incident composite CVD events and it's interaction with HT use, in both the Women's Health Initiative observational study (WHI-OS) and hormone therapy trial (WHI-HT) cohorts. **Design:** Incident CVD events were defined as the earliest of any following CVD outcomes: MI, stroke, Angioplasty of coronary arteries, Coronary bypass surgery, Coronary Heart Disease, Deep Vein Thrombosis, or Pulmonary Embolism. Migraine status was determined based on self-reported physician diagnosis at baseline. Hormone use status was defined by the randomization group within the HT trial (E, E&P and placebo). Cox proportional hazards regression models were used to determine whether migraine status predicts incident CVD, while adjusting for recognized potential confounders. Multivariate imputations were used in all models. The presence of effect modification was evaluated by testing the significance of the interaction between hormone use status and migraine using a Wald test. Where significant interactions were detected, we present the estimated hazard ratio and confidence interval stratified by hormone use. Tests were two-sided and conducted at the 0.05 significance level and all model estimates are shown with 95% confidence intervals. **Results:** WHI OS Analyses: Among 93,676 women in the WHI OS, 25,878 were excluded due to either pre-existing CVD or missing of end follow-up day. Of the remaining 67,903 participants, 7,322 (10.8%) had history of migraine, with the largest proportion (45.1%) in the youngest age group (50-59 years). The migraine group had more whites (87.5% vs 83.1%) and Latinos (4.1% vs 3.9%), while the control group had more African Americans (8.1% vs 5%) and Asians (3.4% vs 2%) Women with migraine tended to drink and exercise less than those without migraine, and had higher vitamin D and calcium intake. Migraineurs were more likely to have night sweats (SMD=0.137) and hot flashes (SMD=0.163). There was no increased risk of incident composite CVD events in women with history of migraine the WHI-OS cohort, with HR (95% CI) of 1.04 (0.82,1.31) in fully adjusted models (p=0.742, Table 1a). WHI HT Analyses: Of 17,357 participants in the HT, 1,482 reported migraine. A non-significant decrease in composite CVD events was observed in migraine group (HR= 0.71 (0.46,1.11) p=0.135) (Table1b). Comparison of women with migraine who received HT (E or E&P) vs placebo did not show HT as an effect modifier for the association between migraine and composite CVD (HR 1.04 (0.42, 2.58) p=0.929). **Conclusion:** We did not detect significant risk of incident composite CVD events associated with history of migraine in this longitudinal cohort of older postmenopausal women. Furthermore, hormone therapy was not an effect modifier of this relationship. As migraine is highly prevalent in the population and women with migraine are often advised to avoid HT, these findings may have significant public health implications. Further work should be done on exploring different categories of CVD events in different subpopulations of women with migraine.

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Table 1.	a) WHI-OS				b) WHI-HT			
	Migraine n(%)	No Migraine n(%)	HR (95%CI)	p-value	Migraine n(%)	No Migraine n(%)	HR (95%CI)	p-value
Composite CVD event	84(10.0%)	751(89.1%)	1.04 (0.82,1.31)	0.742	25(8.5%)	265(89.8%)	0.71 (0.46,1.11)	0.135

S-14.

Neurokinin 3 receptor antagonism is a highly effective, novel treatment for menopausal hot flushes with rapid onset: a phase 2, randomised, double-blind, placebo-controlled trial

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Objective: Hot flushes affect 70% of menopausal women, can be long-lasting, and often severely impact on physical, psychosocial, sexual, and overall wellbeing. Hormone replacement therapy is effective but not without risk. Neurokinin B signalling is increased in menopausal women, and has been implicated as an important mediator of hot flushes. It is estimated that a novel treatment for menopausal flushes could benefit 20 million women in the US alone. **Design:** This phase 2, randomised, double-blind, placebo-controlled, crossover trial assessed the effectiveness of an oral neurokinin 3 receptor antagonist (MLE4901) on menopausal hot flushes in an ambulatory setting (Clinicaltrials.gov NCT02668185). Sixty-eight women were screened between February and October 2016 in a single-centre, of which 37 were randomised and included in an ITT analysis (aged 49-62yrs, experiencing ≥7 hot flushes/24h some of which were reported as bothersome or severe). They each received 4 weeks of MLE4901 and 4 weeks of placebo in random order separated by a 2 week washout period. Randomisation was completed by a central computer, and participants were allocated to treatment number in numerical order. Primary outcome was total number of hot flushes during the final week of both treatment periods. Posthoc time course analysis was conducted in a modified ITT population (minimum n=34) to ascertain the therapeutic profile of MLE4901. **Results:** Primary outcome: MLE4901 significantly reduced the total weekly number of hot flushes by 45 percentage points compared to placebo during the final week of the four week treatment period (adjusted means: placebo 49.01 (CI: 40.81-58.56), MLE4901 19.35 (CI: 15.99-23.42), $p<0.0001$), and by 73% compared to baseline. Time course analysis revealed that when taking MLE4901 the frequency of hot flushes was reduced by 72% compared to baseline as early as day 3 of therapy (CI: -81.3 to -63.3%, $p<0.0001$; 51 percentage point decrease compared to placebo (CI: -63.5 to -38.4)). This treatment effect size was then maintained throughout the four week treatment period ($p<0.0001$ at day 7, 14, 21, and 28 of treatment). After 3 days of treatment with MLE4901, the severity of hot flushes was also reduced by 38% compared to baseline (CI: -46.1 to -29.1%, $p<0.001$; 31 percentage point decrease compared to placebo), as was hot flush bother by 39% (CI: -47.5 to -30.1, $p<0.0001$; 34 percentage point decrease compared to placebo), and hot flush interference by 61% (CI: -79.1 to -43, $p=0.0006$; 37 percentage point decrease compared to placebo). Hot flush severity, bother, and interference continued to improve over the 4 week treatment period. Hot flush frequency, severity, and bother were all positively correlated ($r=0.76$-0.93, $p<0.001$). Sleep also improved as early as day 3 of treatment with MLE4901 compared to placebo ($p=0.0061$ using the MENQOL questionnaire and $p=0.0026$ using the HFRDIS questionnaire), and continued to improve over the 4 week treatment period. There was a linear concordance between the two questionnaire measures ($r=0.70$, $p<0.0001$). Treatment was well tolerated. **Conclusion:** Treatment with a neurokinin 3 receptor antagonist (MLE4901) could be practice changing as it is well tolerated and rapidly relieves hot flush symptoms without the need for oestrogen exposure. Larger scale studies of longer duration are now planned.

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