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Effect of oral hormone therapy on oxidative stress produced by hot flashes in postmenopausal women

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Objective: One of the most common and distressing symptoms of menopause are hot flashes (HFs) that occur in over 75% of menopausal women, and continue for nearly 5 years after menopause. Also in the postmenopausal period the marked reduction in estrogens has been shown to increase levels of oxidative stress (OS); in addition, it is probably that vasomotor episodes contribute to OS production. Hormone therapy (HT) is used to diminish HFs intensity and frequency, but it is unknowing if this treatment has effect on OS associated to HFs, therefore this is the aim of this study. **Design:** A randomized, double-blind placebo controlled trial was carried out in 100 women with age 48-57 years, amenorrhea ≥12 months and without contraindications for use of HT. They were evaluated with the item about vasomotor symptoms, rated according to its severity on a 4-point scale, in the somatic subscale of Menopausal Rating Scale to assess HF intensity and strengthen the concepts pictorially. Participants were allocated at random to receive either 0.625 mg/d of synthetic conjugated estrogens plus 5 mg/10d of medroxyprogesterone (HT) or placebo (n=50 each) during 6 months, with assessments at initial and final moments. We measured lipoperoxides levels (LPO) by TBARS assay, erythrocyte superoxide dismutase (SOD), glutathione peroxidase (GPx) and total plasma antioxidant status (TAS) using Randox Laboratories kits, and we calculated SOD/GPx ratio and antioxidant gap. Alternative cut-off values of each parameter were defined on the basis of the 90th percentile of young healthy subjects, and a stress score (SS) ranging from 0 to 7, represented the severity of the markers modifications was computed. **Results:** Five women of HT and 8 of placebo groups dropped out in different time. Women with HFs had a SS higher than those without HFs (4.3±1.3 vs. 3.5±1.7, $p<0.05$). After 6 months, SS was diminished in HT groups, but more significant in women with HFs with an increment of GPx and decrement in LPO and SOD/GPx (Table), it showing low OS. In placebo groups there are not changes. **Conclusion:** Our findings suggest that HT decreases OS in postmenopausal women with HFs.

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Table. Oxidative stress markers at basal and 6 months in women without/with hot flashes using hormone therapy, (mean ± SD)

Oxidative stress marker	Hormone Therapy Without hot flashes (n = 12)			Hormone Therapy With hot flashes (n = 33)		
	Basal	6 months	p value*	Basal	6 months	p value*
Stress score	3.6±1.2	3.1±1.1	0.309	4.6±1.3	2.6±1.3	<0.0001
Lipoperoxide (µmol/L)	0.320±0.06	0.292±0.06	0.241	0.367±0.05	0.297±0.06	<0.0001
SOD (U/gHb)	1.29±0.14	1.30±0.15	0.663	1.24±0.22	1.19±0.13	0.160
GPx (U/gHb)	58.3±19.5	74.3±29.6	0.027	53.7±20.5	66.5±18.1	0.007
SOD/GPx ratio	0.024±0.01	0.019±0.01	0.040	0.026±0.01	0.019±0.01	0.003
TAS (mmol/L)	977±297	935±175	0.694	1041±202	1093±322	0.471

*** Paired t test.**

P-8.

The Association of Breast Arterial Calcifications (BACs) and Cardiovascular Disease (CVD): Results of a 10-Year Prospective Study

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Objective: Breast Arterial Calcifications (BACs) are calcifications of the medial layer of breast arteries/arterioles that are not consistently reported on mammography reports. It is postulated that the underlying pathophysiology of these calcifications differ from that of intimal calcifications. Whereas a benign nature of BACs have been suggested, intimal calcifications are strongly associated with Cardiovascular Disease (CVD)-related morbidity and mortality. The true clinical significance of BAC presence is not yet known. Thus, the primary objective of this 10-yr follow up prospective study is to assess whether the presence of BACs on routine mammography can be an early marker for predicting the development of CVD in women without CVD at baseline. **Design:** Women presenting for routine mammography between June and August 2004 were recruited for this prospective study. Baseline data collection included risk factors for CVD, as well as any CVD events, including Coronary Artery Disease (CAD) (eg, angina, MI, abnormal coronary angiogram, or CABG) and stroke, experienced by the patient over the 10 years of follow-up. Ten-year follow-up data were correlated with the baseline mammograms, which were screened for BACs along with baseline demographics, CVD presence, and CVD risk factors. **Results:** Of 1,995 subjects who had BAC data at baseline, 1,029 answered questions regarding CAD events at the 10-year follow-up without having a history of CAD or CAD risk factors at baseline. Of 1029, 112 (10.9%) were BAC positive and 917 (89.1%) were BAC negative at baseline, of which 11 (9.8%) and 30 (3.3%) developed CAD by year 10, respectively (p=.001). After controlling for age, BAC positive women were 2.3 times more likely to have CAD, with a confidence interval (CI) of 1.07-5.07 (p=0.034). Of the 1,995, 1,039 had neither history of stroke nor stroke risk factors, and answered questions regarding stroke event at the 10-year follow-up. Of these, 114 (11%) were BAC positive and 925 (89%) were BAC negative at baseline, of which 10 (8.8%) and 19 (2.1%) had at least 1 Stroke event by year 10, respectively (p <.001). After controlling for age, BAC positive women were 3.2 times more likely to have a stroke, with a CI of 1.22-8.41 (p=0.018). **Conclusion:** The presence of BACs on routine mammography may be associated with a significantly increased 10-year risk of developing CAD and stroke. Additional large prospective, population-based studies are needed to confirm BAC as a predictor of future development of CVD.

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Flibanserin in Postmenopausal Women With Hypoactive Sexual Desire Disorder: Results of the PLUMERIA Study

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Objective: Flibanserin is approved by the US Food and Drug Administration for the treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. In the first of two North American studies of flibanserin in naturally postmenopausal women with HSDD (SNOWDROP), significantly greater improvement in number of satisfying sexual events, sexual desire, and sexual distress was obtained with flibanserin 100 mg qhs compared with placebo (Simon JA, et al. *Menopause*. 2014;21(6):633-640). The present report is from the second study conducted to assess the safety and efficacy of flibanserin in this population (PLUMERIA), which was discontinued early by the sponsor for administrative reasons. **Design:** This randomized, double-blind, placebo-controlled, multicenter, 24-week trial was conducted in naturally postmenopausal women with HSDD at 95 sites in North America (United States and Canada; ClinicalTrials.gov registration: NCT01057901). Eligible patients were randomly assigned in a 1:1 ratio to receive once-nightly (qhs) flibanserin 100 mg tablets or matching placebo for 24 weeks. Flibanserin was initially dosed at 50 mg qhs for 14 days and subsequently uptitrated to 100 mg qhs for the remainder of the study. Safety assessment included incidence of adverse events, vital signs, weight, and clinical laboratory measures. Co-primary efficacy outcomes were the number of satisfying sexual events (SSE; count over a 28-day period) and the Female Sexual Functioning Index desire domain (FSFI-d) score. **Results:** The study population (flibanserin, n=376; placebo, n=369) included primarily white women (84.7%), with a mean age of 56.1 years and mean HSDD duration of 5.0 years. When the study was discontinued early by the sponsor, 45.3% of randomly assigned patients had completed Week 16 (which served as the primary analysis time point for the data presented). The most common adverse events (≥5% of patients in either treatment group) in patients receiving flibanserin 100 mg qhs versus placebo, respectively, were insomnia (7.7% vs 3.3%), somnolence (6.9% vs 2.2%), dizziness (6.4% vs 3.5%), nausea (5.3% vs 4.1%), and headache (5.1% vs 6.5%). Overall, 10.4% of patients receiving flibanserin and 7.3% of patients receiving placebo discontinued due to adverse events. The most common adverse events cited for discontinuing flibanserin were insomnia (n=9 [2.4%]), anxiety (n=8 [2.1%]), and headache and somnolence (n=4 each [1.1%]). Improvement from baseline to Week 16 (last observation carried forward) in FSFI-d score was significantly greater for flibanserin compared with placebo (P=0.0108); however, the between-group comparison for SSE did not reach statistical significance. **Conclusion:** Although not approved for use in postmenopausal women, a previous study demonstrated the efficacy and tolerability of flibanserin in postmenopausal women with HSDD. In the present study, flibanserin was generally well tolerated. Flibanserin was associated with significantly greater improvement in sexual desire (as measured by the FSFI-d) compared with placebo; mean improvement in number of SSE was numerically greater with flibanserin but not statistically different from placebo. Despite the greatly reduced power in this study to detect improvement relative to placebo, results suggest that flibanserin may be efficacious in the treatment of HSDD in naturally postmenopausal women.

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P-42.

Dysfunctional beliefs about sleep in women who develop insomnia in the context of the menopausal transition: a target for treatment

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Objective: The prevalence of insomnia increases as women approach menopause, partly in association with the emergence of sleep-disruptive hot flashes, with 40-56% of women having insomnia symptoms and 26% meeting criteria for a clinical insomnia disorder. Sleep-related cognitions, such as faulty beliefs and excessive worry about the potential consequences of insomnia on daytime functioning, are an important factor that can perpetuate insomnia. Here, we aimed to investigate beliefs about sleep in women who had developed insomnia disorder in the context of the menopausal transition (MTI). **Design:** Women in the menopausal transition (MT), defined according to Stages of Reproductive Aging Workshop criteria, were recruited from the community and had a structured clinical interview including a module about sleep. 57 women who met DSM-IV criteria for insomnia disorder that had developed in the context of the MT and with no current depressive or anxiety disorders and no prior history of insomnia, were classified as MTI (age: 49.6±3.4y, BMI: 23.9±3.3Kg.m^{-2}). Forty five women in the MT without insomnia disorder were included as controls (MTC, age: 49.2±3.1y, BMI: 24.4±3.7 Kg.m^{-2}). All women completed questionnaires including the Dysfunctional Beliefs and Attitudes about Sleep (DBAS) scale, a validated measure of 16 items of sleep-disruptive cognitions. **Results:** Women with MTI were more likely to report hot flashes ($p<0.001$), with greater hot flash interference ($p<0.01$), more subclinical depressive symptoms ($p< 0.001$), and a poorer menopause-specific quality of life in vasomotor, psychological, and physical domains ($p<0.05$) than MTC. They had higher total DBAS scores, reflecting more disruptive sleep-related cognitions than MTC ($p<0.001$), and also reported higher levels of pre-sleep cognitive and somatic arousal ($p<0.01$). Analysis of the subscales of the DBAS revealed specific clinically relevant maladaptive cognitions, with MTI women being more likely than MTC to endorse worrying about losing control over their ability to sleep, the unpredictability of having a good or poor night sleep, and attributing suboptimal daytime functioning to a poor night sleep (all $p<0.001$). The groups did not differ on some other subscales, including the belief that they need 8 hours of sleep to function well. **Conclusion:** Women with insomnia that developed in the context of the MT have more dysfunctional beliefs about sleep than women without insomnia, which may perpetuate or even exacerbate insomnia symptoms. Treating these maladaptive beliefs and attitudes about sleep may lessen the disruptive effect of hot flashes on sleep and assist women in coping with sleep disruption and its impact on daily functioning in the MT.

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