

THURSDAY CONCURRENT SESSION #1

S-1.

Use of a Personalized Medicine, Blood-Based Gene Expression Score Was Associated with Lower Diagnostic Testing Costs in Women Presenting to Cardiologists with Symptoms Suggestive of Obstructive Coronary Artery Disease: An Economic Analysis of the IMPACT-CARD (Investigation of a Molecular Personalized Coronary Gene Expression Test on Cardiology Practice Pattern) Trial

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Objective: Patients presenting to physician offices with chest pain and related symptoms undergo extensive non-invasive and invasive cardiac testing, leading to approximately \$6.7B per year in diagnostic testing costs in the United States. Better methods are needed to more accurately evaluate symptomatic patients for the likelihood of obstructive coronary artery disease (CAD), particularly among women. Current methods overestimate CAD presence in women, as evidenced by low prevalence of obstructive CAD in women undergoing diagnostic invasive coronary angiography. Hypothesis: Incorporating a personalized medicine, gene expression score (GES) into clinical care will reduce diagnostic evaluation costs among stable female patients presenting to cardiologists with symptoms suggestive of obstructive CAD. **Design:** The IMPACT-CARD Trial (NCT01251302) prospectively enrolled 88 patients without known CAD who presented with chest pain and related symptoms and were referred to one of six cardiologists. A retrospective control cohort was derived from 88 patients matched to the prospective cohort using clinical characteristics. In the prospective arm, the cardiologist's diagnostic strategy was evaluated before and after the GES was known and was compared to cardiac diagnostic tests performed in the retrospective cohort. The GES test is a previously validated, blood-based diagnostic test that determines the likelihood of obstructive CAD, with a negative predictive value of 96% among patients with low GES (≤ 15). The study analysis included an evaluation of change in medical decision making (clinical utility) as well as an economic analysis of the associated diagnostic plan (economic utility) among female patients in the trial. We estimated per-procedure costs from commercially insured patients with no history of CAD who underwent cardiac diagnostic testing in a large, national health claims database. We calculated weighted averages of median costs for outpatient and inpatient procedures, where costs included all claims with the same date of service or inpatient hospitalization dates. We applied these per-procedure costs to the diagnostic tests performed in the matched historical cohort and recommended in the prospective arm after GES testing to calculate the cost of diagnostic evaluation for each patient in the IMPACT-CARD Trial. **Results:** The 57 women in the IMPACT-CARD Trial had a mean age of 53 ± 12 years and mean GES of 7.6 ± 6 [88% (n=50) low GES, 12% (n=7) elevated GES]. As previously reported, a change in the diagnostic evaluation pre/post GES testing was noted in 34/57 women (60%, 95% CI=46% to 72%, $p<0.001$), with the intensity of testing being reduced in 91% (n=31) and increased in 9% (n=3) of these 34 women ($p<0.001$). Of the 31 women with decreased testing, 94% (29/31) had low GES (≤ 15). When per-procedure costs were applied to these trial results, the economic consequences of the GES test on diagnostic testing were apparent. Cardiac diagnostic testing (e.g., myocardial perfusion imaging, invasive coronary angiography) in the 57 female patients showed a pattern of decreased testing costs versus the 57 matched control patients (\$2,504 versus \$1,960 per patient, inclusive of the GES cost, $p=0.36$). This finding represents a 22% savings (\$544 per patient) in cardiac diagnostic testing costs. **Conclusion:** This personalized medicine, genomic blood-based test may help address an important diagnostic challenge in the care of mid-life women. Clinical incorporation of the GES may be associated with a reduction in costs in the evaluation of women presenting to the cardiologist for evaluation of obstructive CAD. These potential economic savings likely reflect the clinical utility of the GES in the medical decision making process.

S-2.

Association between the vaginal microbiota, menopause status and signs of vulvovaginal atrophy

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Objective: Vaginal microbiota dominated by lactic acid producing bacteria, particularly *Lactobacillus* spp., play a role in preventing colonization by pathogenic organisms, including sexually transmitted and urinary tract infectious agents, and broadly act to maintain a woman's gynecologic and reproductive health. However, little is known about the composition of the vaginal microbiota across the stages of menopausal transition, interactions with estrogen, or the associations with gynecologic complaints and sexual functioning in menopause. We sought to describe the composition of the vaginal microbiota between pre-, peri- and postmenopausal women and to explore the association between the microbiota and vulvovaginal atrophy (VVA). **Design:** 87 women (age 35-60) were selected based on menopausal status (premenopause (n=30), perimenopause

(n=29) or postmenopause (n=28)) according to Stages of Reproductive Aging Workshop guidelines. Additional inclusion criteria were human papillomavirus (HPV) negative, no self-reported history of sexually transmitted infection in the past six months, and no exogenous hormone use. The bacterial composition was characterized using 16S rRNA gene sequence analysis amplified from whole genomic DNA isolated from clinician-collected mid-vaginal swabs. Fisher's exact test and Bayesian multinomial logistic regression were used to assess the association between vaginal microbiota and VVA. **Results:** The proportion of women with *Lactobacillus*-dominated microbiota dropped from approximately 83% in pre- and perimenopausal women to 54% in postmenopausal women. Bacterial communities clustered into six community state types (CSTs) dominated by *Lactobacillus crispatus*, *L. gasseri*, *L. iners*, or *L. jensenii*, while 2 CSTs (termed CST-IV-A and IV-B in prior work) lacked significant numbers of lactobacilli. CST IV-A was characterized by anaerobic bacteria including *Streptococcus* and *Prevotella*, whereas CST IV-B by the genera *Atopobium* and *Megasphaera*. There was a statistically significant association between menopause stage and CST (p -value=0.004) and VVA and CST (p -value=0.002). Perimenopausal women were more likely to be classified as CST IV-A or the *L. gasseri* CST, whereas postmenopausal women were mostly CST IV-A. CSTs dominated by *L. crispatus* and *L. iners* were more prevalent in premenopausal women. Two women were treated for VVA; 19 had signs of mild or moderate VVA. Compared to women with no VVA, the vaginal microbiota of women with mild or moderate atrophy had 25-fold greater odds of assignment to CST IV-A vs. the *L. crispatus* CST (aOR: 25.89, 95% Credible Interval: 2.98-406.79). **Conclusion:** Our data strongly suggest that bacterial communities differ during menopause and the anaerobic bacteria which become more dominant during menopause may play a role in VVA. We found a distinct bacterial community state (CST IV-A) with low relative abundance of lactobacilli that was highly associated with signs of VVA. Interventions that maintain pre-menopausal vaginal microbiota, such as probiotic or prebiotics, may provide insight into the role of the vaginal microbiota in vaginal health during and after menopause.

Table 1. Vaginal Microbiota by Menopause Status, Baltimore, MD (n=87)

	Pre-menopause		Peri-menopause		Post-menopause		p-value*
	n	%	n	%	n	%	
Community state type (CST), dominant bacterial species							.004
CST I, <i>Lactobacillus crispatus</i>	14	46.67	6	20.69	7	25.00	
CST II, <i>Lactobacillus gasseri</i>	1	3.33	6	20.69	1	3.57	
CST III, <i>Lactobacillus iners</i>	10	33.33	11	37.93	5	17.86	
CST IV-A, Low- <i>Lactobacillus</i>	0	0.00	2	6.90	8	28.57	
CST IV-B, Low- <i>Lactobacillus</i> , <i>Atopobium</i> -dominated	5	16.67	3	10.34	5	17.86	
CST V, <i>Lactobacillus jensenii</i>	0	0.00	1	3.45	2	7.14	

*Fisher's exact test

S-3.

Hormonal Therapy Treatment Quality of Life and Menopausal Symptom Burden among Mid-Life Women: Implications of Medication Discontinuation

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Objective: Hormonal therapy (HT) for the treatment of menopausal symptoms can be associated with high rates of discontinuation primarily due to the concern of, or experience with, side effects of therapy. Recent data on HT discontinuation and symptom burden among mid-life women in the United States (US) are limited. This study was designed to evaluate treatment discontinuation rates and causes, as well as health-related quality of life (HRQoL) and menopausal symptoms experienced by women prescribed HT. **Design:** A one-time mail survey was developed and administered to female patients of the Reliant Medical Group in Worcester, Massachusetts. Patients were identified from administrative claims data meeting the following criteria: 45-64 years of age; filled at least one month's supply of oral or transdermal HT between January 1, 2007 and December 31, 2011; no history of breast cancer, venous thromboembolism, stroke, gynecological cancer, or hysterectomy in available data; and enrolled in the Fallon Community Health Plan with a Reliant Medical Group primary care physician as of the date of survey administration. Survey questions included items on: sociodemographic characteristics, HT patterns of use (i.e., discontinuation of HT, reasons for discontinuation, perceptions of HT risk/benefits), overall HRQoL (as measured by the EQ-5D), and menopausal symptom frequency and severity (as measured by the Menopausal Rating Scale [MRS]). Descriptive analyses were conducted of all survey data, with study measures being reported for the overall population, as well as stratified by those currently versus not currently taking HT. **Results:** Among 704 mailed surveys, 265 surveys were returned (37.6% response rate). 72 respondents met study inclusion criteria and provided signed informed consent. The majority of survey respondents were white (96%), with a mean age of 60 years (non-responders did not differ in terms of age). 58% of the study sample was prescribed HT for three or more years. Most respondents expected to benefit from HT prior to initiating treatment (93%) and approximately one-third of patients reported concern about side effects prior to starting HT. 63% of respondents were no longer taking HT at the time of survey administration, with the most common reasons for discontinuation being "doctor told me to stop" (73%), followed by "concerned could cause side effects" (27%), or "side effects bothered me" (18%). HRQoL measured by EQ-5D index score was numerically higher among those currently taking HT (0.86, standard deviation (SD)=0.13) compared to those not currently taking HT (0.83, SD=0.17). Most individual symptoms were

reported as less severe among those currently taking HT. 12% of respondents currently taking HT reported having “severe” or “very severe” hot flushes/night sweats compared with 22% of respondents who discontinued HT. Similarly, 4% of those currently taking HT reported having “severe” or “very severe” vaginal dryness versus 20% of respondents who discontinued HT. The mean total MRS score was also lower among those respondents currently taking HT compared to those not currently taking HT (8 vs. 12). **Conclusion:** This study provides recent, real-world data on HT discontinuation rates among mid-life women in the US. Rates of HT discontinuation in this population were high, with reasons for discontinuation including concern about potential side effects, or having experienced side effects. Women who remained on therapy reported higher HRQoL and lower rates of menopausal symptoms. The high rates of discontinuation due to concerns about, or the experience of, side effects of HT suggest a need for therapies with improved side effect profiles.

S-4. **Effect of Post-Menopausal Hormone Therapy on Disease Progression in Systemic Lupus Erythematosus: A Systematic Review**

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Objective: A systematic review of the existing published literature was conducted to evaluate the effect of post-menopausal hormone therapy (HT) on disease progression in menopausal patients with systemic lupus erythematosus (SLE). **Design:** We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from January 1990 to October 2012 for observational studies and randomized clinical trials (RCT) that evaluated the effect of HT on the frequency and intensity of flares in menopausal patients with SLE. The screening of titles and abstracts, full text review, and risk of bias assessment were conducted by two independent reviewers. **Results:** Out of 12,532 records identified, after removal of duplicates and screening of titles and abstracts, 404 articles were eligible for full text review. After exclusion of irrelevant studies, five studies were assessed for qualitative synthesis. The characteristics of the included studies are summarized in table I. **Conclusion:** This systematic review demonstrates a trend towards an increased risk of developing minor SLE flares in menopausal patients receiving HT. However, HT was also associated with significant improvement in patients’ menopausal symptoms and quality of life. One limitation was that these studies followed patients for a short period of time. To date, there are no recommendations regarding HT for women with SLE. Larger trials are needed to assess the long-term effects of HT on the course of SLE in menopausal patients.

Table I: Characteristics of included studies.

Study name	Study type	Study population	Results
Arden <i>et al.</i> , 1994	Retrospective chart review	30 HT users were compared to 30 never users followed for one year.	No significant difference was found between the two groups in medication change or hospital admission.
Kreidstein <i>et al.</i> , 1997	Retrospective cohort study	16 HT users were matched to 32 non-HT users followed for one year.	No significant difference in incidence of flares was found between the 2 groups.
Mok <i>et al.</i> , 1998	Retrospective chart review	11 HT users were compared to 23 non-HT users for 35 months.	No significant difference was found in the number of flares between the two groups.
Buyon <i>et al.</i> , 2005	RCT for 12 months	174 received HT, 177 received placebo.	Mild to moderate flares were higher in the HT group. No significant difference was found in severe flares between the two groups.
Sanchez-Guerrero <i>et al.</i> , 2007	RCT for 24 months	52 received HT, 54 received placebo.	No significant difference in the incidence of flares was found between the two groups.

S-5. **Are menopausal hot flashes an evolutionary byproduct of post-partum warming?**

Lynnette L. Sievert, PhD, Allison Masley. Anthropology, UMass Amherst, Amherst, MA **Objective:** Hot flashes are associated with declining estrogen levels during the peri- and post-menopausal period. Why, from an evolutionary perspective, are women vulnerable to hot flashes? In 1994, Naftolin *et al.* suggested that menopausal hot flashes may be a vestige – an evolutionary byproduct – of a mother’s physiological response to falling estrogen levels after giving birth. In 2011, Pollycove *et al.* again proposed that maternal postpartum hot flashes may be an adaptive mechanism for warming a nursing infant. From an evolutionary perspective, the post-partum warming of an infant, particularly at night, could have been selected for among early hominins such as *Homo ergaster* who would have lost most body hair in exchange for an increased ability to sweat. Nights on the African savanna would have been cold for newborns and infants. The explanation that menopausal hot flashes may be a byproduct of hormonal changes associated with the post-partum period is an interesting hypothesis that has not been fully tested. The purpose of this study was to test whether or not new mothers demonstrate post-partum warming or hot flashes. **Design:** New mothers were recruited with the aid of a doula network in western Massachusetts, and then by word of mouth. Women who were not new mothers were recruited from among graduate students and their friends. To date, 14 new mothers

and 9 women serving as age-matched comparisons have completed brief surveys to collect demographic, reproductive, and lifestyle information, as well as measures of height and weight. All women were asked “Have you noticed any body temperature changes?” Biolog monitors were worn for approximately 7 hours during the afternoon and early evening to record changes in sweating on the upper chest. Biolog software identified hot flashes that met the criteria of an increase in skin conductance levels of 2 micromho’s within 30 seconds followed by a 20 minute post-hot flash lockout. Data output was examined in detail to verify hot flashes and to consider whether a different criteria might better define hot flashes among new mothers. Participants were asked to indicate hot flashes with button pushes on the monitor. In addition, new mothers were asked to record each breastfeeding episode in order to compare bouts of breastfeeding with the timing of warming or hot flashes. **Results:** New mothers were slightly older on average than the comparison group (34.7 vs. 30.2 years, ns). All new mothers were married (vs. 22% of the comparison group), with relatively high levels of education, “OK” or “comfortable” financial status, moderate BMI (25.4 kg/m2), and all were breastfeeding their babies at the time of the study. Infants had a mean age of 4 months (0.33 years, s.d. 0.2). Within the comparison group, 7 of the 9 had never given birth. With regard to the question about temperature changes, only one woman in the comparison group said “yes,” and reported feeling cold more often. In contrast, 100% of the new mothers reported feeling warmer, with comments such as, “I feel warmer in general since having my first child.” “I feel like I’m exploding when I feed him. I throw off all the covers.” “I’m sweeter at night.” “I wake up sweating and damp.” “I feel hot when carrying the baby, sometimes at night.” With the Biolog monitor, 1 new mother demonstrated 4 hot flashes, 3 mothers demonstrated 1 hot flash, and 10 mothers did not demonstrate any hot flash that met the criteria of an increase of 2 micromho’s in 30 seconds. Two of the mothers who did not demonstrate objective hot flashes reported subjective hot flashes by pushing the buttons on the monitor. Two objective hot flashes corresponded with breastfeeding episodes, and 1 subjective hot flash corresponded with a breastfeeding episode. **Conclusion:** New mothers were more likely to report feeling warm compared to the age-matched comparison group. Most new mothers did not demonstrate changes in skin conductance levels that met the standard criteria for menopausal hot flashes. Only two objectively measured hot flashes were associated with breast feeding episodes, giving limited support to the hypothesis that post-partum hot flashes occur to warm a newborn infant. Funding: Center for Research on Families, UMass Amherst

THURSDAY CONCURRENT SESSION #2

S-6. **Fitness improves sleep quality through improvement in sleep efficiency**
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Objective: In 2011, the first baby boomers turned 65 years old. By 2028, this large cohort will contribute to an accelerated growth in the senior population with a near doubling in the proportion of people aged 65 years and older. Aging is associated with an increase in sleep dissatisfaction as indicated by over 80% of people over the age of 65. Sleep quality is known to decrease in older people; they experience frequent awakenings, as well as a decrease in the duration of rapid eye movement (REM) and slow wave sleep, which corresponds with an increase in lighter sleep stages I and II. Due to poor sleep quality, older people have increased daytime sleepiness which heightens their risk of falling and cognitive decline. Further, individuals with untreated sleep disorders such as obstructive sleep apnea (OSA) carry an increased risk of cardiovascular sequelae including hypertension, coronary artery disease, heart failure, and stroke. Given the risk factors associated with sleep disorders and decreased sleep quality, in addition to the limited long term efficiency and compliance of pharmacological treatments, nonpharmacological treatments are worthwhile exploring as alternative or adjunctive therapy. Physical exercise has been shown to improve sleep quality and may therefore mitigate such decline in older adults. However, despite its potential importance, how the underlying components of sleep quality are involved in this relationship is not well understood. Thus, the primary objective of this study was to determine the effects of aerobic fitness on sleep quality in older adults. **Design:** In a cross sectional study of 49 healthy sedentary adults (30 post-menopausal women and 19 men; 69±6 years, mean±SD), we examined the relationship between maximal aerobic capacity (VO₂max) and several underlying components of subjective sleep quality. VO₂max was determined using a ramped treadmill protocol with continuous monitoring of cardiorespiratory variables (Parvo Medics, USA). Reported sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), composed of a global sleep quality score and seven component scales evaluating sleep latency, duration, habitual sleep efficiency, daytime dysfunction, use of sleeping medication, subjective sleep quality, and sleep disturbances. **Results:** Higher VO₂max was associated with better sleep quality when controlling for age ($r = -.323, p = .025$). Mediated regression analysis revealed this association to be mediated by habitual sleep efficiency (Sobel’s = -2.074, $p = .038$). **Conclusion:** Results from this study suggest that higher aerobic fitness is associated with better overall sleep quality, primarily by improvements in sleep efficiency. A six-month aerobic exercise intervention study is currently underway to determine whether aerobic exercise will promote changes in sleep quality and architecture, and in turn improve

cognition. The implications of this research are considerable and warrant future investigation given the aging population and the magnitude of the burden that this segment of the population has, and will increasingly have, on the health care system. **Acknowledgements:** Supported by the Canadian Institutes of Health Research, the Alzheimer Society of Canada, and the Brenda Strafford Foundation Chair in Alzheimer Research.

S-7.

Lifestyle changes and subclinical atherosclerosis in early postmenopausal Chinese women – a five-year followup study of a population-based cohort
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Objective: Subclinical atherosclerosis progresses silently over a period of time before the clinical manifestations of cardiovascular disease. This study aimed to investigate the progression of subclinical atherosclerosis and the lifestyle determinants in early postmenopausal Chinese women. **Design:** This is a community-based 5-year followup study on a cohort of 518 women recruited from the community through random telephone dialing. All were aged 50-64y and within 10 years menopause. Lifestyle and dietary variables based on validated and structured questionnaires, clinical assessments and fasting blood samples were obtained at baseline (T1) and 5-year followup (T2). A 12.5-MHz linear probe of the HDI 5000 ultrasound scanner (Advanced Technology Laboratory, Bothell, WA) was used for measuring intima-media thickness (IMT) at the near and far walls of three 10-mm segments: distal common carotid, bifurcation, proximal internal carotid of both the left and right carotid arteries. The final IMT was defined as the averages of maximum IMT free of atherosclerotic plaques measured at each of the 12 segments. Atherosclerotic plaques defined as a focal wall thickening of at least 1.5mm were also identified along the defined segments. Plaque was graded as: grade 0, no observable plaque; 1, one small plaque <30% of vessel diameter; 2, one medium plaque between 30-50% of vessel diameter or multiple small plaques; 3, one large plaque >50% vessel diameter or multiple plaques with at least one medium plaque. Repeated measurements of IMT and plaque were also obtained at T2. Plaque progression was computed by subtracting the plaque index at T1 from the plaque index at T2. The IMT assessors (2 sonographers) were blinded to participant characteristics. The within-sonographer intraclass correlations were 0.83-0.88 for IMT and 0.99 for plaque index, and between sonographer correlations were 0.81-0.88 for IMT, and 0.88- 0.99 for plaque index.

Results: The five-year followup study of asymptomatic Chinese early postmenopausal women (mean age 61.5 years at followup) has revealed a progression of IMT of 2.1%/year (standard deviation =1.7) or a progression rate of 0.015 mm/year (standard deviation = 0.013). 17 % were found to have a moderate (change of plaque index score of 1) and 8% severe (change of score ≥ 2) plaque progression. Significant predictors of higher followup (T2) IMT value included age, higher baseline values of total cholesterol, systolic and diastolic blood pressure, LDL-cholesterol and triglyceride. After adjusting for age and baseline (T1) IMT, women with higher fruit and vegetable intake (>median), and maintenance of waist circumference below 80 cm at both T1 and T2 were found to have significantly lower mean IMT at T2. In addition, women with improvements in the following lifestyle variables from T1 to T2: from high to low number of psychological symptoms (>4 to <4); from below median to above median intake of soy protein, and from below median to above median score of physical activities index had lower mean IMT at T2 compared with those with unfavourable values at both T1 and T2. Multivariate logistic regression analysis showed that increasing age, waist circumference ≥ 80 cm, cholesterol ≥ 200 mg/L, having diabetes, regular drinking were significant predictors of plaque progression (≥ 1 versus 0) (adjusted odds ratios from 1.10 to 2.81), while higher vegetable and fruit intake lowered the risk. **Conclusion:** This population-based followup study of a cohort of Chinese asymptomatic midlife women has identified, besides the traditional risk factors, a number of significant lifestyle predictors. Maintenance of high fruit and vegetable intake, avoidance of central obesity, improvements in psychological profiles and physical activity and increase in soy intake over followup were found to reduce the risk of subclinical atherosclerosis.

S-8.

Impact on Body Weight and Sexual Function During Treatment of Vasomotor Symptoms (VMS) Due to Menopause With Low-Dose Mesylate Salt of Paroxetine (LDMP)

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Objective: Nonhormonal treatment options are needed for women with VMS due to menopause. Some antidepressants such as selective serotonin reuptake inhibitors may be efficacious for VMS; however, side effects such as weight gain and sexual dysfunction at dosages used for psychiatric indications may result in drug discontinuation or noncompliance. Two randomized, double-blind, placebo-controlled Phase 3 trials demonstrated that LDMP reduced the frequency and severity of VMS and had a favorable tolerability profile. Using pooled data from these studies, the impact of LDMP 7.5 mg/d on body weight and sexual function was evaluated. **Design:** Postmenopausal women aged ≥ 40 y with moderate to severe VMS (>7-8 hot flashes [HF]/d or 50-60 HF/wk) received

once-daily placebo and recorded number and severity of HFs in daily diaries during a 12-day, single-blind, run-in period. Compliant patients who met eligibility criteria entered the double-blind treatment period and were randomized 1:1 to receive LDMP 7.5 mg or placebo once daily at bedtime for 12 (Study 1) or 24 wks (Study 2). Co-primary efficacy endpoints were mean change from baseline (BL) in frequency and severity of VMS at Wks 4 and 12. Additional assessments included mean changes in body weight and body mass index (BMI); Arizona sexual experiences (ASEX) scale; HF-related daily interference scale (HFRDIS) sexuality subscore; and adverse events (AEs) related to sexual dysfunction. An exploratory analysis examined weight gain $\geq 7\%$ (a generally accepted criterion of clinically significant weight gain in patients receiving antidepressants). Rank-transformed analysis of covariance/nonparametric method with BL value as covariate was used to evaluate changes in body weight and BMI. Chi-square test was used to assess results from the HFRDIS and ASEX scales. **Results:** Pooled efficacy and safety populations comprised 1174 (LDMP, 585; placebo, 589) and 1175 (LDMP, 586; placebo, 589) patients, respectively. BL values were similar for median weight (LDMP, 74.5 kg; placebo, 75.8 kg), median BMI (LDMP, 27.9 kg/m²; placebo, 28.2 kg/m²), and sexual dysfunction using the ASEX scale (LDMP, 59%; placebo, 58%). No clinically meaningful or statistically significant changes from BL in weight or sexual function assessments occurred in the LDMP group (Table). Small but statistically significant increases in weight and BMI were observed in the placebo group at Wk 4. No significant difference was observed in the proportion of patients who had a gain in body weight $\geq 7\%$ at Wk 4, 12, or 24 between treatment groups. Rates of AEs suggestive of sexual dysfunction were low and were similar in both treatment groups. **Conclusion:** LDMP was effective in reducing the frequency and severity of VMS due to menopause and had a favorable tolerability profile. At a dosage of 7.5 mg/d, LDMP treatment did not result in weight gain or negative changes in sexual function.

Impact of LDMP on Body Weight and Sexual Function During Treatment of VMS Due to Menopause

Assessment	LDMP, n=585	Placebo, n=589	p Value
Median (min, max) change from BL in weight, %			
Week 4	0.00 (-8.13, 11.11)	0.21 (-11.04, 37.31)	0.0002
Week 12	0.17 (-9.56, 9.21)	0.52 (-19.59, 39.55)	0.1124
Week 24 (Study 2 only)	0.48 (-18.06, 14.89)	0.09 (-25.93, 35.82)	0.2941
Median (min, max) change from BL in BMI, kg/m ²			
Week 4	0.00 (-2.17, 2.66)	0.07 (-3.08, 9.15)	0.0003
Week 12	0.06 (-2.33, 2.58)	0.16 (-7.44, 9.70)	0.1383
Week 24 (Study 2 only)	0.16 (-4.81, 3.76)	0.02 (-6.78, 8.79)	0.3173
Patients reporting sexual dysfunction (ASEX scale), %			
Week 4	55.81	55.81	1.0000
Week 12	54.82	52.06	0.3998
Week 24 (Study 2 only)	56.10	56.77	0.8925
HFRDIS sexuality subscore responders, n/N (%)			
Week 4	308/527 (58.44)	300/530 (56.60)	0.5451
Week 12	301/487 (61.81)	304/482 (63.07)	0.6847
Week 24 (Study 2 only)	131/216 (60.65)	124/196 (63.27)	0.5849

S-9.

Menopause-specific Quality of Life With Bazedoxifene/Conjugated Estrogens

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Objective: Bazedoxifene/conjugated estrogens (BZA/CE), a tissue selective estrogen complex, has demonstrated efficacy in the treatment of menopausal symptoms and prevention of postmenopausal osteoporosis in the Selective estrogens, Menopause, And Response to Therapy (SMART) trials. Here we describe the effects of BZA/CE on health-related quality of life (HRQOL) in different populations of healthy postmenopausal women enrolled in 4 of the SMART trials. **Design:** The SMART trials were randomized, double-blind, placebo (PBO)- and active-controlled phase 3 studies in nonhysterectomized postmenopausal women with specific durations and enrollment as follows: SMART-1 (2-year; N=3397; generally healthy), SMART-2 (3-month; N=318; moderate-to-severe vasomotor symptoms [VMS]), SMART-3 (3-month; N=652; moderate-to-severe vulvar vaginal atrophy [VVA]), SMART-5 (1-year; N=1843; HRQOL evaluated in a subset with moderate-to-severe VMS). HRQOL was assessed using the Menopause-specific Quality of Life (MENQOL) questionnaire at baseline and Month 3 (also Month 12 for SMART-1 and SMART-5 and Month 24 for SMART-1). Changes from baseline in MENQOL scores were evaluated using a one-way analysis of variance with treatment as a factor (SMART-1) or an analysis of covariance with treatment and study site as factors and baseline value as a covariate (SMART-2, SMART-3, SMART-5); comparisons of HRQOL endpoints were not adjusted for multiplicity, except total MENQOL score in SMART-2. The clinical relevance of changes in MENQOL domains and total score were also evaluated. Results are presented for women who received BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, and PBO. **Results:** Pooled demographics for all 4 trials were generally balanced across treatment groups. At Months 3 and 12, improvements in vasomotor functioning and total MENQOL scores were significantly greater with both BZA/CE doses compared with PBO in SMART-1 (Table). Benefit was maintained at Month 24. Significant improvements were also seen in vasomotor functioning and total MENQOL scores at 3 months with both doses of BZA/CE in the population experiencing

moderate-to-severe VMS (SMART-2) and those experiencing VVA (SMART-3). In addition, the VVA population had statistically significant improvements in sexual functioning with both BZA/CE doses at Month 3. Improvements in sexual functioning were also seen for the other populations. In the population with bothersome VMS and sleep disturbance (SMART-5), significant improvements were seen in vasomotor functioning and total MENQOL score at 3 and 12 months (except for total MENQOL score for BZA 20 mg/CE 0.45 mg at 3 months). At trial endpoint, the statistically significant improvements with BZA/CE compared with PBO were shown to exceed clinically important differences (CIDs) for total MENQOL score (BZA 20 mg/CE 0.625 mg in SMART-2 and SMART-5) and VMS domain score (both BZA/CE doses in SMART-2 and SMART-5 and BZA 20 mg/CE 0.625 mg in SMART-3 [also BZA 20 mg/CE 0.625 mg at 3 and 12 months in SMART-1]), indicating that these differences are clinically meaningful. **Conclusion:** BZA/CE provided consistent statistically significant and clinically meaningful improvements in vasomotor functioning and overall HRQOL, and statistically significant improvements in sexual functioning compared with PBO across different populations of healthy postmenopausal women participating in the SMART trials.

Table. Adjusted Mean Change From Baseline in MENQOL Scores

MENQOL domain	Time	SMART-1			SMART-2			SMART-3			SMART-5		
		BZA 20 mg/CE 0.45 mg (n=433)	BZA 20 mg/CE 0.625 mg (n=414)	PBO (n=427)	BZA 20 mg/CE 0.45 mg (n=127)	BZA 20 mg/CE 0.625 mg (n=128)	PBO (n=63)	BZA 20 mg/CE 0.45 mg (n=219)	BZA 20 mg/CE 0.625 mg (n=218)	PBO (n=105)	BZA 20 mg/CE 0.45 mg (n=112)	BZA 20 mg/CE 0.625 mg (n=112)	PBO (n=112)
VMS	Month 3	-1.26 ^a	-1.45 ^{a,c}	-0.56	-3.27 ^{b,c}	-3.81 ^{b,c}	-1.58	-1.33 ^a	-1.67 ^{a,c}	-0.51	-2.37 ^b	-2.75 ^{b,c}	-1.45
	Month 12	-1.49 ^a	-1.74 ^{a,c}	-0.75	-	-	-	-	-	-	-2.79 ^{b,c}	-2.79 ^{b,c}	-1.14
	Month 24	-1.57 ^a	-1.77 ^a	-0.96	-	-	-	-	-	-	-	-	-
Physical	Month 3	-0.53	-0.55	-0.45	-1.07	-1.28 ^{b,c}	-0.78	-0.64	-0.70 ^a	-0.42	-0.92	-1.11	-0.87
	Month 12	-0.49	-0.55 ^b	-0.35	-	-	-	-	-	-	-0.93	-1.18 ^b	-0.75
	Month 24	-0.42	-0.53	-0.39	-	-	-	-	-	-	-	-	-
Psychosocial	Month 3	-0.44	-0.48	-0.35	-0.89	-1.19 ^b	-0.73	-0.45	-0.50	-0.49	-0.67	-0.84	-0.74
	Month 12	-0.44	-0.43	-0.35	-	-	-	-	-	-	-0.87	-1.00	-0.70
	Month 24	-0.39	-0.46	-0.41	-	-	-	-	-	-	-	-	-
Sexual	Month 3	-0.81	-0.76	-0.65	-1.18	-1.45 ^b	-0.73	-1.95 ^a	-1.91 ^a	-1.24	-1.20	-1.40	-1.04
	Month 12	-0.81 ^b	-0.66	-0.41	-	-	-	-	-	-	-1.16	-1.48 ^b	-0.87
	Month 24	-0.86 ^b	-0.90 ^b	-0.47	-	-	-	-	-	-	-	-	-
Total	Month 3	-0.78 ^a	-0.81 ^a	-0.51	-1.62 ^b	-1.94 ^{b,c}	-1.00	-1.09 ^a	-1.18 ^a	-0.67	-1.27	-1.53 ^b	-1.03
	Month 12	-0.81 ^a	-0.84 ^a	-0.46	-	-	-	-	-	-	-1.42 ^b	-1.60 ^{b,c}	-0.87
	Month 24	-0.78 ^b	-0.92 ^a	-0.54	-	-	-	-	-	-	-	-	-

^a*P*<0.001 vs PBO.

^b*P*<0.05 vs PBO.

^cDifference between BZA/CE and PBO exceeds CID, indicating clinically relevant benefit with BZA/CE vs PBO.

S-10.

Does chemotherapy induced ovarian failure lead to different menopausal symptoms? Comparison of chemo and non-chemotherapy induced menopause after breast cancer: nature, severity, impact on quality of life and sexual function

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Objective: Chemotherapy induced ovarian failure is a common consequence of breast cancer treatment in younger women. In order to provide appropriate and adequate care for breast cancer survivors, it is important to understand menopausal symptoms in breast cancer survivors may differ in terms of their nature, severity and impact on quality of life and sexual function. No previous studies have compared these outcomes in large populations of breast cancer patients and with a clinic based population experiencing spontaneous menopause. **Design:** Prospective cohort study. Data were collected for all first visits to the Menopause Symptoms After Cancer (MSAC) clinic at the largest tertiary women's hospital in Western Australia. Patients completed the Greene Climacteric Scale, a validated instrument measuring 21 menopause symptoms grouped into anxiety, depression, psychological, somatic and vasomotor domains. Women were asked frequency and severity of hot flashes. The likelihood of severe symptoms was compared between groups using logistic regression adjusted for age at menopause, age at clinic visit, and use of hormone therapy at the time of clinic visit. **Results:** There were no significant differences in any symptom domain, nor in severity or frequency of hot flashes between breast cancer survivors with chemotherapy-induced menopause (N=263) and those with other causes of menopause (N=545). We did observe a significant difference in "cold sweats", which were more troublesome to women with chemotherapy-induced menopause (adjusted OR 1.99, 95% confidence interval 1.13-3.50). **Conclusion:** This is the first study to evaluate the relative frequency, severity and troublesomeness of menopausal symptoms following chemotherapy-induced ovarian failure in breast cancer patients compared with survivors with menopausal symptoms due other causes. Although it has been claimed that chemotherapy-induced ovarian failure leads to more severe menopausal symptoms, this was not confirmed in our study.

TOP SCORING SCIENTIFIC ABSTRACT SESSION

S-11.

Efficacy of Gastroretentive Gabapentin in the Treatment of Menopausal Hot Flashes: Results of Combined Phase 3 Program

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Objective: To assess the efficacy and safety of gastroretentive gabapentin (G-GR) 1800 mg daily (600 mg AM, 1200 mg PM) compared with placebo in reducing from Baseline the average daily frequency and severity of moderate-to-severe hot flashes (HF) in postmenopausal women at Weeks 4 and 12 of the efficacy treatment period. **Design:** Three large prospective, multicenter, randomized, double-blind, placebo-controlled studies of 12 or 24 weeks duration. Primary endpoints: frequency and severity of hot flashes at Weeks 4 and 12 using the last observation carried forward (LOCF) imputation. Secondary endpoints included Patient/Clinician Global Impression of Change (P/CGIC). Severity was defined as, Mild: sensation of heat without sweating (scored 1); Moderate: sensation of heat with sweating (scored 2), or Severe: sensation of heat with sweating, causing cessation of activity (scored 3). **Results:** 1324 patients (placebo, 654; G-GR 1800 mg, 670) were enrolled in the three studies. The mean patient age was 53.5 years, 68% were Caucasian, 38% had a BMI >30, and 28% had a bilateral oophorectomy. Baseline mean HF frequency (placebo/G-GR) was 11.6/11.4 HF per day and mean severity was 2.5 in both arms. The LS mean change from Baseline at Weeks 4 and 12 shown in the table. At Week 4, patients treated with G-GR were 2.35 times more likely to have a 50% reduction in HF frequency and 1.83 times more likely to have a 50% reduction in HF severity compared with patients who received placebo. At Week 12, the corresponding rates were 1.74 times for HF frequency and 1.59 for HF severity. There was a significantly higher proportion of patients in the G-GR group who were "Much" or "Very much" improved compared with patients in the placebo group: PGIC (60.1% vs. 46.2%, *p*<0.0001); CGIC (61.3% vs. 45.0%, *p*<0.0001). **Conclusion:** This integrated analysis of the three Phase 3 studies demonstrated that G-GR 1800 mg/day (600 mg with breakfast and 1200 mg with the evening meal) is modestly efficacious for the treatment of moderate-to-severe HF due to menopause and may provide an alternative for women who are unwilling or unable to take hormone therapy.

LS Mean Change in Frequency and Severity of Hot Flashes

	Placebo (n=654)	G-GR (n=670)
FREQUENCY		
Week 4 LS mean (SEM)	-5.19 (0.189)	-6.76 (0.186)
Delta (p-value)	-1.57 (p<0.0001)	
Week 12 LS mean (SEM)	-6.42 (0.212)	-7.42 (0.208)
Delta (p-value)	-1.0 (p<0.0001)	
SEVERITY		
Week 4 LS mean (SEM)	-0.27 (0.031)	-0.48 (0.031)
Delta (p-value)	-0.21 (p<0.0001)	
Week 12 LS mean (SEM)	-0.50 (0.042)	-0.71 (0.041)
Delta (p-value)	-0.21 (p<0.0001)	

G-GR=gastroretentive gabapentin, LS=least squares, SEM=standard error of the mean

S-12.

Transdermal Testosterone Improves Selective Serotonin Reuptake Inhibitor-associated Female Sexual Dysfunction; a Randomized, Double-blind, Placebo-controlled Trial

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Objective: Female sexual dysfunction (FSD) is an established side-effect of selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor (SNRI) therapy, with the most common symptoms being low libido, arousal difficulties and anorgasmia. There is no established treatment for SSRI-associated FSD other than discontinuation of therapy. Transdermal testosterone (TT) has been shown to be effective for the treatment of low libido/arousal in women not using antidepressants. The aim of this study was to investigate the efficacy of TT in women at midlife who are experiencing SSRI/SNRI-associated FSD. **Design:** This was a double-blind, randomized, placebo-controlled, single-center study of TT in women aged 35 to 55 years on stable SSRI or SNRI therapy for at least 3 months with treatment-associated FSD. Women were excluded if they were taking conjugated estrogen, had used any androgen therapy, had another medical condition interfering with normal sexual function or had relationship issues. Participants were randomly assigned to treatment with a TT patch (TTP) delivering 300mcg/day of testosterone, or to an identical placebo patch (PI) for 12 weeks. Sexual function was assessed at baseline and 12 weeks using the Sabbatsberg Sexual self-rating Scale (SSS). Other outcomes included the 4-week frequency of Satisfactory Sexual Events (SSEs) (recorded 4 weeks prior to randomization and week 12), the domains of the SSS, the Female Sexual Distress Scale-Revised (FSDS-R), the Psychological General Well-Being Index (PGWB), the Beck Depression Inventory (Beck-II) and the Profile of Mood

States (POMS). The analysis was by intention-to-treat (ITT). Modelling was performed for each primary and secondary outcome using linear or Poisson regression, with the outcome variable being the 12 week value and the independent variables: treatment group, baseline value and menopause status. In the linear regression, a bootstrapping approach with 5000 repetitions was used to address the issue of outlying values. **Results:** Of 44 women randomized, 36 women (20 in the TTP group and 16 in the PI group), mean age 47.7± 5.6 years, completed the study and provided data for analysis. At baseline, there were no differences between the treatment groups for any of the sexual function measures or total serum testosterone (TTP median 0.55 nmol/L vs. PI 0.3 nmol/L). At baseline, the median number of SSEs in the TTP and PI groups were 2 and 1.5 events/month, respectively. At 12 weeks, the median number of SSEs/month were 6 (TTP) vs. 2 (PI), ($p<0.001$). At 12 weeks, compared with PI, the TTP group had significantly more sexual thoughts and fantasies ($p<0.001$), sexual arousal ($p=0.031$), total sexual events ($p=0.015$) and initiation of sex ($p=0.006$). The difference between the TTP and PI groups in terms of the FSDS-R score approached significance ($p=0.06$). There were no significant differences between treatment groups at 12 weeks for the SSS total and its domains, the PGWB, the POMS or the Beck-II scores. The median total serum testosterone level at 12 weeks in the TTP group was 1.9 nmol/L (reference range for young premenopausal women 0.3-2.9 nmol/L). No women withdrew because of androgenic adverse events. **Conclusion:** TTP therapy was associated with an increase in the number of SSEs, enhanced sexual interest, arousal and increased total sexual activity in women with SSRI/SNRI-associated FSD. This provides the first evidence that TT therapy may be a treatment option for women with SSRI/SNRI-associated FSD who need to remain on their antidepressant therapy.

S-13.

Safety of Oral Ospemifene in Phase 2/3 Placebo-controlled Clinical Trials

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Objective: Vulvar and vaginal atrophy (VVA), is a chronic and progressive condition producing physiological changes to the vaginal epithelium that do not reverse without treatment. Prescription treatment options for postmenopausal women with VVA have been limited to estrogen-based systemic or topical vaginal preparations. For some women, concerns about steroidal estrogen safety or inconvenience can present barriers to treatment. Oral ospemifene, a tissue selective estrogen agonist/antagonist, was recently approved by the Federal Food and Drug Administration (FDA) for the treatment of dyspareunia in postmenopausal women, a symptom of VVA. Reported here are results of an evaluation of 12- and 52-week safety data from Phase 2/3 placebo-controlled trials in the ospemifene clinical development program. **Design:** Seven Phase 2/3 double-blind placebo-controlled trials assessed the safety of ospemifene in subjects receiving at least 1 dose of study drug ranging from ≤15 to 90mg/day compared to placebo. Subjects were postmenopausal (naturally or surgically), aged 40-80 years; median age was 59 years. The majority of subjects had an intact uterus, (67.2% ospemifene, 59.6% placebo). Endometrial biopsies were performed at Baseline, 12 weeks and 12 months (and at any other time as necessary) for incidence of endometrial hyperplasia and carcinoma. **Results:** In this safety population, postmenopausal women receiving ospemifene or placebo ($n=1696$; $n=958$) were evaluated. Treatment emergent adverse events (TEAEs) were reported in 1118 (65.9%) vs 518 (54.1%) subjects; the majority were classified as mild or moderate in severity. No clear dose-related increase in adverse events (AEs) was seen with ospemifene. For ospemifene, the most commonly reported TEAE was hot flush (8.5% vs 3.3% for placebo) and incidence of TEAEs from venous thrombotic events (0.1%) was low. Across all 7 clinical trials, discontinuation due to TEAEs was low for ospemifene (7.0%) and for placebo (3.8%). Overall discontinuation due to hot flush was 0.9% for ospemifene vs 0.3% for placebo, and 1.0% for the ospemifene 60mg registration dose. Serious adverse events (SAEs) were experienced by 39 (2.3%) ospemifene vs 17 (1.8%) placebo subjects. No endometrial hyperplasia or carcinoma was reported with ospemifene or placebo at 12 months. No deaths were reported in any of the trials. **Conclusion:** Ospemifene was well-tolerated in 7 double-blind, Phase 2/3, placebo-controlled trials that evaluated safety up to 52 weeks in postmenopausal women with VVA. Patient disposition and safety data were not different at 12 and 52 weeks. Discontinuation due to TEAEs, including hot flush, and incidence of SAEs for ospemifene was low. Evaluation of safety data from Phase 2/3 trials supports use of ospemifene as the first oral alternative to estrogen prescription therapies for the treatment of dyspareunia in postmenopausal women.

S-14.

Effects of Stellate Ganglion Block on Vasomotor Symptoms: Findings from a Randomized Clinical Trial in Postmenopausal Women

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Objective: Vasomotor symptoms (VMS), which include hot flashes and night sweats, are cardinal menopausal symptoms and affect up to 80% of women. Although hormone therapy is the most effective treatment for VMS, women seek alternative therapies due to contraindications to hormone therapy, safety concerns, and personal preference. Several uncontrolled open-label intervention studies have demonstrated improvements in the frequency and intensity of VMS following stellate ganglion blockade (SGB) with local anesthetic. Here we present findings from the first randomized, sham-controlled trial of SGB for the treatment of VMS. We hypothesized that SGB would significantly reduce both self-reported and objective VMS. **Design:** The study design was a randomized, sham-

controlled, parallel-group trial examining the impact of active versus sham SGB on VMS in postmenopausal women with moderate-to-severe VMS. Entry criteria included age 30-65 years, postmenopausal status due to surgery or natural menopause, moderate-to-severe VMS (defined as 25 or more episodes per week as indicated on diaries), and willingness to undergo fluoroscopy-guided SGB. Active stellate ganglion injection was performed with fluoroscopic guidance on the anterolateral aspect of the right C6 vertebra using 0.5% bupivacaine 5 cc. Successful SGB was confirmed by Horner's syndrome (miosis, ptosis, anhidrosis). Sham stellate ganglion injection involved the same positioning, monitoring and sterile preparation, but the needle was placed in the subcutaneous, superficial tissues overlying the C6 tubercle and not in the plane of the stellate ganglion; 5 cc of preservative free normal saline was injected. Randomization was performed by the injectionist immediately prior to the injection procedure. Participants and all other study personnel were blinded to group assignment. Participants reported frequency and severity (mild, moderate, severe, very severe) of VMS for two weeks prior to the injection procedure and for six months thereafter in a daily log. Objective VMS were recorded over a 24-hour period using an ambulatory sternal skin conductance monitor (Biolog Model 3991x/2-HFI) before randomization and three months after injection. **Results:** A total of 40 participants were randomized between February, 2009 and November, 2012. There were no group differences in the frequency or severity of VMS at baseline. Two intent-to-treat analyses were performed on VMS frequency, one on total number regardless of severity and another on moderate-to-severe VMS. The intent-to-treat analysis for all VMS showed no significant group differences in VMS frequency from baseline to 1 week or from baseline to 1-3 months post-injection. There was a trend toward a group difference in VMS frequency from baseline to 4-6 months post-injection ($p=.10$). A placebo effect was observed in the sham group until 3 months post-injection. In the intent-to-treat analysis of moderate-to-severe VMS, SGB-treated women showed significantly greater reductions (50%) from baseline to 4-6 months compared to the sham group (0%) (RR 0.50, CI 0.34-0.73, $p<0.001$). A total of 35 participants had valid objective VMS data (18 in active SGB, 17 in sham). The total number of objective hot flashes from baseline to 3 months was reduced to a greater degree in the SGB group compared to the sham group (RR 0.71, CI 0.64-0.99, $p<0.05$). There were no study-related serious adverse events. **Conclusion:** The first prospective, randomized sham-controlled trial demonstrates the efficacy of SGB on the reduction in frequency of moderate-to-severe VMS in women with natural or surgical menopause. The beneficial effect of SGB on VMS was supported by the observation that SGB significantly reduced the number of objective VMS compared to sham. Although previous studies have suggested quite sizeable effects of SGB on VMS, the current study suggests a reduction of 50% in moderate-to-severe VMS when compared to a sham (0%) and a 21% reduction on the total number of objectively measured VMS. Larger studies are needed to verify these findings.

FRIDAY CONCURRENT SESSION #1

S-15.

Breast Safety of Bazedoxifene/Conjugated Estrogens: Pooled Analysis of Phase 3 Trials

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Objective: The tissue selective estrogen complex partnering bazedoxifene (BZA) with conjugated estrogens (CE) has demonstrated efficacy in the treatment of menopausal symptoms and prevention of postmenopausal osteoporosis. In preclinical models, BZA blocked CE-induced breast tissue proliferation. In the phase 3 Selective Estrogens, Menopause, And Response to Therapy (SMART)-1 and SMART-5 trials, BZA/CE did not increase mammographic breast density. The breast safety profile of BZA/CE was assessed based on pooled data from the SMART clinical trial program. **Design:** Data for BZA 20 mg/CE 0.45 mg ($n = 1,585$), BZA 20 mg/CE 0.625 mg ($n = 1,583$), CE 0.45 mg/medroxyprogesterone acetate (MPA) 1.5 mg ($n = 399$ [SMART-4 and -5 only]), raloxifene (RLX) 60 mg ($n = 423$ [SMART-1 only]), and placebo (PBO; $n = 1,241$) were pooled from 5 randomized, double-blind, PBO- and active-controlled phase 3 studies in non-hysterectomized postmenopausal women (2-year SMART-1, 12-week SMART-2, 12-week SMART-3, 1-year SMART-4, and 1-year SMART-5). The incidence of breast procedures (including biopsies, aspirations, and nipple discharge cytology evaluations) was pooled from all 5 SMART trials (data not available for RLX). Mammography data were pooled from SMART-1, SMART-4, and SMART-5. Mammograms were classified as normal or abnormal in SMART-1 and evaluated using Breast Imaging-Reporting and Data Systems (BI-RADS) in SMART-4 and -5 (abnormal mammograms were defined as BI-RADS 4 [SMART-4] or BI-RADS 4 and 5 [SMART-5]). Incidence of breast pain/tenderness, as measured by daily diaries, was pooled from SMART-1, -2, -4, and -5 (breast pain/tenderness data not collected in SMART-3) for 3 time periods (Weeks 1-4, 5-8, and 9-12). Breast-related adverse events (AEs) were pooled from all 5 SMART trials; breast cancer incidence was determined from cumulative meta-analysis with inverse variance weighting. **Results:** Pooled data from the 5 SMART trials showed demographics were generally balanced across treatment groups. The overall incidence of breast cancer per 1000 woman-years was 1.00 (95% confidence interval [CI], 0.00-3.21) for BZA 20 mg/CE 0.45 mg, 0.00 (95% CI, 0.00-1.54) for BZA 20 mg/CE 0.625 mg, 1.05 (95% CI, 0.00-6.89) for CE 0.45 mg/MPA 1.5 mg, 0.00 (95% CI, 0.00-2.20) for RLX 60 mg, and 1.40 (95% CI, 0.00-4.17) for PBO (Table). Incidences of abnormal mammograms were similar with both BZA/CE doses compared with PBO and CE/MPA and significantly lower compared with RLX 60 mg (Table). The percentage of subjects who had follow-up breast procedures was similar for BZA 20 mg/CE 0.45 mg (0.76%), BZA 20 mg/CE 0.625 mg (0.88%), and PBO (0.89%); the percentage of subjects was numerically higher for CE 0.45 mg/MPA 1.5 mg (1.50%) and RLX 60 mg (1.33%). Based on daily diary

data, the incidence of breast pain/tenderness with BZA 20 mg/CE 0.45 mg (9.8%-11.5%) and BZA 20 mg/CE 0.625 mg (9.8%-10.2%) was similar to PBO (8.1%-11.2%) and RLX (6.2%-8.7%) and significantly lower than with CE 0.45 mg/MPA 1.5 mg (21.6%-29.1%; $P < 0.001$) at all time points evaluated (Table). The incidences of breast-related AEs such as breast calcifications, cyst, mass, and neoplasm were low ($\leq 1\%$ for each AE) and similar among groups. **Conclusion:** Pooled phase 3 clinical trial data showed that BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were associated with an acceptable breast safety profile with no increase in breast-related tolerability concerns.

Table. Summary of Breast Cancer Incidence (SMART-1-5), Pooled Abnormal Mammograms (SMART-1, SMART-4, SMART-5) and Pooled Breast Pain/Tenderness (SMART-1, SMART-2, SMART-4, SMART-5)

Treatment	Breast cancer incidence per 1000 woman-years (95% CI)	Number (%) of women with abnormal mammogram at		Number (%) of women reporting breast pain/tenderness		
		Month 12	Weeks 1-4	Weeks 5-8	Weeks 9-12	
BZA 20 mg/CE 0.45 mg	1.00 (0.00-3.21)	20 (2.58) ^a	128 (11.50) ^b	96 (10.75) ^b	84 (9.82) ^{3,4}	
BZA 20 mg/CE 0.625 mg	0.00 (0.00-1.54)	20 (2.60) ^a	109 (9.78) ^b	87 (9.95) ^b	88 (10.22) ^{3,4}	
CE 0.45 mg/MPA 1.5 mg	1.05 (0.00-6.89)	3 (1.66)	66 (21.57) ⁴	60 (29.13) ⁴	55 (28.21) ⁴	
RLX 60 mg ^c	0.00 (0.00-2.20)	16 (5.33)	36 (8.67)	33 (8.21)	24 (6.20)	
PBO	1.40 (0.00-4.17)	20 (3.16)	99 (11.17)	73 (11.13)	51 (8.07)	

^a $P < 0.05$ for BZA/CE vs RLX.

^b $P < 0.001$ for BZA/CE vs CE/MPA.

^c $P < 0.001$ for CE/MPA vs PBO.

^d $P < 0.001$ for CE/MPA vs RLX.

^eStatistical tests of RLX vs PBO and RLX vs CE/MPA were not done.

S-16.

Mammographically detected Breast Arterial Calcifications and Coronary Artery Disease: A meta-analysis

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Objective: Coronary artery disease (CAD) and strokes continue to be the leading causes of morbidity and mortality among women in the United States. Regular screening mammograms are recommended for women after age 40 due to their ability to assist in the early detection of breast cancer. The investigators of many recent studies have analyzed the relationship between breast arterial calcifications (BACs), seen on mammography, with both CAD and strokes. We conducted a meta-analysis of the current literature to deduce the strength of this association. **Design:** Using the search terms "breast arterial calcification", "breast artery calcium", "breast vascular calcification", "coronary artery disease", "coronary heart disease", "cardiovascular disease", "myocardial infarction", "angina pectoris", "abnormal coronary angiography", "coronary artery bypass graft", "stroke" and "peripheral vascular disease", our literature search revealed 75 articles. Limiting our search to articles that analyzed only CAD and/or stroke, 35 full manuscripts were reviewed. Of these articles, 16 were included in the final analysis. **Results:** Two cohort studies were analyzed, one prospective and one retrospective where $n=14,215$. The odds ratio (OR) for developing CAD in those with BAC, vs. those without BAC, is 1.61, 95% CI: 1.33-1.95, and $p<0.0001$. For stroke, the OR=1.79, 95% CI: 1.55-2.23 and $p<0.0001$. There were 10 cross-sectional studies analyzed with CAD as the primary outcome, diagnosed by coronary angiography, where $n=3,952$. The OR of CAD in those with BAC, vs. those without BAC, is 3.86, 95% CI: 3.25-4.59 and $p<0.0001$. For stroke, 7 cross-sectional studies were analyzed where $n=19,011$. The OR of stroke in those with BAC, vs. those without BAC, is 1.77, 95% CI: 1.45-2.16 and $p<0.0001$. **Conclusion:** These results suggest that BAC is significantly associated with both CAD and stroke. Although previous studies have been criticized regarding sample sizes and study designs, a recent prospective study along with this robust data set and meta-analysis adds to our knowledge. While more prospective studies are warranted to clarify whether BACs are truly a predictor of the future development of CAD and stroke, there clearly appears to be an association. In light of this, it may be beneficial to routinely report BACs on mammograms to alert providers to the increased risk for the presence of, vs. development of, CAD and / or stroke.

S-17.

Higher Volumes of Ectopic Cardiovascular Fat Depots are Associated with Menopausal Status: The Study of Women's Health Across the Nation (SWAN) Ectopic Cardiovascular Fat Ancillary Study

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Objective: Cardiovascular risk increases in women after menopause. Mounting evidence demonstrates a role of ectopic cardiovascular fat (ECF), fat surrounding the heart and the vasculature, in the pathogenesis of coronary heart disease (CHD). Whether ectopic cardiovascular fat is higher in women transition through menopause is not known. Using data from the SWAN Ectopic Cardiovascular Fat Ancillary Study, we evaluated the cross-sectional associations between volumes of epicardial (EAT), pericardial (PAT), total thoracic (TAT; TAT=EAT+PAT) and perivascular (peri-aortic) (PVAT) adipose tissues in middle-aged women at various stages of the menopausal transition. **Design:** The Study of Women's Health Across the Nation (SWAN) is an ongoing longitudinal, community-based study. The current study uses cross-sectional data from the ectopic cardiovascular fat SWAN ancillary study at the Pittsburgh and Chicago sites. Volumes of ECF were quantified using electron beam computed tomography scans. Linear regression was used for analysis and log transformation was applied to all ECF volumes to achieve normality. **Results:** The study included 243 women (32.9% black and 67.1% white; 57.2% pre-/early peri-menopausal and 42.8% late peri-/postmenopausal) aged 46-58 years with data on any of the 4 ECF depots ($n=217$ with EAT, PAT and TAT data and $n=138$ with PVAT data). Pre-/early peri-menopausal women have less EAT (median (Q1, Q3): 34.99(28.20,

52.49) cm³ vs. 43.77(33.08, 58.25) cm³, P value=0.01) and TAT (median (Q1, Q3): 42.50(33.11, 64.46) cm³ vs. 51.86(38.98, 74.33) cm³, P value=0.03) compared to late peri-/postmenopausal women, respectively. These differences were attenuated (EAT p -value: 0.07 and TAT p -value: 0.08), after adjusting for age, race, income, site, obesity (BMI ≥ 30 Kg/m²), current smoking, use of medications (antihypertensive, anti-diabetic and/or lipid lowering) and co-morbidity (history of hypertension, stroke, angina, heart attacks and/or diabetes). Significant interactions by race and menopausal status showed that these associations were more pronounced in black women in the final models with pre-/early peri-menopausal black women having significantly less volumes of EAT and TAT as compared to black or white late peri-/postmenopausal women, P values ≤ 0.05 for all comparisons, (adjusted for multiple comparisons). **Conclusion:** The current study reported higher volumes of EAT and TAT in late peri-/postmenopausal women compared to pre-/early peri-menopausal women. These associations were more pronounced in black women and were independent of demographics, age, obesity, smoking, medication use and co-morbidity. Perhaps ECF plays a role in the higher risk of CHD reported in women after menopause. Acknowledgments: The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). The Study of Women's Health Across the Nation Heart is supported by the National Heart, Lung, and Blood Institute (Grants HL065581, HL065591). The SWAN Ectopic Cardiovascular Fat Ancillary Study was supported by an award from the American Heart Association Great River Affiliation Clinical Research Program: 12CRP11900031

S-18.

Venous Thromboembolism and Cardiovascular Disease Complications in Women using Transdermal Versus Oral Menopausal Estrogen Therapy

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Objective: Venous thromboembolism (VTE) and cardiovascular diseases (CVD) are serious complications associated with hormone therapy. The aim of this study was to evaluate the risk of VTE and CVD complications and compare healthcare costs in women using estradiol transdermal system (ETS; Vivelle-Dot®) relative to oral menopausal estrogen therapy. **Design:** Health insurance claims from 60 self-insured US companies covering the period 01/1999-09/2011 were analyzed. Women ≥ 35 years old, newly initiated on an ETS or oral estrogen therapy with ≥ 2 dispensings were included. VTE was defined as ≥ 1 diagnosis code for deep vein thrombosis (DVT; ICD-9 codes: 451.1x, 451.2, 453.4x, 453.8, 453.9) or pulmonary embolism (PE; ICD-9 codes: 415.1x) and CVD was defined as ≥ 1 diagnosis code for one of the following conditions: ischemic heart disease, other forms of heart disease, cerebrovascular disease, unspecified hypertensive heart disease, tachycardia unspecified, and palpitations (ICD-9 codes: 402.9x, 410.xx-414.xx, 420.xx-438.xx, 785.0, and 785.1). Women with a history of VTE or CVD, or using any estrogen agents within 180 days before the initiation of ETS or oral estrogen therapy were excluded. Both cohorts were matched 1:1 based on exact factors and propensity score matching methods. The incidence rates of the composite endpoint of VTE or CVD complications, as well as VTE and CVD events separately, were calculated for all events and hospitalization-related events. The incidence rate ratio (IRR), assessed through both unadjusted and conditional Poisson models adjusting for matched pairs and progestin/estrogen agents used during the observation period, was used to compare the rates of events for ETS relative to oral estrogen therapy cohorts. Matched cohorts were also compared for all-cause healthcare costs using linear regression models to assess per-patient per-month (PPPM) cost differences. VTE/CVD-related costs, defined as the subset of claims with a diagnosis of VTE or CVD, were also calculated. Confidence intervals and p -values were determined using a nonparametric method for cost endpoints. **Results:** Among the 7,558 women receiving ETS and 41,433 receiving oral estrogen therapy, 7,552 users in each cohort were matched to form the study population. The mean age for both cohorts was 50 years. The mean drug exposure for the ETS and oral estrogen therapy cohorts was 533 and 532 days, respectively. Progestin agents were used by 12.4% and 11.7% of ETS and oral estrogen therapy users at baseline, respectively. A total of 718 ETS users developed VTE or CVD complications compared to 828 women in the estrogen therapy cohort (adjusted IRR: 0.79; 95% CI: 0.70-0.89, $P<0.001$). Table 1 shows that ETS users had significantly lower risk of developing VTE/CVD, VTE, and CVD for all events as well as hospitalization-related events, relative to oral estrogen therapy users. ETS users also incurred significantly lower adjusted all-cause and VTE/CVD-related healthcare costs relative to oral estrogen therapy users (all-cause PPPM cost difference [95% CI]=\$56 [-109], $P=0.026$; VTE/CVD-related PPPM cost difference [95% CI]=\$24 [-51], $P=0.024$). **Conclusion:** This large matched-cohort study of over 15,000 women based on real-world data suggests that women receiving ETS have significant lower incidences of VTE and CVD events compared to women receiving oral estrogen therapy and that they also incur significantly lower healthcare costs.

Table 1. Incidence rate ratios of VTE/CVD of the ETS cohort relative to the Oral estrogen therapy cohort

Outcome Measures	Frequency of Event		Incidence Rate (per 100 person-years)		Univariate Analysis		Adjusted Conditional Poisson	
	ETS	Oral Estrogen	ETS	Oral Estrogen	IRR (95% CI)	P-value	IRR (95% CI)	P-value
All Events								
VTE or CVD	718	828	7.15	8.28	0.86 (0.78 - 0.95)	0.0040	0.79 (0.70 - 0.89)	0.0001
VTE	36	56	0.33	0.51	0.64 (0.42 - 0.97)	0.0375	0.53 (0.31 - 0.90)	0.0186
CVD	696	794	6.91	7.91	0.87 (0.79 - 0.97)	0.0094	0.80 (0.71 - 0.91)	0.0005
Hospitalization-related								
VTE or CVD	108	177	0.99	1.64	0.61 (0.48 - 0.77)	<0.0001	0.52 (0.39 - 0.68)	<0.0001
VTE	7	16	0.06	0.15	0.44 (0.18 - 1.06)	0.0675	0.14 (0.04 - 0.44)	0.0008
CVD	104	167	0.95	1.54	0.62 (0.48 - 0.79)	0.0001	0.54 (0.40 - 0.72)	<0.0001

S-19.

Premenopausal Antimüllerian Hormone is a Risk Marker for Postmenopausal Coronary Artery Atherosclerosis Progression in Cynomolgus Monkeys

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Objective: Antimüllerian hormone (AMH) is a marker of ovarian reserve, is a predictor of peripheral (iliac) artery atherosclerosis progression in monkeys (Appt et al., Menopause, 2012) and has been associated with cross-sectional measures of cardiovascular disease (CVD) risk markers in women (Bleil et al., Menopause, 2013). The purpose of this study was to determine if AMH, measured prior to ovariectomy, predicted post-menopausal coronary artery atherosclerosis extent in cynomolgus monkeys. **Design:** Subjects were 19 socially housed, female cynomolgus monkeys (Macaca fascicularis, women's equivalent age ~ 45 years). Monkeys consumed a typical Western diet for 7 months prior to bilateral ovariectomy (OVX) and for an additional 26 months post-OVX. After 26 months of diet consumption, coronary arteries were collected for measurement of plaque extent (atherosclerosis intimal area, mm²) and plaque severity (American Heart Association grading system, AHA grades 1-6). Plasma AMH, estradiol (E2), follicle stimulating hormone (FSH), lipids and lipoproteins and body weight were measured prior to OVX, and after 26 months of diet consumption. **Results:** Premenopausal monkeys with plasma AMH concentrations below the median prior to ovariectomy developed greater coronary artery plaque extent than those with AMH above the median (AMH-LO - 0.33 ± 0.06; AMH-HI - 0.14 ± 0.05, mm², p = 0.027). Plaque severity grades (maximum and mean AHA grade) followed a similar pattern but did not reach significance (AMH-LO_max AHA = 3.8 ± 0.4 vs. AMH-HI_max AHA = 2.9 ± 0.4, p = 0.13). Premenopausal estradiol area under the curve across a single menstrual cycle was lower in monkeys below the median AMH (AMH-LO_E2 = 718.2 ± 60 vs. AMH-HI_E2 = 947.3 ± 64, p = 0.025). However, premenopausal estradiol was not correlated with postmenopausal atherosclerosis extent (r = -0.01, p = 0.97). Premenopausal follicular phase FSH also did not differ according to premenopausal AMH group (AMH-LO_FSH = 0.59 ± 0.08 vs. AMH-HI_FSH = 0.71 ± 0.08, p = 0.34). Premenopausal and postmenopausal lipids, and premenopausal body weight, were correlated significantly with atherosclerosis extent. However, no differences were observed at baseline or post-intervention in body weight or plasma lipids when data were analyzed by AMH-LO vs. AMH-HI groups. Post-ovariectomy, estradiol and AMH were below the level of assay detection and FSH increased greater than 10-fold (FSH pre-OVX = 0.64 ± 0.06 vs. post-ovx = 8.2 ± 1, p < 0.0001). **Conclusion:** Premenopausal ovarian reserve may be an indicator of risk for coronary artery atherosclerosis development following oophorectomy. This association was independent of premenopausal E2, FSH and plasma lipids and was also independent of postmenopausal lipid profiles.

FRIDAY CONCURRENT SESSION #2

S-20.

Trends in Exogenous Hormone Therapy Before and After WHI: Data from the Study of Women's Health Across the Nation (SWAN)

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Objective: Prescriptions of hormone therapy (HT) declined dramatically after the July 2002 halt to the Women's Health Initiative (WHI) estrogen-progestin trial. Prior studies used databases from pharmacies or insurance claims, which provide detailed information on prescriptions but have limited data on correlates of HT use or women's reasons for starting or stopping. We analyzed up to 10 years of prospective data from 3087 SWAN participants, aged 42-52 and pre- or early perimenopausal at baseline, to compare pre- and post-WHI: 1) percent and correlates of starting and continuing HT use; and 2) reasons for starting and stopping HT. **Design:** SWAN measured medication use since the last study visit, HT start and stop reasons, and covariates annually. Analyses used generalized estimating equation logistic regression to handle within-woman correlation, and adjusted for propensity scores for post- vs. pre-WHI to account for changes in cohort characteristics over time. **Results:** Non-HT users pre-WHI (2989 women) were more likely to start HT by the next visit than were non-HT users post-WHI (2417 women) - 8.0% vs. 3.0%

respectively, p < 0.0001. Among non-HT users, those with frequent vasomotor symptoms (VMS) were most likely to start HT both pre- and post-WHI, although more so pre-WHI (12.4% pre- vs. 3.6% post-WHI). Declines in the percent of women starting HT post-WHI also were largest in the late perimenopause (13.2% pre- vs. 3.5% post-WHI). Similarly, HT users pre-WHI (644 women) were more likely to continue HT at the next visit than were HT users post-WHI (699 women) - 76.2% vs. 57.5% respectively, p < 0.0001. Both pre- and post-WHI, HT users with concurrent frequent VMS were less likely to continue HT than other HT users, perhaps due to lack of symptom relief, with a lower percent continuing post-WHI (73.3% pre- vs. 39.4% post-WHI). The decline in the percent of women continuing HT was more marked for those with more than a high school education (77.9% pre- vs. 57.65 post-WHI) than in less-educated women (69.0% pre- vs. 59.0% post-WHI). Pre- vs. post-WHI differences in starting and continuing HT were similar across White, Black, Chinese, Hispanic, Japanese groups. Reasons for starting HT changed post-WHI, with the percent of HT users reporting reduction of heart disease risk or osteoporosis prevention as a reason for starting declining dramatically (26.4% pre- vs. 4.4% post-WHI, p < 0.0001 and 36.3% pre- vs. 11.2% post-WHI, p < 0.0001, respectively). In contrast, changes were much smaller for the following starting reasons: menopausal symptom relief (72.6% pre- vs. 68.9% post-WHI, p = 0.32) and health care provider advice (79.1% pre- vs. 71.8% post-WHI, p = 0.03). Regarding reasons for stopping HT, bleeding-related reasons were listed less often (19.7% pre- vs. 7.6% post-WHI, p = 0.0002) as were minor side effects such as breast pain (19.4% pre- vs. 8.9% post-WHI, p = 0.004) while health care provider advice (13.1% pre- vs. 28.9% post-WHI, p < 0.0001) and media reports (0.9% pre- vs. 19.5% post-WHI, p < 0.0001) were mentioned more often as reasons for HT discontinuation after WHI. **Conclusion:** In SWAN, self-reported HT use decreased post-WHI, particularly in women with frequent VMS and higher education, but decreases did not differ by race/ethnicity. Changes in reasons for starting/stopping HT were consistent with the health-related messages conveyed by the early cessation of the WHI. The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). The content of this abstract is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

S-21.

Staging reproductive aging using STRAW+10 in urban African women in the Study of Women Entering and in Endocrine Transition (SWEET)

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Objective: There is a paucity of research on accurately diagnosing mean age at final menstrual period (FMP) and on staging the menopause transition (MT) in sub-Saharan African women. There is also very little data documenting the correlation between the MT and non-communicable diseases (NCDs) in African women, although there is considerable research on this topic in women in high-income countries. Obesity is prevalent in middle-aged, urban African females but there are very few studies analyzing the relationship between obesity and the MT and its effect on the prevalence of vasomotor symptoms (VMS), NCD's and associated risk factors. VMS are one of the defining symptoms of the MT, and have been linked to an increased risk of cardiovascular disease. Accurate staging of reproductive aging is fundamental to understanding these relationships. Here we assess the reliability of using STRAW+10, considered the gold standard for staging reproductive aging, to classify ovarian status in urban South African women. In addition, the effect of obesity on FMP and VMS was analyzed. **Design:** This cross sectional study randomly recruited black urban South African women between the ages of 40 and 60 years from mothers of the Birth to Twenty cohort (n=702). STRAW+10 was used to categorize women into late reproductive (stages -3b and -3a), early transition (stage -2), late transition (stage -1), early (stages 1a, 1b and 1c) and late (stage 2) postmenopause. The Menopause Rating Scale (MRS) was used to measure the prevalence of VMS. We used VMS and levels of follicle-stimulating hormone (FSH) and estradiol (E2) as supportive criteria for staging. Use of hormone therapy, hormonal contraception and hysterectomy were recorded. The women were also asked about their understanding of the menopause ('change of life'). Anthropometric measures were taken. Differences in mean FSH and E2 levels across the 7 menopause groups were analyzed using ANCOVA with adjustment for age and BMI. The risk of VMS of any grade within each menopause stage was analyzed by logistic regression with the -3b group used as the reference, with adjustment for age and obesity. **Results:** This analytical sample contained 637 women for whom the prevalence of obesity (BMI ≥ 30kg/m²) was 67.6%. Only 48.3% of the group had an understanding of the MT. Menopausal stage could not be ascertained in 57 (9.1%) women due to contraceptive use (n=27), hysterectomies (n=29) and hormone therapy (n=1). The number of women in each menopausal stage, as assessed using STRAW+10, was as follows: -3b, 182; -3a, 25; -2, 43; -1, 69; 1a+1b, 33; 1c, 111; 2, 118. The mean (±SD) age at FMP was 46.0±4.6 years (range, 27-57 years; n=210), and was similar in obese (46.1±4.69 years) and non-obese (45.8±4.59 years) women. Prevalence of VMS of any degree was 61.7%. The mean FSH level (IU/L) increased across the 7 groups: -3b, 13.4±19.7; -3a, 13.8±13.1; -2, 26.8±31.8; -1, 40.4±33.2; 1a+1b, 67.2±42.7; 1c, 59.5±33.2; 2, 69.2±24.1 (p < 0.0001). The mean E2 levels (pmol/L) fell across the menopause stages (p < 0.0001), being highest at stage -3b (440±916) and lowest at stage 2 (49.7±55.1). Risk for VMS (expressed as OR [95% CIs]) was significant (p < 0.05) in menopausal stages -1 (2.04 [1.09, 3.82]), 1a+1b (2.59 [1.07, 6.31]) and 1c (1.95 [1.06, 3.60]). Obesity was not associated with an increased risk of VMS (0.81 [0.56, 1.18]; p = 0.28). **Conclusion:** Although 51.7% of the group had no understanding of the MT, STRAW+10 appeared to

be a reliable method of staging reproductive aging, showing a strong association of MT stage with FSH, E2 and VMS levels. This finding suggests that STRAW+10 may be appropriate for staging reproductive aging in resource-limited settings. However, validated interviewer questions, and simplification of technical terms may further improve accuracy. Age at FMP was lower than that observed in studies of Western women and was not associated with obesity. As expected, VMS were strongly associated with the stages of late menopausal transition and early postmenopause, but unlike many large multi-ethnic studies, including the Study of Women's Health Across the Nation (SWAN), obesity was not associated with VMS.

S-22.

Burden of Menopausal Symptoms: Analysis of healthcare resource utilization using the Medical Expenditure Panel Survey (MEPS)

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Objective: To explore the relative cost burden associated with menopausal symptoms in comparison to other chronic conditions among a nationally representative sample of women ages 45-65. **Design:** Women in the 2009 MEPS, ages 45-65 years, with no history of hysterectomy, were included in this analysis. Study subjects included women with self-reported menopausal symptoms (as defined by the MEPS classification code), osteoporosis, fibromyalgia, overactive bladder, depression or cardiovascular disease. Subjects with more than one of the above conditions were excluded from the study sample. All women were compared to controls defined as females who reported none of the medical conditions listed above during the study period (1/01/09-12/31/09). Economic burden was calculated as direct costs and included total expenditures and total charges for inpatient, outpatient, and emergency department visits. **Results:** 47% of the study population was classified as White with a mean age of 53.4 years. Women with menopausal symptoms had a mean age of 53.6 and 68.8% were classified as White. The annual direct health care costs among women experiencing menopausal symptoms were significantly higher than those of the control population. Costs associated with menopausal symptoms were not significantly different from those associated with osteoporosis, depression, and overactive bladder in this sample of women. **Conclusion:** In a sample of women drawn from the 2009 MEPS, annual direct health care costs in women experiencing menopausal symptoms were significantly higher than those of controls and comparable to those associated with osteoporosis, depression, and overactive bladder.

Table 1: Study Sample Demographics

Condition (n)	Age (SD)	Race-Ethnicity, %				
		White	Black	Asian	Hispanic	Other
Controls (411)	52.3 (5.6)	29	20	13.6	35.8	1.7
Menopausal Symptoms (77)	53.6 (5.0)	68.8	11.7	2.6	14.3	2.6
Osteoporosis (55)	58.4 (5.4)	58.2	1.8	20	20	0
Fibromyalgia (241)	54.0 (5.8)	49.8	22.4	6.2	18.7	2.9
Overactive Bladder (9)	52.1 (4.7)	55.6	22.2	0	22.2	0
Depression (294)	53.3 (5.6)	60.9	14.3	3.1	20.7	1
Cardiovascular Disease (21)	56.7 (5.7)	47.6	23.8	0	28.6	0

Table 2: Annual Direct Health Care Costs from MEPS 2009

Condition	Annual Direct Healthcare Costs in 2009, \$ (p-value)	
	Estimated* Difference from Controls	Estimated* Difference from Menopausal Symptoms
Menopausal Symptoms	72.1 (<.0001)	-
Osteoporosis	42.3 (0.0072)	-29.9 (0.4152)
Fibromyalgia	488.0 (<.0001)	415.9 (<.0001)
Depression	92.5 (<.0001)	20.3 (0.5553)
Overactive Bladder	188.6 (0.0107)	116.5 (0.3717)
Cardiovascular Disease	532.5 (<.0001)	460.4 (0.0053)

*Adjusted for age, race, ethnicity, insurance status, education level, and income.

S-23.

Incremental Direct and Indirect Cost of Untreated Vasomotor Symptoms (VMS)

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Objective: Most women with moderate to severe VMS are untreated. With the ageing population leading to an increase in women of menopausal age in the workforce, the incremental direct and indirect cost associated with untreated VMS is of growing interest. The objective of this study is to evaluate the healthcare resource use, work loss, and cost burden associated with untreated VMS using a large employer database. **Design:** An analysis of health insurance claims (1999-2012) from 69 self-insured US companies was conducted. Adult women with ≥1 diagnosis for VMS (ICD-9: 627.2) continuously enrolled for ≥6 months before the first VMS claim (index date) were matched 1:1 with controls (no-VMS) women using a propensity scores algorithm. Women with pregnancy-related diagnoses or receiving VMS treatment were excluded. Healthcare resource utilization and work productivity loss (disability + medically-related absenteeism) were compared between cohorts using incidence rate ratios (IRRs) and conditional Poisson models. Mean per-patient-per-year (PPPY) direct and indirect costs were also calculated and compared between cohorts using non-parametric (bootstrap) methods. **Results:** The untreated VMS and control cohorts (n=252,273 in both, including 35,933 with disability coverage) were matched and balanced with respect to age (mean=56 years), region, payer type, industry type, beneficiary status, year of index date, history of a recent hysterectomy

and baseline menopause-related diagnoses. Approximately 40% of women were from the southern US and about half were listed as the primary beneficiary of their insurance plan. During the first 12 months following the index date, untreated VMS women had significantly higher all-cause and VMS-related healthcare resource utilization than controls (e.g., 82% and 121% higher for all-cause and VMS-related outpatient visits, respectively; Table 1a). Average direct costs PPPY were also significantly higher for untreated VMS women (direct cost difference [95% CI]: \$1,346 [\$1,249; \$1,449]; Table 1b). Untreated VMS women also had 57% more indirect work productivity loss days than controls, corresponding to an incremental indirect cost PPPY associated with untreated VMS of \$770 (95% CI: \$726; \$816). **Conclusion:** This large study showed that untreated VMS is associated with a significantly higher frequency of outpatient visits (82% higher, totaling an excess of 1.5M outpatient visits over one year), and an incremental direct and indirect cost per women of \$1,346 (totaling \$339,559,458 over one year) and \$770 (totaling \$27,668,410), respectively. These results substantiate the need for additional treatment options for VMS.

Table 1a. Direct and Indirect Resource Utilization

	Incidence Rate Ratio [95% CI] Untreated VMS relative to Controls		P-value	Incidence Rate Ratio [95% CI] Untreated VMS relative to Controls		P-value
	All-cause			VMS-related		
Pharmacy claims	1.21	[1.20; 1.22]	<.0001	1.18	[1.17; 1.19]	<.0001
Outpatient visits	1.82	[1.81; 1.83]	<.0001	2.21	[2.18; 2.24]	<.0001
Emergency-room visits	1.32	[1.29; 1.36]	<.0001	1.35	[1.30; 1.40]	<.0001
Hospitalizations	0.98	[0.96; 1.01]	0.1999	0.97	[0.94; 1.00]	0.0545
Other visits	1.69	[1.66; 1.72]	<.0001	2.16	[2.10; 2.21]	<.0001
Work loss	1.57	[1.51; 1.63]	<.0001	1.89	[1.77; 2.02]	<.0001
Disability claims	1.05	[0.95; 1.17]	<.0001	1.16	[0.93; 1.44]	0.1893
Medically-related absenteeism	1.88	[1.84; 1.93]	<.0001	2.20	[2.11; 2.29]	<.0001

Table 1b. Direct and Indirect Costs

	Average Cost (PPPY)		Cost Difference [95% CI]	Average Cost (PPPY)		Cost Difference [95% CI]
	Untreated VMS	Controls		Untreated VMS	Controls	
	All-cause			VMS-related		
Total direct costs	\$5,183	\$3,837	\$1,346 [1,249; 1,449]	\$1,710	\$1,287	\$423 [371; 470]
Pharmacy costs	\$939	\$771	\$168 [154; 182]	\$196	\$162	\$33 [27; 39]
Outpatient costs	\$2,907	\$1,773	\$1,135 [1,083; 1,184]	\$1,031	\$636	\$395 [360; 428]
Emergency-room costs	\$66	\$53	\$14 [11; 16]	\$23	\$18	\$5 [3; 6]
Hospitalization costs	\$1,042	\$1,067	-\$25 [-95; 45]	\$394	\$44	-\$332 [-66; -1]
Other visit costs	\$228	\$173	\$55 [44; 66]	\$66	\$44	\$22 [18; 26]
Total indirect costs	\$1,697	\$927	\$770 [726; 816]	\$587	\$261	\$326 [302; 352]
Disability costs	\$297	\$232	\$65 [35; 98]	\$77	\$50	\$28 [10; 47]
Medically-related absenteeism costs	\$1,401	\$695	\$705 [678; 736]	\$510	\$212	\$299 [284; 315]

S-24.

Estimating the national procedure burden associated with management of breakthrough vaginal bleeding in postmenopausal women receiving fixed-dose estrogen plus progestogen therapy (E+P) or bazedoxifene plus conjugated estrogens (BZA/CE)

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Objective: Up to 40% of postmenopausal women receiving E+P to manage vasomotor symptoms (VMS) present with abnormal postmenopausal bleeding (PMB) after therapy initiation. Treatment guidelines recommend evaluation of PMB occurring ≥6 months after E+P initiation to distinguish benign PMB from PMB due to underlying pathology. PMB evaluation typically includes endometrial biopsy and/or transvaginal ultrasonography (TVUS), often followed by increasingly invasive procedures. The present analysis was conducted to estimate the annual volume of procedures performed in the United States (US) for abnormal PMB evaluation in non-hysterectomized postmenopausal women (aged 40-64) receiving fixed-dose E+P for moderate to very severe VMS, and to estimate the reduction in such procedures that would occur if these women were alternatively initiated on BZA/CE. **Design:** A mathematical model was developed to estimate the aforementioned outcomes in patients presenting with PMB ≥6 (base case) or ≥3 months (scenario analysis) after therapy initiation. US Census (2010) and literature-based epidemiologic data were used to estimate the annual number of non-hysterectomized postmenopausal women aged 40-64 experiencing moderate to very severe VMS. National epidemiologic survey and market research data were combined to estimate the number of E+P-treated women seeking medical care for VMS. The number of treated women who develop PMB ≥3 and ≥6 months after therapy initiation was subsequently estimated on the basis of prospective randomized trial data comparing BZA/CE to CE plus medroxyprogesterone acetate (CE/MPA), as it was assumed that CE/MPA bleeding rates would be generalizable to fixed-dose E+P. The volume of PMB-evaluative procedures, including TVUS, endometrial biopsy, hysteroscopy-guided biopsy, and blind dilation and curettage (D&C) was estimated assuming that those with abnormal PMB following treatment initiation with fixed-dose E+P or BZA/CE would be managed according to treatment guidelines and clinical expert opinion. The number of evaluative procedures in the BZA/CE arm was estimated by replacing CE/MPA bleeding rates with BZA/CE bleeding rates in the model. **Results:** Based on the model and its assumptions, of the approximately 52 million US females aged 40-64, an estimated 24 million were postmenopausal with an intact uterus. Of these, approximately 1,700,000 were estimated to experience moderate to very severe VMS and approximately 500,000 were predicted to seek treatment for these symptoms. Of those seeking treatment, 66,677 were estimated

to receive fixed-dose E+P; 17,616 of whom experienced PMB >6 months after therapy initiation. If these 66,677 women were treated with BZA/CE instead of fixed-dose E+P, 4607 would experience PMB >6 months after therapy initiation. Corresponding estimates after ≥ 3 months were 23,484 vs. 6481, respectively. The model assumed that 100% of PMB patients were initially evaluated: 90% with TVUS and 10% with endometrial biopsy. Of the 100% of initially evaluated patients, 55% and 25% underwent subsequent hysteroscopy guided biopsy and D&C, respectively. The procedure volumes in the fixed-dose E+P arm were 31,709 (≥ 6 months) and 42,271 (≥ 3 months). If patients were alternatively initiated with BZA/CE, the model predicted an annual reduction of 23,417 procedures (from 31,709 to 8293) for PMB occurring ≥ 6 months after therapy initiation and of 30,605 (from 42,271 to 11,666) for occurring ≥ 3 months after therapy initiation. **Conclusion:** Based on this exploratory modeling exercise, fixed-dose E+P to treat moderate to very severe VMS is associated with approximately 32,000-42,000 PMB evaluation procedures annually. Under assumptions used herein, this procedure burden may be reduced by up to 75% (i.e., 23,000 to 31,000) through the use of BZA/CE instead of the current standard of care. Additional research is warranted to explore how different VMS treatment strategies affect PMB-associated procedure burden in the US.

BASIC SCIENCE POSTER PRESENTATIONS

P-1.

Influence of the hyperprolactinemia on collagen fibers in the lacrimal gland of female mice

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Objective: To evaluate the influence of hyperprolactinemia on collagen fibers in the lacrimal gland of female mice during the proestrus phase and pregnancy. **Design:** 40 adult female mice were randomly divided into two groups: control (Ctrl1) and treated with 200 µg/day of metoclopramide (Hpr1) for 50 consecutive days. After treatment, half of the animals from each group were sacrificed, while the remaining animals were mated to constitute more two groups: Control pregnant (Ctrl2) and experimental pregnant (Hpr2), which continued to receive treatment for more 28 days and then sacrificed on day 6th of gestation. Afterwards, the lacrimal glands were removed and fixed in 10% formaldehyde. Then specimens were processed for paraffin inclusion and sections of 3µm were stained with hematoxylin and eosin (HE) and with Masson trichrome method (collagen staining). uterine horns were fixed for 24 hours in 10% formaldehyde in phosphate-buffered saline (PBS). The photomicrographs were collected using Axion vision (Zeiss, Germany) and the semiquantification analysis from ImageLab® (Software Informatics Ltd., Brazil). Data were statistically analyzed by ANOVA ($p < 0.05$). **Results:** morphological analysis evidenced greater structural tissue disorganization of the lacrimal glands in groups treated with metoclopramide. The total content of collagen fibers was significant higher ($p < 0.05$) in the Hpr1 groups compared to the Ctrl1 group, while between the Ctrl2P and Hpr2P groups the difference was not significant. **Conclusion:** Our results suggest that the hyperprolactinemia increase the amount of collagen fibers only in not pregnant mice, but not in pregnant ones.

P-2.

Evaluation of estrogenic pathway genes in the vagina of rats treated with genistein or estrogen immediately or later after castration

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Objective: To evaluate the activity of genes ESR1, ESR2, Bcl2, and VEGF MKI67 in the vagina of rats treated with 17β-estradiol (5 µg / kg) or genistein (50mg/Kg) after castration. **Design:** We used 60 adult rats castrated divided into six groups GI = received vehicle (propylene glycol); immediately after castration; GII = received genistein immediately after castration; GIII = received genistein 30 days after castration; GIV = received only the vehicle after 30 days of castration; GV = received 17β-estradiol immediately after castration; GVI = received 17β-estradiol after 30 days of castration. Drugs were administered by gavage (0.5 ml) for 30 consecutive days, and after the last administration, the animals were anesthetized and the vaginas were removed. A part of this was dipped in liquid nitrogen for gene expression analysis by RT-PCR method, and the other part was fixed in 10% formalin for histological processing. Sections were stained by hematoxylin and eosin or subjected to immunohistochemistry for evaluation of VEGF-A (vascular growth factor) and Ki-67 (cell proliferation). The analysis of gene expression by quantitative PCR were performed on a custom plate to the signaling pathway of estrogen. **Results:** The gene expression of ESR1, ESR2, Bcl2, and VEGF MKI-67 was higher in the groups treated with 17β-estradiol and GIII showed the highest expression of Bcl2 gene. The thickness of the vaginal epithelium, irrigation (VEGF-A) and cell proliferation (Ki-67) were higher for the GIV and GV, and the data were similar to those found in the analysis of gene expression. Regarding the antiapoptotic process (Bcl2) we observed higher reactivity in GIII, GIV and GV. The gene expression of ESR1 receptor (alpha) and ESR2 (beta) was higher in GIV and GV, whereas the largest increase was observed in the of beta type **Conclusion:** Our data showed that genistein has positive effects on the vagina of rats, but this action is less than estrogen.

P-3.

Early and late effects of soy isoflavones extract on mammary gland of ovariectomized rats

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Objective: To evaluate the early and late treatments of ISO on mammary gland of ovariectomized (OVX) rats. **Design:** 30 adult female rats were equally divided in six groups: GI - SHAM-operated; GII - OVX - orally treated with vehicle solution of propilenoglicol; GIII - treated by gavage with 150 mg/Kg of ISO, one day after OVX (early treatment); GIV - OVX treated by gavage with 150 mg/Kg of ISO, 30 days after OVX (late treatment); GV - OVX - subcutaneously treated with 10 µg/Kg of estrogen one day after OVX (early treatment); GVI - OVX - subcutaneously treated with 10 µg/Kg of estrogen 30 days after OVX (late treatment). All treatments lasted 30 consecutive days and the animals were euthanized 24 hours after the last dose. Subsequently, the first inguinal par of some mammary glands were removed, fixed in 10% formaldehyde, processed for paraffin inclusion and sections (4µm) were stained with hematoxylin and eosin or subjected to immunohistochemistry for the detection of Ki-67. Some specimens were destined to biochemical analysis for glycosaminoglycans (GAGs) quantification. **Results:** The GV and GIV groups presented the higher presence of mammary alveoli, the content of GAGs (chondroitin and heparan sulfate) and the higher immunoreactivity of Ki-67, compared to the other groups. These parameters were similar in the GIII and GIV groups when compared to the GI and GII groups. **Conclusion:** Early and late treatments of soy isoflavones do not have trophic effects on mammary gland of ovariectomized rats.

P-4.

Evaluation of genes involved in the signaling pathway of estrogen in the uterus of rats treated with estrogen or genistein immediately or later after castration

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Objective: To evaluate the activity of the genes ESR1, ESR2, Bcl2, VEGF and MKI67 in the uterus of rats treated with 17β-estradiol (5 µg / kg) or genistein (50mg/Kg) after castration. **Design:** : Were used 60 adult castrated rats divided into six groups: GI = received vehicle (propylene glycol); immediately after castration; GII = received genistein immediately after castration; GIII = received genistein 30 days after castration; GIV = received only the vehicle after 30 days of castration; GV = received 17β-estradiol immediately after castration; GVI = received 17β-estradiol after 30 days of castration. Drugs were administered by gavage (0.5 ml) for 30 consecutive days, and after the last administration, the animals were anesthetized and the uteri were removed. One of the uterine horns was dipped in liquid nitrogen for gene expression analysis by qRT-PCR, and the other horn was fixed in 10% formalin for histological processing. Sections were stained by hematoxylin and eosin or subjected to immunohistochemistry for evaluation of VEGF-A (vascular growth factor) and Ki-67 (cell proliferation). The analysis of gene expression by quantitative PCR was performed on a custom plate to the signaling pathway of estrogen. **Results:** We observed an increased thickness of the uterine epithelium and the number of glands, as well as the reactivity of VEGF-A and cell proliferation (Ki-67) in the uteri of animals belonging to GII, GIII, GV and GVI. groups Quantitative PCR assay showed a greater amount of genes expressed in the groups treated with estrogens or genistein (GV = GVI> = GIII GII> GI = GIV, $p < 0.05$). Regarding the antiapoptotic process (Bcl2) we observed greater reactivity in the groups GVI> GV> GIII ($p < 0.05$). In gene expression of ESR1 and ESR2 (alpha and beta) we noticed an increase of both types, with a higher alpha type in GV and GVI groups. **Conclusion:** Our data suggest that the longer the time castration greater the gene inactivity, and that genistein and estrogens have beneficial effects on the uterus of rats.

P-5.

Melatonin treatment enhances the immunoexpression of cleaved caspase 3 in the ovary of pinealectomized rats

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Objective: To analyze the immunoexpression of cleaved caspase-3, an apoptotic marker, in the ovary of pinealectomized (PNT) rats treated with melatonin. **Design:** 30 female adult virgin rats were PNT and then divided into three groups of ten animals each: GI - Sham-operated that received vehicle solution; GII - PNT that received vehicle solution; GIII - PNT treated with melatonin (10µg/night per animal); drugs were administered subcutaneously during 60 consecutive days. After treatment, the animals in the proestrous phase were euthanized by overdose of ketamine and xilazine, the ovaries were processed for paraffin embedding and sections with 5µm tick were subjected to immunohistochemistry for the detection of cleaved caspase-3. Five regions of interest in each slide were captured under the objective of 40x, using a light microscope (Axiolab

Standard 2.0 - Carl Zeiss) linked to an image analysis system (AxioVision Rel. 4.8.2 - Carl Zeiss). The images were analyzed and quantified according to the color intensity of the immunoreactivity by the software Image J Pro Plus. Data were statistically analyzed by ANOVA followed by the Tukey-Kramer test ($p < 0.05$). **Results:** The cleaved caspase-3 was highly immunoreactive in the PNT melatonin treated group ($GIII = 60.93 \pm 3.95$) when compared with the Sham ($GI = 40.39 \pm 3.05$) and PNT groups ($GII = 51.09 \pm 2.85$) ($p < 0.05$). **Conclusion:** Our data showed that melatonin enhances apoptosis in the ovary of pinealectomized rats.

P-6.

New frontiers in prevention of early menopause during chemoradiation for cancer treatment

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Objective: Survival following many common female cancers is improving. Treatment for common cancers in reproductive-aged women, such as for breast cancer, or for less common haematological malignancies, often induces oocyte death and early menopause. This is particularly problematic for breast cancer patients who should avoid HRT since it may increase the risk of breast cancer recurrence. **Design:** We will present a brief summary of the options available for women wishing to retain their fertility following cancer treatment, including a novel Decision Aid specifically developed for younger women with breast cancer considering fertility preservation. **Results:** Although many younger women wish to retain their fertility and ovarian function during adjuvant chemotherapy or radiotherapy for breast and other malignancies there are currently no effective interventions to protect ovarian function in-situ during DNA-damaging cancer therapies. In particular, ovarian suppression with GnRH agonists does not appear to prevent oocyte damage during chemotherapy as was hoped. An exciting new development from our group is the discovery of the role of BH3-only proteins in the initiation of primordial follicle oocyte death in response to DNA damaging gamma-irradiation. In wild-type mice, γ -irradiation resulted in loss of all primordial follicles and infertility. However, in mice lacking PUMA and NOXA a cohort of primordial follicles were protected from apoptosis and remarkably, these mice were able to generate healthy offspring with no apparent adverse health outcomes. **Conclusion:** The potential clinical implications of these novel findings for the prevention of infertility and early menopause due to cancer therapies, prevention of premature ovarian insufficiency and, potentially, regulation of the female reproductive lifespan will be discussed. 1. Partridge AH. Ovarian suppression for prevention of premature menopause and infertility: empty promise or effective therapy? *J Clin Oncol* 2012;30:479-81. 2. Peate M, Saunders, C., Gregson, J., Thewes, B., D'Abrew, N., Meiser, B., White, K., Hickey, M. Development and Evaluation of an Information Booklet about Breast Cancer and Early Menopause. *Breast J* 2012;18:95-6. 3. Kerr JB, Hutt, K.J., Michalak, E.M., Cook, M., Vandenberg, C.J., Liew, S.H., Bouillet, P., Mills, A., Scott, C.L., Findlay, J.K., Strasser, A. DNA Damage-Induced Primordial Follicle Oocyte Apoptosis and Loss of Fertility Require TAp63-Mediated Induction of Puma and Noxa. *Mol Cell Endocrinol* 2012;48:343-52.

P-7.

Old trade-offs and new extremes: an evolutionary medical perspective on postmenopausal lifespan and women's health

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Objective: This paper will discuss some of the concepts and tools used by evolutionary physiologists to understand critical therapeutic windows and trade-offs associated with hormone therapy during the menopausal transition. **Design:** According to evolutionary theory, natural selection shaped physiological trade-offs between our reproductive success and sustained physical health (long-term somatic maintenance). When examined from the standpoint of "evolutionary medicine," the pleiotropic effects of reproductive hormones and growth factors – and their roles in the health of older women – can be more fully appreciated. **Results:** The trajectory of the human life course has undergone a profound shift in industrialized societies over the past 200 years. Since 1900, the average life expectancy in the U.S. has increased over 30 years. This "longevity bonus" means that, unlike our pre-industrial ancestors, millions of modern women will live for up to a third or more of our lives in a postmenopausal state. Cultural change, including advances in medicine and public health, has outpaced evolutionary change. In long-lived animals like humans, developmental and endocrine processes that are essential for sexual maturation and reproduction early in life can have aging-associated costs as fertility wanes. Some of these costs can be exacerbated by modern lifestyles and the recent shift in the major causes of illness and death to later-onset, chronic diseases. **Conclusion:** Employing an evolutionary medical perspective can suggest ways in which medical approaches can be fine-tuned to better promote healthy aging and prevent disability in postmenopausal women.

P-8.

Treatment with aromatase inhibitor acts indirectly through the estrogen receptor pathway causing decreased junction plakoglobin mRNA expression and vaginal atrophy

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Objective: Vaginal atrophy causes troublesome symptoms, which are recognized problems in aromatase inhibitor (AI)-treated postmenopausal women with breast cancer. Vaginal estrogen therapy is considered contraindicated, and non-steroidal treatment options are seldom sufficient for long-term use, leaving these women without adequate care. The aim of this study was to examine the effects of AI treatment on vaginal gene expression in relation to estrogen levels, vaginal pH, and symptoms of vaginal atrophy. **Design:** Affymetrix array was used to study mRNA gene expression in vaginal biopsies from AI-treated postmenopausal women with breast cancer ($n=4$) compared with healthy postmenopausal control women treated with vaginal estrogen therapy ($n=5$). Differentially expressed genes were further investigated using bioinformatics tools. Array data was validated by using quantitative real-time (qRT)-PCR in samples from both groups; AI-treated women ($n=15$) and controls ($n=22$). **Results:** The gene expression of 278 genes, showing a fold change of at least 2, differed significantly between the two groups. Out of these, 83 genes were up-regulated and 196 genes were down-regulated in AI-treated women compared with controls. Database of Annotation, Visualization, and Integrated Discovery (DAVID) analysis revealed involvement of these differentially expressed genes in epidermis development, in differentiation of epidermal and epithelial cells, and in cellular components such as desmosomes, cornified envelopes, and cell to cell junctions. Ingenuity Pathway Analysis (IPA) showed dysregulation of gene pathways involved in dermatological diseases and conditions, which for some of these genes were found to be in an indirect interaction with the estrogen receptor pathway. Differential expression of junction plakoglobin (JUP), desmocollin 2 (DSC2), keratin 8 (KRT8) and protocadherin 8 (PCDH8), all known to interact with the estrogen receptor pathway, was seen. Validation using qRT-PCR showed significantly lower expression of JUP and a trend towards significant increase in PCDH8, while DSC2 and KRT8 did not differ between the groups. JUP was positively correlated with estrone levels and negatively correlated with vaginal pH and atrophy, while DSC2 and PCDH8 were negatively correlated with vaginal pH and vaginal atrophy, respectively. **Conclusion:** Of special interest is JUP, which is a vital protein for cell adhesion, desmosome function and cell-cell junctions and has also been suggested to play a role in cell signaling and cell proliferation. AI-treatment, causing extremely low estrogen levels, seems to interact through ER thereby resulting in decreased vaginal JUP mRNA expression. This might be part of an explanation for high vaginal pH and development of vaginal atrophy.

P-9.

The Effect of Pomegranate on Bone Histomorphometry in Ovariectomized Rat and on Proliferation and Differentiation of Human Mesenchymal Stem Cell in Vitro

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Objective: To determine whether or not pomegranate extract can affect bone histomorphometry in ovariectomized rats and proliferation and differentiation of human mesenchymal stem cell. **Design:** Human mesenchymal stem cells were cultured in vitro. Proliferation assay and Alkaline phosphatase activity were measured. Seventy-nine female Sprague-Dawley rats were used: A, no intervention; B, sham operation and distilled water; C, ovariectomy and distilled water; D, ovariectomy and 10% dilute pomegranate; E, ovariectomy and 20% pomegranate; and F, ovariectomy and 40% pomegranate. The study samples were obtained 4 weeks later. The following parameters were investigated for analyses: 24-hour food intake, body weight, bone histomorphometry, serum bone turnover markers, and sex hormones. **Results:** Pomegranate extract (1/1000 dilution) significantly increase the growth of human mesenchymal stem cell. However, pomegranate extract did not increase Alkaline phosphatase activity. Bone volume was decreased after ovariectomy and the 40% pomegranate extract had a lower trabecular separation. There were lowering effect in serum phosphate. **Conclusion:** Pomegranate extract has a beneficial effect on bone histomorphometry in ovariectomized rat and human mesenchymal stem cell function.

P-10.

Aging of human pluripotent stem cell-derived cardiomyocytes during prolonged in vitro culture : a possible model for postmenopausal heart

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Objective: Aging of cardiomyocytes (CMs) is natural phenomenon observed in human cardiac cells, however, there are limitations for the use of human heart cells. Therefore, we used human pluripotent stem cell (hPSCs)-derived cardiomyocytes as aging model and analyzed the aging phenomenon in hPSC-derived cardiomyocytes. **Design:** We induced differentiation into CMs from hPSC and classified them into three stages: early (day 12), middle (day 18) and late (day 24)-stage, based on their functionality. We observed the morphological and functional changes of hPSC-derived CMs, and performed senescence-associated (SA) β -gal staining and counted positively-stained cells. **Results:** Cardiac features of differentiated cells were examined by expression of cardiac specific markers in each stage of differentiation such as Nkx2.5, cardiac Troponin I and myosin heavy chain. Middle and late-staged hPSC-derived CMs showed increase of pigmented cells and demonstrated slower beating rate due to the in vitro cultivation period. In SA- β -gal staining, human PSC-derived CMs at day 12 showed small population of stained cells and at day 18 showed larger population of stained cells. Positively-stained cells were abundant in day 24 hPSC-derived CMs. **Conclusion:** As we demonstrated in this study, we characterized the aging phenomenon in hPSC-derived CMs. These results imply possible usage of hPSC derivatives for studies on aging and menopausal changes of human cells (A111539).

P-11.

CYP17 immunorexpression in ovary of pinealectomized female rats in proestrous phase treated with melatonin

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Objective: analyze the immunorexpression of CYP17, an enzyme related with pregnenolone and androstenedione production in the pinealectomized female rats ovary treated with melatonin **Design:** Twenty female adult and virgin rats (*Rattus norvegicus albinus*), from Universidade de São Paulo – Escola Paulista de Medicina (UNIFESP/EPM) biotory, were utilized. After evaluation of the estrous cycle, animals were separated in two groups of 10 animals each: GI – pinealectomized which received vehicle; GII – pinealectomized with melatonin reposition (10 μ g/night, each animal) for 60 consecutive days. After this period, animals were anesthetized and ovaries were collected, fixed in 10% formaldehyde and processed for paraffin embedding. From the paraffin blocks, 5 μ m thick sections were collected to silanized slides and submitted to immunohistochemistry for CYP17 detection. Images were obtained using a light microscope (Axiolab Standard 2.0 - Carl Zeiss) attached to a high definition camera (AxioCam MRC - Carl Zeiss) and by the image analyzing software (AxioVision Rel. 4.8.2 - Carl Zeiss). Reaction expression was analyzed and quantified according with the color intensity with the aid of the Image J Pro Plus, having photographed 5 fields each slide, with the 40x objective. Obtained data was submitted to statistical analysis using t-student test (p<0.05). **Results:** In pinealectomized group, we identified the presence of ovarian cysts and the absence of corpora lutea in the ovary cortical region. In the group treated with melatonin (GII), we could identify ovarian follicles at several development stages and the presence of corpora lutea. The CYP17 expression was smaller in the group treated with melatonin when compared with Control group (GII = 40,88 $\pm$ 0,95 < GI=50,28 $\pm$ 0,77*, p<0.05). **Conclusion:** Melatonin decreases CYP17 expression, presenting a possible influence on the production of pregnenolone in rat ovary.

P-12.

Immunorexpression of vascular endothelial growth factor (VEGF-A) in the uterus of pinealectomized female rats treated with melatonin

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Objective: to evaluate the expression of VEGF-A in the uterus of female pinealectomized rats treated with melatonin. **Design:** Twenty adult female and virgin rats, with regular estrous cycle were pinealectomized (PNT) and then divided in two groups (10 animals each): GI – PNT which received vehicle; GII – PNT that received melatonin reposition (10 μ g/night, each animal) for 60 consecutive days. After treatment, animals were anesthetized in the estrous phase and ovaries were collected, fixed in 10% formaldehyde and processed for paraffin embedding. Sections with 5 μ m thick were collected in silanized slides and submitted to immunohistochemistry for the detection of VEGF-A. Images were obtained using a light microscope (Axiolab Standard 2.0 - Carl Zeiss) attached to a high definition camera (AxioCam MRC - Carl Zeiss) and by an image analyzing software (AxioVision Rel. 4.8.2 - Carl Zeiss). At the objective of 40x, five fields in each slide were captured. The immunorexpression reaction was analyzed and quantified according to the color intensity using the Image J Pro Plus Program. Data was submitted to statistical analysis using t-student test (p<0.05). **Results:** Immunoreactivity of VEGF-A was expressed at a higher percentage in the pinealectomized rats that received melatonin reposition, in both superficial (GII = 85.2 $\pm$ 3.4 > GI = 5.7 $\pm$ 2.7; p < 0.001) and glandular epithelium (GII = 82.4 $\pm$ 6.3 > GI = 7.9 $\pm$ 5.8; p < 0.001). However, these immunoreactivity

was lower in the lamina propria of the melatonin treated animals (GII = 4.8 $\pm$ 2.5 < GI = 54.8 $\pm$ 9.7; p<0.001). **Conclusion:** Our data suggest that melatonin is related to the vascularization of the endometrium in rats.

P-13.

Immunorexpression of ERK2/p42 MAPK in the ovary of pinealectomized female rats in proestrous phase treated with melatonin

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Objective: To evaluate the immunorexpression of the kinase protein regulated by extracellular signs (ERK2) in female rats ovary after melatonin treatment. **Design:** Thirty female, adult and virgin rats (*Rattus norvegicus albinus*), from Universidade de São Paulo – Escola Paulista de Medicina (UNIFESP/EPM) biotory, were separated in three groups of 10 animals each: GI – Sham (falsely pinealectomized) received vehicle; GII – pinealectomized who received vehicle; GIII – pinealectomized with melatonin reposition (10 μ g/night, each animal) for 60 consecutive days. After this period, animals were anesthetized and ovaries were collected, fixed in 10% buffered formaldehyde and processed for paraffin embedding. Sections with 5 μ m thick sections were collected to silanized slides and submitted to immunohistochemistry for ERK2 detection. Images were obtained using a light microscope (Axiolab Standard 2.0 - Carl Zeiss) attached to a high definition camera (AxioCam MRC - Carl Zeiss) and by the image analyzing software (AxioVision Rel. 4.8.2 - Carl Zeiss). Reaction expression was analyzed and quantified according with the color intensity with the aid of the Image J Pro Plus, having photographed 5 fields each slide, with the 40x objective. Obtained data was submitted to statistical analysis using ANOVA test complemented by the Tukey-Kramer test (p<0.05). **Results:** ERKs, involved with cellular proliferation, are serine treonine kinases which belongs to the kinase proteins superfamily activated by mitogens (MAPK). ERKs 1 and 2 are also known as p44 and p42. Histological sections submitted to ERK2 immunorexpression displayed increased expression in pinealectomized group (GII = 227.74 $\pm$ 5.90* compared to Sham group (GI = 161.81 $\pm$ 4.06) and pinealectomized treated with melatonin (GIII = 178.88 $\pm$ 8.90) (*p<0.05). **Conclusion:** Our data showed that melatonin interferes in the proliferative activity of pinealectomized female rats ovary.

P-14.

Melatonin may influence ovarian function by the overexpression and down-regulation of steroidogenesis related genes in ovary of pinealectomized rats in proestrous phase

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Objective: To analyze the expression of genes related to steroidogenesis in ovary of pinealectomized rats **Design:** 32 adult female adult and virgin rats, with regular estrous cycle, were pinealectomized (PNE) and equally divided into two groups, as follows: GI – control group (PNE that received vehicle solution) and GII (PNE treated with melatonin, 10 μ g/night, per animal), during 60 consecutive days. After treatment, the animals were euthanized by overdose of ketamine and xilazine, some ovaries were collected, kept in liquid nitrogen and stored at -80°C for posterior expression analyses of genes related to ovarian functions, by cDNA microarray (Kit GeneChip® Rat Genome 230 2.0 Array, Affymetrix). The microarray assay was carried out in triplicate for each group. Data were normalized and subjected to the GeneChip® Operating Software and later confirmed by the DNA-Chip Analyzer (dChip) software of secondary analyses. Gene expressions were considered significantly different when they were 1.5x over or low expressed, when compared to the control group. Some samples were appropriately kept for posterior RT-PCR analyses and others were processed for paraffin embedding. **Results:** The GII showed one hundred one overexpressed genes and seventy-two low expressed genes compared to GI. The genes related to ovarian steroidogenesis were statistically significant overexpressed (Inibin beta-A, Folistatin and Abl-Interactor1) and low expressed (Prostaglandin D2 synthase, LIM Homeobox 9 and Glutathione S-transferase Mu 1), in the GII. Among the overexpressed genes, the Inibin beta-A showed the higher expression. Based on these data, we later confirmed the overexpression of Inibin beta-A by RT-PCR (GII > GI, p<0.01) and by immunohistochemistry, which showed higher immunoreactivity in GII (74.43 $\pm$ 2.89) in the follicular and interstitial cells, as well as in the inner teca cells, compared to GI (54.32 $\pm$ 4.32). **Conclusion:** Our data show that melatonin may influence ovarian function by the overexpression and down-regulation of steroidogenesis related genes in ovary of PNE rats.

P-15.

Enhanced vasorelaxation in ovariectomized rat tail arteries with S-equal supply

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Objective: Many reports indicate that soy-isoflavone based diets could guard against myocardial infarction. Genistein and daidzein are included in polyphenolic isoflavones and intestinal bacteria metabolize daidzein to equol, which is considered to be a key role not only to reduce hot flushes, but to inhibit atherosclerosis. However approximately 75%

of westerns and 50% of Asians do not play host to the converting bacterias and clinical researches revealed that S-equal administration to these non-producers had showed the beneficial effects in menopausal symptom and cardiovascular disease. Recently, the elevation of ovariectomized rat tail skin temperature (TST) as a hot flushes model was canceled by the S-equal containing nutrition, and therefore S-equal was supposed to have some action on the tail circulation system. As far as we investigated, there was no report about the direct effect of s-equal as a humoral factor to control the endothelial function including nitric oxide (NO) production. Therefore, this study was arranged to clarify NO regulation by controlled S-equal released with osmotic pump to ovariectomized rat small arteries, and to compare this effect with estradiol supplementation as similar estrogen receptor (ER) agonist. **Design:** Twelve weeks female Sprague-Dawley rats underwent abdominal ovariectomy and were fed by soy-bean free diet, AIN-93G for 2 months in order to eliminate the effect of endogenous S-equal. After 16th week, Alzet osmotic pumps containing estradiol (E2 group : 7 µg/day dissolved in DMSO, n=10), S-equal (EQ group : 0.2 mg/day in DMSO : n=10) or DMSO only (Control group, n=10) were subcutaneously implanted and all rats were sacrificed at 20 week. Rat tail arteries were harvested and mounted in the auto dual wire myograph (DMT, Danish) in the modified Krebs solution after removing surrounding connective tissue. Measuring the internal diameter of the artery, the specimen was stretched with the optimal resting tension, 0.3 g for 1 hour and chemical agonists were applied to the chamber. Under stable contraction evoked by U46619 (10 (-7) M), acetylcholine (ACh: 10 (-9) - 3x10 (-6) M), as an endothelium dependent agonist, induced relaxation was evaluated by the isometric tension change with or without nitric oxide synthase inhibitor (NG nitro L-arginine: LNA) or cyclooxygenase inhibitor (indomethacin: IM). Also blood concentration of estradiol, s-equal was evaluated by RIA or gas chromatography. **Results:** The diameter of rat tail was 95.7 ± 1.4 µm and no difference was observed among 3 groups. The plasma concentration of estradiol was 11.2 ± 5.7 (pg/ml), 5.4 ± 5.4 and 33.5 ± 4.7 in control, EQ and E2 group, respectively. On the other hand, S-equal was determined only in EQ group (632±144 nmol/L), which was considered within the physiological concentration. In control rat tail artery, ACh-induced concentration dependent relaxation was abolished by denaturation or LNA pretreatment, but was not altered by IM. These results indicated that the relaxation was perfectly mediated with endothelium derived NO in control group. E2 group showed significantly enhanced relaxation by ACh administration and the relaxation was abolished by LNA, which suggested the E2 enhanced NO release. On the other hand, EQ group showed similar enhancement as E2 in ACh induced relaxation, but which was not perfectly abolished by LNA. Additionally, the relaxation in EQ group was partly decreased by IM pretreatment, which suggested the existence of prostaglandin pathway in ACh relaxation. **Conclusion:** In isoflavone free condition, S-equal administration enhanced the ACh relaxation through NO and PG pathway activation in rat tail artery, which might suggest another mechanism than E2, and be related to reduce hot flushes and cardiovascular disease with soy bean isoflavone.

P-16.

S-equal increases NO production of thoracic aorta in ovariectomized rats

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Objective: Soy isoflavones are thought to activate estrogen receptors and exhibit estrogen like effect as SERM. It is expected that this role as phytoestrogen of soy isoflavones may have beneficial effects without side effects as estrogen replacement therapy to the women with menopausal disorders. We assessed about the role of S-equal for the function of nitric oxide (NO) production of vascular endothelial cells in an ovariectomized rat model. **Design:** Twelve-week-old female Sprague-Dawley rats were assigned to one of four ovariectomized groups: control (n=9), E2 (7µg per day, 17β-estradiol, n=7), S-equal (200µg per day S-equal, n=12), and normal diet group (n=9). Rats except normal diet group were fed the AIN-93G diet, which contained no soy oil or soy protein three days after ovariectomy. At sixteen weeks, administration of each drug with subcutaneous osmotic pumps was started. At twenty weeks, all rats were sacrificed, and we measured uterine weight, plasma levels of estradiol and soy isoflavones (S-equal, Daizein, Genistein), cyclic GMP levels within the vessel walls and changes in isometric tension of thoracic aorta. In the experiment of changes in isometric tension, specimens of thoracic aorta were cut into 5mm length, which was stretched to an optimal resting tension of 500mg for one hour in organ chamber in modified Krebs solution. During contraction caused by norepinephrine 10-6M, acetylcholine (ACh; 10-9 to 3x10-5M) or A23187 (3x10-7M) was given in order to measure the endothelial dependent relaxation. Sodium nitroprusside (SNP; 10-10 to 3x10-5M) as an NO donor and NG-nitro-L-arginine (LNA; 10-4M) as an endothelial NO synthase inhibitor were used. ACh and SNP were applied into organ chamber in a cumulative fashion at increasing concentrations of 0.5 log unit. The levels of cyclic GMP as 2nd messenger of NO were determined by radioimmunoassay kit. All results are expressed as mean±SEM. Statistical analyses were performed with t-test or two-way ANOVA of stat view J 5.0 program. Values of p<0.05 were considered as statistically significant. All studies complied with the Animal Welfare Regulations of the Tokyo Medical and Dental University. **Results:** There was no change of body weight among control, S-equal and normal diet groups, whereas that of E2 group was decreased than others significantly. Uterine weight per body weight in E2 group was significantly increased than other groups. Plasma level of S-equal was determined only in S-Equal group and normal diet group, and that of Daizein and Genistein were determined in normal diet group alone. Plasma E2 level was higher only in E2 groups. The relaxation in response to ACh or A23187 was abolished by the endothelial removal and preincubation with LNA, suggesting that the relaxation is endothelium-dependent and mediated through activation of endothelial NOS. ACh and A23187 induced relaxations in the groups of E2,

S-equal and normal diet were likewise increased than control group. On the other hand, SNP induced relaxations in all groups showed no difference, suggesting there was no change in NO sensitivity of smooth muscle cells. The levels of cyclic GMP in the groups of E2, S-equal, normal diet were significantly increased than control group. **Conclusion:** It was suggested that E2 and soy isoflavones similarly increase NO production of endothelial cells of thoracic aorta in an ovariectomized and isoflavone free rats. But S-equal had no influence upon uterine weight like E2. S-equal may have a beneficial role for increased release of endothelial nitric oxide and for prevention of arteriosclerosis.

P-17.

Uterine effects on post menopausal rats after repeated vaginal treatment with phenolphthalein a phytoestrogen isolated from Momordica charantia (bitter melon) seeds

Sharanabasappa A. Patil, Ph.D. Zoology, Gulbarga University, Gulbarga, Gulbarga, India **Objective:** Momordica charantia Linn. has been used as a dietary / medicinal supplement for health care. The plant has a long history in worldwide people for the usage of vaginal discharge, to promote menstruation and to induce abortions. Topical estrogen therapy is recommended for the treatment of vaginal atrophy. Therefore, the present study was carried out to evaluate the uterotrophic effects of phenolphthalein a phytoestrogenic molecule isolated from M. charantia seeds in post menopausal albino rats as an experimental model. **Design:** Uterine effects of phenolphthalein a phytoestrogenic molecule isolated from seeds of Momordica charantia Linn. were evaluated in post menopausal female albino rats. Each one of the formulations was administered intravaginally to groups of post menopausal rats with cytologically confirmed vaginal atrophy. The animals having groups I & II were treated with 2ml of 1% and 2% phenolphthalein gel (prepared by using Glycerol) respectively. In the Group III animals were treated with 2ml of 0.001% of 17-β - estradiol (prepared by using Glycerol) and group IV served as control treated with glycerol. The doses were adjusted by animal body weight. After daily treatment for 14 days, the animals were sacrificed and their vaginas and uteri removed. All uteri were weighted. Uteri were fixed for histological and biochemical evaluation. **Results:** Both the doses of phenolphthalein gel and single dose of 17-β - estradiol proved to be very effective in the cytological reversal of vaginal atrophy. The uterotrophic effects of phenolphthalein and 17-β - estradiol produced a significant increase in uterine weight, myometrial and endometrial thickness as well as histological modifications in the endometrium suggestive of estrogenic activity. The biochemical evaluation of uteri showed phenolphthalein produced a dose dependent increase in DNA concentration. **Conclusion:** There is a significant uterotrophic effect of phenolphthalein gel as tested in a rat model of vaginal postmenopausal atrophy. There were dose dependent effective in reversing vaginal atrophy and significant estrogenic effect on the uterus. The study results suggested that M. charantia seeds having phytoestrogen phenolphthalein possess uterotrophic properties in experimental animals. Interestingly, in recent years, the popularity of different kinds of pharmaceutical preparations containing phytoestrogens has constantly increasing. Therefore, studies of the influence of the above mentioned plant components on female reproduction have become more important in future.

P-18.

Effects of Gender and Menopause on Mucosal Integrity Mediates HIV Pathogenesis

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Objective: Human Immunodeficiency Virus (HIV) infection is one of the leading causes of death in women in Africa. HIV infection results in loss of CD4+ T-cells in Gut-Associated Lymphoid Tissue (GALT). HIV disease progression correlates with immune activation which is higher in women compared to men. Antiretroviral therapy (HAART) effectively suppresses viral replication and stimulates immune reconstitution. HIV+ women on HAART have higher levels of T-cell activation than men on HAART. As the HIV epidemic continues more women are surviving to reach and pass menopause. There is very little information regarding the effects of gender and menopause on HIV pathogenesis and response to HAART. We hypothesize that HIV+ postmenopausal women have higher levels of immune activation and decreased epithelial integrity compared to premenopausal women and age matched men. The objective of this study was to compare the effects of menopause on T cell activation and mucosal integrity in HIV+ women on HAART. **Design:** HIV+ and HIV- women and age matched men were enrolled in this study using IRB approved protocols. Small intestine mucosal samples were obtained by upper GI endoscopy. We compared gene expression profiles in gut epithelium, using laser capture microdissection and gene expression arrays. Plasma levels of microbial products in male and female HIV+ participants were assayed by real-time PCR and ELISA. Immunophenotypic analysis was performed using 12 color flow cytometry. The effect of estradiol replacement on epithelial integrity was assayed using 3-D in vitro culture systems. **Results:** A greater proportion of HIV+ women on HAART had sustained levels of GALT CD4+T-cell activation (37.4% vs 6.5%) and CD8+T-cell activation (42.7% vs 12.52%) than men (p<.05) measured by the expression of the surface marker HLA-DR. Postmenopausal women had higher levels of T cell activation compared to premenopausal women and age matched males. A significantly higher percentage of CD8+ T cells produced TNFα on stimulation in postmenopausal women compared to premenopausal women. Villus epithelium from jejunum was isolated using laser capture microdissection. Comparison of gene expression in these samples showed down-regulation of epithelial regeneration pathways and tight junction proteins in postmenopausal women associated with an increase in epithelial inflammation compared to premenopausal HIV+ women

and men on HAART. Indicators of microbial translocation, such as plasma LPS, and bacterial 16S rRNA, were increased in women compared to men on HAART. Epithelial cells grown in the presence of β E2 had increased proliferation (up to 40% higher) in a dose-dependent manner. Cells grown in the presence of HIV/SIV had a decrease in proliferation of >50%, which was abrogated in the presence of β E2. Epithelial integrity measured by the trans-epithelial resistance (TER) also decreased by 25% in the presence of SIV infection; however, low basal levels of exogenous β E2 restored the TER. Increase in TER was associated with increased expression of the tight junction protein, ZO1. **Conclusion:** These preliminary data suggest that increased inflammation secondary to microbial translocation may explain why women, especially postmenopausal women, have sustained CD4+T-cell activation, despite effective control of viral replication. The loss of estradiol may be a mechanism involved. Studies investigating the effects of HAART in women should focus on the maintenance of mucosal integrity and health following menopause

P-19.

Melatonin may influence CYP19 immunoreactivity in ovary of female rats in proestrous phase

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Objective: to determine the immunoreactivity of cytochrome P-450 (CYP19), an enzyme associated with the conversion of androstenedione to estradiol, in the ovaries of pinealectomized female rats after melatonin treatment. **Design:** Thirty female adult and virgin rats (*Rattus norvegicus albinus*) were separated in three groups of 10 animals each: G1 – Sham (falsely pinealectomized) received vehicle; G2 – pinealectomized who received vehicle; G3 – pinealectomized with melatonin reposition (10 μ g/night, each animal) for 60 consecutive days. After this period, animals were anesthetized and ovaries were collected, fixed in 10% buffered formaldehyde and processed for paraffin embedding. From the paraffin blocks, 5 μ m thick sections were collected to silanized slides and submitted to immunohistochemistry for CYP19 detection. Images were obtained using a light microscope (Axiolab Standard 2.0 - Carl Zeiss) attached to a high definition camera (AxioCam MRC - Carl Zeiss) to the analyzing image (AxioVision Rel. 4.8.2 - Carl Zeiss). Reaction expression was analyzed and quantified according with the color intensity with the aid of the Image J Pro Plus, having photographed 5 fields each slide, with the 40x objective. Obtained data was submitted to statistical analysis using ANOVA test complemented by the Tukey-Kramer test ($p < 0.05$). **Results:** Histological sections underwent immunostaining CYP19 showed that the expression of CYP19 was higher in pinealectomized (G2 = 84.43 $\pm$ 5.90 *) compared to Sham groups (G1 = 64.71 $\pm$ 4.06) and pinealectomized treated with melatonin (G3 = 58.35 $\pm$ 8.90) (* $p < 0.05$). **Conclusion:** Our results showed that melatonin affects ovarian steroidogenesis in female rats.

P-20.

Surgical Menopause Enhances Neurodegenerative JNK Signaling in the Hippocampus: Potential Role for Estrogen Receptor Co-regulator PELP1

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Objective: Prematurely menopausal women have a doubled lifetime risk of dementia and a 5-fold increased risk of mortality from neurological disorders, although the mechanisms underlying the increased risks remain unclear. Previously, we showed that female rats subjected to 10-week ovariectomy exhibited a loss of estradiol (E2) neuroprotection against global cerebral ischemia (GCI), a switch to amyloidogenic processing of amyloid precursor protein (APP), and a corresponding profound induction of Alzheimer's disease (AD)-related proteins in the hippocampus. We, thus, hypothesized that neural E2 signaling may be altered following surgical menopause and decided to examine the role of a proposed key estrogen receptor (ER) co-regulator: Proline-, Leucine-, and Glutamate-Rich Protein 1 (PELP1), in the brain. **Design:** To investigate, we utilized a rat model of surgical menopause and initiated subcutaneous E2 therapy either immediately or 10 weeks (LTED – long-term E2 deprived) following bilateral ovariectomy. One week after continuous treatment, all animals were subjected to GCI to assess PELP1 expression and E2 neuroprotection status. Since our previous studies identified JNK as a critical mediator of post-ischemic AD-related protein induction, we next examined the role of PELP1 in E2's regulation of JNK activation, APP phosphorylation, and in E2-induced neuroprotection. To accomplish this goal, we knocked-down PELP1 intracerebroventricularly with anti-sense oligonucleotides prior to inducing GCI. **Results:** Intriguingly, we observed that PELP1 was significantly down-regulated in the hippocampus of LTED females. In the PELP1 knockdown animals, we observed a loss of E2 neuroprotection, enhanced JNK activation, and increased APP phosphorylation after GCI, similar to what was previously observed in the LTED females. Furthermore, immunoprecipitation and mass spectrometry studies suggested that, in addition to ER α , PELP1 physically binds to JNK, as well as its upstream signaling effectors, Mitogen-Activated Protein Kinase Kinase 7 (MKK7) and Mixed-Lineage Kinase 3 (MLK3), in the brain. **Conclusion:** Collectively, these studies shed light on the complex mechanisms underlying the increased risk of dementia following surgical menopause and suggest that PELP1 may play a key role in E2 neuroprotection.

P-21.

Hyperprolactinemia interacts with estroprogestative therapy and enhance endometrial VEGF immunoreactivity in the uterus of mice

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Objective: To evaluate the effects of estrogen and progesterone replacement in the uterus of mice with hyperprolactinemia. **Design:** 24 adult virgin female mice (100 days old) were divided into two groups with 12 animals each: G1 - vehicle (0.2 mL of saline solution at 0.9%) and G2 – treated with 200 μ g/day of metoclopramide (MCP) dissolved in vehicle; also, 48 adult virgin female mice (100 days old) were oophorectomized (Ovx) and after 28 days were divided into four groups, with 12 animals each: G3 – Ovx + MCP; G4 – Ovx + MCP + 1 μ g/day of estradiol (E); G5 – Ovx + MCP + 1mg/day of micronized progesterone (P) and G6 – Ovx + MCP+E+P. Drugs were subcutaneously administered during 50 consecutive days. After treatments, the animals were euthanized, blood was collected for prolactin, estrogen and progesterone serum measurements by RIA; the uterine horns were removed and fixed in 10% formaldehyde and then subjected to the histological routine processing for paraffin inclusion. Sections were submitted to immunohistochemistry for the detection of vascular endothelial growth factor (VEGF). The photomicrographs were collected using Axion vision (Zeiss, Germany) and the semiquantification analysis from ImageLab® (Software Informatics Ltd., Brazil). Obtained data were subjected to analysis of variance (ANOVA) ($p < 0.05$). **Results:** The G2 group showed higher VEGF immunoreactivity compared to other groups (G1>G3>G4>G5>G6, $p < 0.05$). Among the OVX groups, the G6 was the one that presented the higher VEGF immunoreactivity ($p < 0.05$). **Conclusion:** Our results suggest that prolactin interacts with estroprogestative therapy and then increase endometrial proliferation by enhancing endometrial VEGF immunoreactivity in adult female mice.

P-22.

Melatonin may influence the immunoreactivity of proteins and the up-and-down regulation of ovarian functions related genes in the ovary of pseudopinealectomized rats in proestrous phase

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Objective: To identify the target genes of melatonin in the ovarian tissue of adult pseudopinealectomized rats. **Design:** Thirty-two adult virgin rats (*Rattus norvegicus albinus*) were divided into two groups: G1 - control treated with vehicle, G2 - pseudopinealectomized that received melatonin (10mg / night each animal) for 60 consecutive days. After treatment, the animals were anesthetized and the collected ovaries were immediately placed in liquid nitrogen and then frozen at - 80 ° C for further cDNA microarray analyzes. To determine the expression of various genes, a GeneChip® Kit Rat Genome 230 2.0 Affymetrix Array was used, according to the supplier specifications and the experiment was repeated three times for each group. Obtained data were normalized, subjected to GeneChip® Operating Software program and confirmed by the software analysis of the secondary DNA-Chip Analyzer (dChip). Upregulation and downregulation of genes were considered significant when it was 1.5x higher or lower from the control group. Genes related to ovarian function was further confirmed by immunohistochemistry. **Results:** We found an upregulation of adenylate cyclase type 9 and inhibin beta B genes and a downregulation of Element modulator cyclic AMP gene in the ovarian tissue of G2, compared to control group. On the other hand, the immunoreactivity of c-Kit, Ki-67, CYP17 and CYP19 was higher in G1, compared to G2. **Conclusion:** Our data suggest that melatonin supplementation may decrease the cyclic AMP gene expression in the ovaries of pseudopinealectomized female rats, also altering steroidogenesis and estrogen synthesis.

P-23.

Study of the vascular endothelial growth factor (VEGF) on the pseudopregnant uterus of hyperprolactinemic mice

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Objective: To evaluate the action of hyperprolactinemia on the VEGF in pseudopregnant uterus. **Design:** 40 adult female mice were divided into two groups: Control (Ctrl1) – treated with 0.2 mL of saline solution at 0.9% and experimental (HPr11) –subcutaneously treated with 200 μ g/day of metoclopramide, for 50 consecutive days. After treatment, half of the mice were sacrificed. The remaining animals were mated with castrated male mice to obtain the pseudopregnant groups (Ctrl2 and HPr12). Part of these animals was treated with metoclopramide to constitute the metoclopramide-treated pseudopregnant group (HPr12). The groups Ctrl2 and HPr12 were sacrificed on the 6th day of pseudopregnancy. Following euthanasia of the animals, the blood was collected for measurement of prolactin, estrogen and progesterone serum by ELISA and RIA; the uterine horns of all animals were removed and fixed in 10% formaldehyde and then submitted to the histological routine processing for paraffin inclusion. Sections were subjected to the immunohistochemical method for the detection of VEGF. The photomicrographs were collected using Axion vision (Zeiss, Germany) and the semiquantification analysis from ImageLab® (Software Informatics Ltd., Brazil). The

results were submitted to statistical analysis by the ANOVA test ($p < 0.05$). **Results:** The highest level of prolactin was seen in the animals treated with metoclopramide (HPr1 and HPr2) ($p < 0.05$). The immunoreexpression of VEGF was higher in HPr1 group when compared to Ctrl1 group ($p < 0.05$), while the Ctrl2 group showed lower VEGF immunoreexpression compared to HPr2 but higher when compared to Ctrl1 group ($p < 0.05$). **Conclusion:** These results show that hyperprolactinemic state changes the VEGF immunoreactivity in the uterus of metoclopramide-treated pseudopregnant mice.

P-24.

Vaginal and systemic cytokines in postmenopausal women with and without symptoms of vulvovaginal irritation

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Objective: The aim of this exploratory pilot study was to determine the correlation between postmenopausal vulvovaginal irritative symptoms (itching, burning, or pain) with vaginal cytokine levels. **Design:** Postmenopausal women ($n=34$) not using hormone therapy and presenting with or without symptoms of vulvovaginal irritation were asked to volunteer for this study, which was approved by the local Ethics Committee. Each participant after signing an informed consent underwent a vaginal examination with emphasis on the presence or absence of infectious vaginitis using pH, and wet preparations. A vaginal lavage with 5.0 mL of sterile saline was carried out and a peripheral blood sample was obtained. The vaginal lavage and serum samples were assayed for interleukin (IL)-1b, IL-6, IL-8, and Tumor Necrosis Factor- α (TNF- α) by specific ELISAs. Results were adjusted to total protein concentration and presented as the amount of cytokine per protein [pg/mcg protein]. Statistical analysis was performed using SAS 9.3 (Cary, NC). The means and standard deviations of all variables among women with and without vulvovaginal irritation, were compared using independent samples t test. **Results:** A total of 26 postmenopausal women were enrolled into the study (symptomatic: $n=15$; asymptomatic: $n=11$). Mean vaginal pH for all participants was 5.9 ± 1.2 . There were no significant differences ($p > 0.05$) among symptomatic versus asymptomatic women: age, age at menopause, vaginal pH and all vaginal and serum cytokines and chemokines (IL-1b, IL-6, IL-8, TNF- α). IL-8 was the most abundant vaginal cytokine with mean vaginal IL-8 levels being 4.1 ± 3.4 pg/mcg of protein and 3.1 ± 3.9 pg/mcg of protein in the symptomatic versus asymptomatic groups, respectively ($p=0.55$). **Conclusion:** Postmenopausal vulvovaginal symptoms did not correlate with vaginal inflammatory markers. There was no difference in serum or vaginal cytokines between postmenopausal women with or without symptoms commonly associated with vaginal atrophy implying that this is a local reaction. The clinical symptoms of vulvovaginal atrophy appear to be related to the epithelium of the vulva and are not reflected in altered vaginal or systemic cytokine concentrations.

P-25.

Evaluation effects of estrogens and isoflavones on reactive oxygen species in the uterus of rats

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Objective: To evaluate the pro-oxidant and antioxidant balance in the uterus of ovariectomized (Ovx) rats treated with isoflavones or estrogens. **Design:** We used 20 rats of three-months-old, divided into four groups: GI - sham-operated (estrous phase), GII - Ovx with receiving propylene glycol; GIII - Ovx with receiving isoflavones (150mg/Kg) and GIV - Ovx with receiving 17beta-estrogen (10µg/Kg). All drugs were administered by gavage daily and after 30 days of treatment, the animals were euthanized and a part of the uterine horn was fixed in 10% formalin and processed for histomorphometry. The thickness of the endometrium, myometrium and the glandular area were evaluated. The remainder uterine horns were dipped in liquid nitrogen and subsequently analyzed for: quantification of reactive oxygen species. (ROS) by fluorescence method with diclorodihidro-fluorescein diacetate (DCFH-DA); to evaluate the levels of total antioxidants by reducing Cu²⁺ and to the detection of the products of lipid peroxidation by the method of thiobarbituric acid reactive substances (TBARS). The results were analyzed by ANOVA complemented by Tukey-Kramer test ($p < 0.05$). **Results:** The GIV showed increased thickness of the myometrium compared to other groups, and the thickness of the endometrium and glandular area did not differ significantly with respect to GI. Furthermore, these parameters did not differ significantly between the groups GII and GIII, however, were lower compared to GI. The group treated with isoflavones had lower levels of ROS and lipid peroxidation compared to GII, as well as higher levels of total antioxidants that GI and GIV. The GIV showed lower levels of total antioxidants that GII and GIII, lower levels of lipid peroxidation, without changing significantly the ROS when compared with GII, however, with higher levels of ROS that GI and GIII. **Conclusion:** Isoflavones improve the levels of total antioxidants and reduce oxidative stress without promoting trophic effect in the uterus of rats.

P-26.

Influence of hyperprolactinemia on the immunoexpression of estrogen and progesterone receptors in the uterus of pseudopregnant mice

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Objective: To evaluate the effects of metoclopramide-induced hyperprolactinemia in the expression of estrogen and progesterone receptors in pseudopregnant uterus of mice. **Design:** 40 adult female mice were divided into two groups: Ctrl1: (received 0.2 mL of saline solution) and HPr11 (treated with metoclopramide - 200 µg/day). After 50 consecutive days of subcutaneous treatment, half of the mice were sacrificed. The remaining animals were mated with castrated male to obtain the pseudopregnant control group (Ctrl2). Part of these animals was treated with metoclopramide, which constituted the metoclopramide-treated pregnant (HPr2) group. The Ctrl2 and HPr2 groups were sacrificed on the 6th day of pseudopregnancy. Following euthanasia of the animals, the blood was collected for measurement of prolactin by ELISA and, estrogen and progesterone serum by ELISA and RIA and the uterine horns were removed for immunohistochemical analysis for the semiquantification of estrogen and progesterone receptors. The photomicrographs were collected using Axion vision (Zeiss, Germany) and the semiquantification analysis from ImageLab® (Software Informatics Ltd., Brazil). Statistical analysis was carried out by ANOVA ($p < 0.05$). **Results:** The immunoreactivity of the progesterone and estrogen receptors in the HPr11 was lower compared to Ctrl1 ($p < 0.05$) and HPr2 groups, but higher when compared to Ctrl2 group ($p < 0.05$). The highest level of prolactin was seen in the animals treated with metoclopramide (HPr1 and HPr2) ($p < 0.05$). **Conclusion:** Our data showed that the hyperprolactinemia induces changes the hormonal preparation of the endometrium in regular cycle or pseudopregnancy in mice and this effect may be related to disruptions in the hormone receptors signaling pathways.

P-27.

Comparative study of cell proliferation (PCNA) and apoptotic cell death (Caspase-3) in the pseudopregnant uterus of hyperprolactinemic mice female

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Objective: To evaluate the cell proliferation and cell death in the pseudopregnant uterus of hyperprolactinemic mice female. **Design:** 40 adult female mice were divided into two groups: Ctrl1: (received 0.2 mL of saline solution) and HPr11 (treated with metoclopramide - 200 µg/day). After 50 consecutive days of subcutaneous treatment, half of the mice were sacrificed in proestrus phase. The remaining animals were mated with castrated male to obtain the pseudopregnant control group (Ctrl2). Part of these animals was treated with metoclopramide, which constituted the metoclopramide-treated pregnant (HPr2) group. The Ctrl2 and HPr2 groups were sacrificed on the 6th day of pseudopregnancy. Following euthanasia of the animals, the blood was collected for measurement of prolactin by ELISA and, estrogen and progesterone serum by ELISA and RIA and the uterine horns were removed for immunohistochemical analysis for the semiquantification of PCNA and caspase-3 cleaved. Statistical analysis was carried out by ANOVA ($p < 0.05$). The photomicrographs were collected using Axion vision (Zeiss, Germany) and the semiquantification analysis from ImageLab® (Software Informatics Ltd., Brazil). **Results:** The immunoreactivity to PCNA and to caspase was inversely proportional. In proestrus phase (regular estrous cycle) significantly increased cell proliferation and decreased apoptosis ($p < 0.05$). In pseudopregnant groups there was no difference between the Ctrl2 group and HPr2 group. The highest level of prolactin was seen in the animals treated with metoclopramide (HPr11 and HPr2) ($p < 0.05$). **Conclusion:** Our data showed that the hyperprolactinemia induces cell mitosis in proestrus phase. This did not occur in animals' pseudopregnancy.

CLINICAL POSTER PRESENTATIONS

P-28.

Disproportionately Higher Prevalence of Low Bone Mineral Density in Postmenopausal Women with Gynecological Cancers Compared to those with Breast Cancer

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Objective: In postmenopausal women undergoing bone mineral density (BMD) assessment, we hypothesized variability in BMD in relation to type of cancer. Site-specific BMD (g/cm²) at lumbar spine (LS), mean femoral neck (FN) & total hip (TH) were compared between two groups of women with gynecological cancers – Gyn-ca (uterine/endometrial, cervical, ovarian, vaginal, vulvar) & breast cancer – Br-ca. **Design:** Medical records for postmenopausal women undergoing first BMD assessment by dual energy X-ray absorptiometry (DXA) at the Bone Center at Gynecologic Oncology division at Yale were retrospectively reviewed over a 2-year period. Information regarding

age, height, weight, body mass index (BMI), ethnicity, race, history of fractures, current medications, site of malignancy, chemo-radiation therapy and BMD parameters including bone mass and T scores (TSc) was collected. BMD parameters between the two groups were compared utilizing Student's T-Test. $T_{sc} < -1.0$ at the hip identified low BMD. Multivariable linear & logistic regression analyses assessed relationship between Gyn-ca vs. Br-ca with TH & mean FN BMD & with low BMD at hip after adjusting for age, BMI & race respectively. **Results:** Of 244 women, 137 were diagnosed with Gyn-ca (56%) & 107 had Br-ca. (44%). Women with Gyn-Ca were older (64 ± 12 vs. 62 ± 11 , $p=0.11$), & were significantly heavier ($BMI\ 31 \pm 8$ vs. 29 ± 7 , $p=0.03$). BMI correlated positively with BMD at LS, FN & TH ($p<0.01$). Women with Gyn-ca had significantly lower BMD at FN (877 ± 115 vs 918 ± 122 g/cm², $p=0.01$) & TH (934 ± 126 vs. 972 ± 129 g/cm², $p=0.02$) compared to those with Br-ca; likelihood for low BMD at hip was increased by 76% in those with Gyn-ca compared to Br-ca ($p=0.03$). Adjusting for BMI, age & race, women with Gyn-ca were almost twice as likely to have low BMD at hip compared to those with Br-ca (OR 1.8, 95% CI 1.05-3.15). **Conclusion:** Our data identify that women with Gyn-ca (all types) are more likely to manifest low BMD compared to those with Br-ca; mechanisms underlying the observed differences in BMD are unclear & merit further study.

P-29.

Outcome of Zoledronic acid infusion at the Center for Specialized Women's health, Cleveland Clinic

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Objective: To evaluate the change in bone mineral density and patient compliance with zoledronic acid infusions. **Design:** This is a retrospective study of postmenopausal women who received Zoledronic acid infusion (5 mg) between 2008 and 2012 at the Center for Specialized Women's health of the Cleveland Clinic for diagnosis of Osteoporosis (defined by BMD T-score ≤ -2.5), Clinical Osteoporosis (defined as Osteopenia with fragility fracture) and Osteopenia (defined by BMD T-score between -2.5 and -1.0) using WHO classification. BMD of patients available before and after Zoledronic acid infusion were reviewed. Whether there was a statistically significant change or not was noted as determined by the centers precision error. Number of infusions per year and compliance of patients were reviewed. The normality of values were evaluated. Categorical values were summarized by frequency and percentage. Change in bone mineral density were compared by a paired t-test. **Results:** The number of patients receiving Zoledronic acid yearly in the center has increased, from 48 in 2008 to 134 in 2011 and 118 in 2012. A total of 238 patients were reviewed, 64% (148) had Osteoporosis, 18% (43) had Clinical Osteoporosis and 19% (47) had Osteopenia. 67% (161) had improvement or stability in their bone density, 5% (12) deteriorated, and 27% (65) had no follow up scans. Of the 65 who had no follow up scans, 50 were not due to get their DXA scans yet, 1 was due to insurance coverage, and 14 did not get follow up scans, despite being called to follow up. **Conclusion:** The number of patients receiving Intravenous Zoledronic acid in our center has increased from 2008 to 2012. Majority of these patients had stability or improvement in their bone density after their first infusion. These women were also noted to be compliant with their treatment regimen and continued to show bone density improvement/stability thus improving their Osteoporosis or Osteopenia. From a cost effective standpoint, since majority of the women showed improvement/stability in their bone mineral density after their first infusion, we might be able to extend the timing of repeat DXA scans. However longer term studies involving larger number of patients will need to be done to support this.

P-30.

Musculoskeletal pain in perimenopause: A qualitative study

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Objective: Although aches and pains are one of the most common symptoms endorsed by perimenopausal women in large longitudinal studies, little is known about the location, quality, intensity, or functional consequences of musculoskeletal pain which onsets in perimenopause. Focus groups were conducted to enable women to describe the symptom experience and coping strategies for managing perimenopause-associated musculoskeletal pain. **Design:** Women with onset or exacerbation of musculoskeletal pain during perimenopause were recruited by flyers, direct mail, and word-of-mouth. Eight focus groups are planned, and to date five have been completed. Participants for four of the groups are Hispanic women recruited from the Washington Heights/Columbia University Medical Center community. Participants for the other four groups were recruited from the upper east side of Manhattan. Participants were given the NAMS Menopause Guidebook and compensated \$25 cash. Focus groups were audiotaped and transcribed. NVivo software (QSR International) will be used to help organize and code themes, subthemes and relationships. **Results:** Themes which have emerged during the focus groups include the nature of the pain, palliating factors, and aggravating factors. The most commonly endorsed locations were hips, back, knees, hands and feet. The pain was most often described as aching, stiff, and worst in the morning. Participants visited a variety of physicians, including internists, gynecologists, and rheumatologists without relief. Their concerns were dismissed as "part of getting older", and women did not think providers appreciated the severity of their pain. Many women had not discussed their pain with friends or family. Almost all tried alternative treatment approaches, but the consensus was that massage and anti-inflammatory medication gave only transient relief and stretching and exercise provided more sustained benefit. Very few had considered hormone replacement as a treatment strategy. Hispanic women talked about salsa dancing as an important social and physical therapy and the use of Spanish cable television shows on

fitness as a way to make time for exercise. Participants also discussed the negative impact of the pain, which manifested as functional limitations such as carrying groceries and other loads, opening jars, changing clothes, making a bed, going down steep stairs of a bus, and participating in running, dancing, and yoga. As a result, several participants stated that they were more cautious in their activities due to concerns that recovery from a fall would be difficult. Pain also disrupted sleep for many women, particularly if they moved during sleep. **Conclusion:** For some women, pain which onsets during perimenopause is of sufficient severity to impact functioning. Women felt their symptoms were not appreciated by health care practitioners and had been disappointed by interactions with physicians. Exercise, stretching and NSAIDs were the treatment approaches most often endorsed by participants, although many noted a marked drop in their ability to exercise due to pain. Supported by Translational Research Institute on Pain in Later Life (TRIPPL) P30AG022845, and NCATS Grants at Weill Cornell UL1TR000457 and Columbia UL1TR000040

P-31.

Patient-Centered Care for the Transgender Menopausal Patient

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Objective: The issue of gender identity has become a topic of great interest in both the medical and lay press, as more individuals are expressing a divergence between their assigned gender at birth and their gender identity. There is a growing openness, awareness and support of Lesbian, Gay, Bisexual and Transgender (LGBT) which will translate into healthcare practices treating more of these patients, hopefully in an environment that is conducive to patient-centered care. According to the DSM-V, LGBT individuals will not longer be classified as having a psychiatric condition, and specifically, the transgender group will no longer be classified as having a gender identity disorder. Instead clinical focus will be on the potential marked incongruence between one's experienced gender and assigned gender (gender dysphoria). However, the transgender menopausal population will present to the healthcare provider with some unique medical needs and concerns. Transgender females with an assigned or surgically created female sex will need management geared to continued hormonal management and to the risk factors identified in this population. **Design:** This review evaluated the literature on transgender medicine identified through PubMed over the last decade. **Results:** The scant research directed to the aging transsexual female population reports that this population is reluctant to seek medical care for prevention and intervention. Most health care facilities fail to recognize this population, or have no experience or guidelines in dealing with them. Elderly care facilities are equally hesitant to see transgender patients, since conventional patterns dictate that the spouse, child, or other immediate family member become the support for the patient. For many older transgender women, life partners and unconventional families are their support system. Aging transgender women, in addition to having life long estrogen needs that may increase their risks of estrogen related adverse consequences, such as estrogen dependent tumors, are also vulnerable to symptoms of anxiety, depression, and psychological distress. Further, Medicare often does not cover hormonal therapies and other care related to transitioning and maintaining their gender identity. A termination of hormonal therapy in this group may cause additional physical and mental health risks. Moreover, aging transgender women may be more vulnerable to discrimination and victimization. Having a template for care is critical to assure that this population is provided with appropriate health care management. **Conclusion:** The increasing awareness of the transgender community in the social sphere should be carried over to the health care profession. With the growth of transgender people seeking treatment and body modifications, particularly at a young age, the medical community should be equipped to deal with the needs of this population. Practices that care for menopausal patients should be geared to work with the special needs of transgender women, including their hormonal needs. Of importance, more research should be initiated on all aspects of the aging transgender community.

P-32.

The Treatment Effects of Physical Exercises on Perimenopausal Syndrome and Blood Lipids in Perimenopausal Women: A Randomized, Placebo-controlled Trial

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Objective: The aim of the present study was to evaluate the treatment effects of physical exercises for menopausal symptoms among middle-aged female medical staffs who were suffering from perimenopausal syndrome. **Design:** 157 female medical staffs in the age group of 40 to 55 years, of whom Kupperman index (KMI) was no less than 15 points, were randomized into intervention group (78 people) and control group (79 people) in a ratio of 1:1. The intervention group was given physical exercises while the natural state of the control group was recorded. A follow-up was made at baseline, 4th week, 8th week and 12th week, recording the total KMI score and the individual scores, meanwhile testing fasting blood glucose, triglycerides(TG), total cholesterol(TC), high density lipoprotein (HDL), low density lipoprotein (LDL), weight and waist circumference. The effects of physical exercise therapy on perimenopausal syndrome were evaluated by comparing the change of those parameters discussed above between the two groups. **Results:** At the 12th week, the total KMI score and individual score of paraesthesia, insomnia, irritability, joint pain or muscle pain, fatigue, headache, skin formication and sexual life as well as

POSTER PRESENTATIONS *(continued)*

TC, TG in the intervention group was significantly lower than the control group, the difference was statistically significant ($P < 0.05$). The total KMI score and individual scores of weight, BMI, waist circumference in Intervention group, as well as TG and TC were lower than their baseline, which were also statistically significant ($P < 0.05$). **Conclusion:** Physical exercises therapy can reduce menopausal symptoms and improve their blood lipid and bodyweight status substantially.

P-33.

Content Analysis of Websites Promoting CAM Treatment for Menopausal Symptoms

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Objective: Access to herbal medications has increased with the growth of retailers and websites marketing them. In the US an estimated 38% of adults use complimentary and alternative medicine (CAM) including herbal products with women and people with higher education being more likely to use CAM. Although menopausal symptoms do not make up the most common ailments treated with CAM; soy supplements were among the top 10 natural products in 2002. Considering that 59% of American adults accessed the internet for health information in the past year and multiple websites market CAM products directly to consumers; it is not surprising that more people are purchasing herbal products online. **Design:** Using Google, Bing and Yahoo search engines; websites marketing herbal products for menopausal symptoms were identified for content analysis. Websites must be in English, directly sell or clearly indicate where to purchase product and promote only one brand of products for menopausal symptoms relief. Ten websites met inclusion criteria and were reviewed by a single author. **Results:** All websites promoted their product as “safe” and “natural”. All product websites were based in the US. The majority of products (90%) claimed to relieve hot flashes with the next most commonly listed symptom improvement as mood/irritability, fatigue, sexual desire, weight gain and sleep. Ingredients varied widely among the products with 70% containing Black Cohosh, 30% soy isoflavones and 30% yam. Half of all products contained additional vitamins. 80% of products were delivered via PO route in capsules, tablets, chews or liquid; the remaining 20% were topical creams. Listed prices ranged from \$17.95 to \$295. All but one website featured personal testimonials with 40% featuring a medical doctor giving an endorsement. Scientific claims also varied widely with 40% websites listing articles supporting use of single ingredients in products, 40% listing no articles and 2 websites listing articles for the specific product although both were published in foreign journals. Interestingly 30% of websites did not include statements explaining that the FDA does not evaluate the claims of the products. When evaluating the safety of the products; only 60% recommended that the consumer consult with their physician before taking and none cautioned on the potential risks of the ingredients **Conclusion:** Herbal products are an increasingly popular form of medical treatment among consumers. The internet provides companies an effective mode of marketing and allows consumers to purchase without consulting with a doctor or pharmacist. For people without medical training it is easy to be swayed by promises of symptom relief and non-stringent research. We as healthcare professionals should routinely inquire and advise patients desiring to treat menopausal symptoms with CAM.

Website Name	Product Name	Formulation	Cost	Ways to purchase	Endorsements	Recommended to consult MD?	Caution regarding herbal ingredients?	Symptoms	Ingredients	Research
Menopause-org.com	Estro900	topical cream	\$39.99-149.95	online	spokesperson is MD	yes	no	hot flashes, night sweats, vaginal dryness	Estro900 and Estro900 with source listed as yams	option of spokesperson
estrothin.com	EstroThin	PO liquid	\$49.95-249.75	online, toll free or fax	consumer	yes in tiny print at bottom of website	no	weight gain, energy, mood swings	Eleuthero root, schradra berry, green tea extract, etc...	75,000 clinical studies have been performed proving the effectiveness; however none are listed
i-coolformenopause.com	i-cool	tablet	no price listed	links to retailers	consumer	no	no	hot flashes, night sweats	genVeda	1 study in Maturitas; 1 survey of Red Hot Mamas
womenstowomen.com	Herbal Equilibrium	tablet	\$59-295	online or toll free	founder is OB/Gyn NP	yes in the FAQs section	no	hot flashes, night sweats, irritability, anxiety, insomnia, mood	Red clover extract, Ashwagandha extract, passionflower extract	multiple articles for each individual ingredient
naturalrelief.com	Natural Relief	tablet	no price listed	online or toll free	consumer	no	no	hot flashes, night sweats, mood swings	Dong Quai Root, aratylodes rhizome, chaste berry extract	none listed but several alluded to in a paragraph
dreambrands.com	Internal harmony	topical cream	\$27.99	online, toll free or find local retailer using zip code	consumer	no	no	anxiety, hot flashes, sexual desire, muscle mass, stamina, endurance, focus	natural progesterone, grape-seed oil, avocado oil, carpopapaville niglyverides	none listed
amheren.com	Amheren	capsules	\$99.98	online and toll free	14 “doctor” endorsements including: colon hydro therapy, acupuncturist, naturopathic physician, health coach, chiropractor, certified health advisor, registered nurse, registered dietitian, no degree listed and MD	yes	no	hot flashes, weight gain, sleeplessness, irritability	ammonium acetate, calcium disuccinate, monosodium L-glutamate	2 murine Russian studies, 1 Russian RCT in humans
estroviv.com	Estroviv	tablets	no price listed	online and link to retailers	consumer	no	no	hot flashes, night sweats, irritability	Black cohosh, soy isoflavones, magnolia bark	reference review of 17 articles with no reference listed
avimil.com	Avimil	tablet	\$39.950-149	online or toll free	states “doctor recommended” but no specific comments listed	yes	no	fatigue, mood swings, hot flashes, libido	isoflavones, black cohosh, sage leaf	none listed

P-34.

Is Uterine Leiomyomata Associated With Postmenopausal Bleeding? A Retrospective Review

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Objective: To identify whether uterine fibroids are associated with postmenopausal bleeding **Design:** Retrospective cohort analysis **Results:** Overall, 199 women were assessed including 98 (49.3%) with and 101 (50.7%) without bleeding. The proportion of women with uterine fibroids in the bleeding cohort (53.1%) was similar to that of women in the non-bleeding cohort (53.5%), ($p = 0.954$). However, the uterine volume was significantly larger in the bleeding cohort (median = 73.0 cm, range: 21.3 cm to 1054 cm) compared to the cohort without bleeding (median = 40.8 cm, range: 6.2 cm to 741.5 cm) ($p = 0.0003$). **Conclusion:** Our retrospective chart review did not find a significant difference in the prevalence of fibroids between postmenopausal women with complaints of bleeding and those without complaints of bleeding.

Demographics and uterine size among postmenopausal women with complaints of bleeding compared with women without complaints of bleeding.

Variable	Bleeding Group	No Bleeding	Chi-Square p value
Age	58.5	60.0	0.117
BMI	33.0	27.0	0.0001
Uterine Volume	73.0	40.8	0.0003

Data are presented as Median

Uterine pathology identified in postmenopausal women with complaints of bleeding compared with women without complaints of bleeding.

Pathology	Bleeding group	No bleeding group	p Value
Uterine Fibroids	52/98 (53.1%)	54/101 (53.5%)	0.954
Suspected Endometrial Polyp	34/98 (34.7%)	4/101 (3.96%)	0.001
Suspected Adenomyosis	13/98 (13.3%)	11/101 (10.89%)	0.607

P-35.

The relationship between endometrial cancer and bone density

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Objective: A variety of neoplasms are related to osteoporosis in the absence of metastasis. We sought to evaluate bone mineral density (BMD) in patients with endometrial cancer. **Design:** We retrospectively analyzed the BMD of the spine and femur using dual-energy X-ray absorptiometry (DEXA) in 43 patients with endometrial cancer and 80 control women. The control group was treated with surgery for benign disease. All patients with

endometrial cancer and all control women had experienced menopause. There were no bone metastases in patients with endometrial cancer. We compared age, height, body weight, body mass index (BMI), and BMD of the spine and femur between the endometrial cancer and control groups, and compared BMD between stage I and stage II III, and IV endometrial cancer patients. **Results:** There were no differences in the BMD of the spine or femur in patients with endometrial cancer and those in the control group. There were also no differences in the BMD of the spine or femur in patients with stage I versus stage II III, and IV endometrial cancer. **Conclusion:** Endometrial cancer appeared to have no effects on BMD before treatment. However, to define is detailed effect on BMD, a prospective study with large sample size is needed.

P-36.

Comparison of the Efficacy and Safety of the Unicenta and Melsmon Injection for the Menopausal symptoms

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Objective: The objective of this study was to evaluate the efficacy of Human Placenta Extracts the Unicenta and Melsmon in women with the menopausal symptoms by analyzing the changes in the Kupperman index (primary endpoint), and the hormonal change (secondary endpoint) **Design:** This is a randomized, multi-Center, double-blind, parallel, non-inferiority clinical study of four different tertiary medical centers. We began the participant recruitment in September 2011, with 218 patients applied over 7 months. All participants had the last visit in April 2012. **Results:** The Unicenta injection was not inferior to that of Melsmon as measured by the Kupperman index following the injection in both the intent-to-treat and the pre-protocol populations ($p=0.63$, $p=0.85$, respectively). Side effects occurred in 14.0% of the cases (15 patients / 18 cases) in the case group. And in 12.6% (14 patients / 15 cases) in the control group ($p=0.7599$). None were reported to be associated with the medication. The laboratory results and the vital signs showed no statistically significant risk for safety. **Conclusion:** This study showed that Unicenta is not inferior to Melsmon in the change of the Kupperman index after 12 days of injection. The efficacy and safety of Unicenta was shown, with the improvement of the menopausal symptoms.

P-37.

Ospemifene Improves Objective Measures of Vulvar and Vaginal Atrophy (VVA)

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Objective: Ospemifene is a once daily oral estrogen agonist/antagonist that exerts agonist tissue selective effects on the vaginal epithelium with agonist/antagonist effects on the endometrium. Ospemifene was recently approved by the Federal Food and Drug Administration (FDA) for the treatment of moderate to severe postmenopausal dyspareunia, a symptom of vulvar and vaginal atrophy (VVA). In Phase 3 studies, ospemifene has been shown to improve physiologic changes (superficial and parabasal cells, vaginal pH) and physical findings of VVA on visual exam. Currently, only estrogen-based systemic/topical prescription therapies are available for postmenopausal women to treat both the physiologic changes and the symptoms (dyspareunia and dryness) of VVA. Over-the-Counter vaginal products (lubricants/moisturizers) are also available, but have limited to no effect on the underlying physiological changes that occur in VVA. Ospemifene has previously been reported to provide relief of dyspareunia associated with VVA in postmenopausal women. This presentation reports the effects of ospemifene on objective measures of VVA including the correlation between cellular changes and the physical findings on vaginal examination. **Design:** Standard objective measures of VVA [change from Baseline in percent of superficial and parabasal cells in the Maturation Index (MI) of the vaginal smear and vaginal pH] and visual examination of the vagina were performed at Baseline, Weeks 4, 12, and 52. Visual evaluation of the vaginal exam findings assessing petechiae, pallor, friability, vaginal dryness and erythema was reported using a 4-point scale (0=none, 1=mild, 1=moderate, 3=severe). Evaluation of each of the 5 parameters was performed as part of the gynecological examination. A comparison of the ITT population randomized to either placebo or ospemifene 60 mg/day was carried out. Correlation between the MI and visual examination was performed. **Results:** Across three Phase 3 studies, mean changes from Baseline to Week 12/LOCF for objective measures of percent superficial cells (range: 10.8% to 13.4% ospemifene 60 mg vs 1.8% to 3.6% placebo), percent parabasal cells (range: -30.1% to -41.8% ospemifene vs 0% to 3.9% placebo), and vaginal pH (range: -0.98 to -1.01 ospemifene vs -0.09 to -0.24 placebo), showed consistently statistically significant improvement of ospemifene 60 mg/day vs placebo. At Week 52, the statistically significant improvement of ospemifene vs placebo was sustained (superficial cells 5.2% ospemifene vs 0.1% placebo; parabasal cells -46.4% ospemifene vs 15.0% placebo; vaginal pH -1.3 ospemifene vs -0.07 placebo). Improvement in the visual examination of the vagina was observed in all 5 parameters at Weeks 4, 12 and 52 for the 60 mg/day group with statistical significance vs placebo ($p<0.0001$). Correlation between the objective measures of Maturation Value, pH and visual examination revealed a strong correlation in the ospemifene 60 mg/day group. **Conclusion:** Significant changes from Baseline in objective measures of VVA, which included the Maturation Index, vaginal pH and visual examination, indicate improvement in the underlying physiologic findings of postmenopausal VVA in those women treated with ospemifene 60 mg/day. These findings were sustained through 52 weeks. Of interest, there was a highly statistically significant correlation between cellular changes (MI), pH

and physical findings indicating not only dyspareunia symptom relief, which has been previously reported, but treatment of the underlying condition with changes more consistent with premenopausal vaginal epithelium.

P-38.

Endometrial Safety of Ospemifene: Results of the Phase 2/3 Clinical Development Program

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Objective: To assess the endometrial safety of ospemifene based upon the Phase 2/3 clinical trials of postmenopausal women with up to 52 weeks of exposure to ospemifene 60 mg/day vs. placebo. **Design:** The endometrial safety of ospemifene 60 mg daily was evaluated in a development program of five Phase 2/3 randomized, double-blind, placebo-controlled, parallel-group studies of postmenopausal women between ages 40 and 80 years with vulvar and vaginal atrophy (VVA). Subjects were randomized 1:1 to ospemifene 60 mg/day or placebo in four clinical trials of either 6 weeks ($n=1$) or 12 weeks duration ($n=3$), an additional 40 weeks in an extension study of one of the 12 week pivotal trials, and in a separate 52 week trial in which subjects were randomized 6:1 to ospemifene 60 mg/day or placebo. Endometrial safety of ospemifene was assessed by endometrial histology (biopsy), thickness (TVU), and gynecological examinations. **Results:** There were 1,242 women exposed to ospemifene 60 mg/day in the randomized, double blind, placebo-controlled Phase 2/3 clinical trials who were evaluable for safety assessment. There were 851 (68.5%) ospemifene and 570 (59.6%) placebo participants randomized and who had an intact uterus. Endometrial biopsies were obtained at Baseline in 770 ospemifene and 466 placebo subjects; at 12 months 342 ospemifene and 83 placebo subjects had endometrial biopsies. Endometrial hyperplasia occurred in <1% of ospemifene treated subjects and no endometrial cancer was reported. At 52 weeks, active endometrial proliferation was observed in 1% of ospemifene treated subjects, similar to that reported with raloxifene. Vaginal bleeding incidence was similar for treated and placebo subjects. Endometrial thickness as assessed by TVU revealed variability in detecting measurements less than 1 mm with the null hypothesis supported for expected increases and decreases of thickness. **Conclusion:** These data indicate that up to 52 weeks of treatment with oral ospemifene 60 mg daily for VVA was safe on the endometrium; there was no increase in the incidence of endometrial cancer or hyperplasia in postmenopausal women.

P-39.

Reproductive History Correlates with Late-Life Cognitive Function in Postmenopausal Women

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Objective: The effect of reproductive hormones and events on late-life cognitive function is not well understood. We aimed to examine these relationships using reproductive history variables and 14 comprehensive cognitive test scores (summarized as a Global Weighted Cognitive Score (GWCS)) in postmenopausal women. **Design:** The Women's Isoflavone Soy Health (WISH) and Early versus Late Intervention Trial with Estradiol (ELITE) are two randomized clinical trials that have comparable study design, data collection processes and a comprehensive cognitive battery. Baseline information from 909 healthy postmenopausal women participating in these two trials was used in this study. Age at first pregnancy (never pregnant, ≤ 24 years old, >24 years old), age at last pregnancy (never pregnant, <36 years old, ≥ 36 years old), age at menarche (<13 years old, ≥ 13 years old), years of hormonal contraceptive use (none, 1-4 years, 5-10 years, >10 years), and number of pregnancies (never pregnant, full-term, non full-term pregnancies) were tested for their relationships with GWCS by linear regression modeling. GWCS was computed as the sum of 14 standardized cognitive test scores weighted by their inverse correlation among each other (tests having low correlations with others had higher weights). All analyses were adjusted for race or ethnicity, years since menopause, depression score, and years of education. **Results:** The final multivariate model was based on 761 observations. Mean (SD) age at enrollment was 60 (7) years old and mean time since menopause was 10.5 (8) years. The multivariate model showed greater duration of hormonal contraceptive use ($p=0.001$), higher age at last pregnancy ($p=0.02$), and lower age at menarche ($p=0.01$) were independently associated with higher mean levels of GWCS (Figure 1). Age at first pregnancy ($p=0.79$), number of pregnancies ($p=0.09$), and age at menopause ($p=0.09$) were not associated with GWCS. **Conclusion:** Hormonal contraceptive use, late age at last pregnancy (≥ 36 years), and younger age at menarche (<13 years) were associated with better cognition. Increased exposure to estrogen over the reproductive life may play a beneficial role on cognitive function later in life.

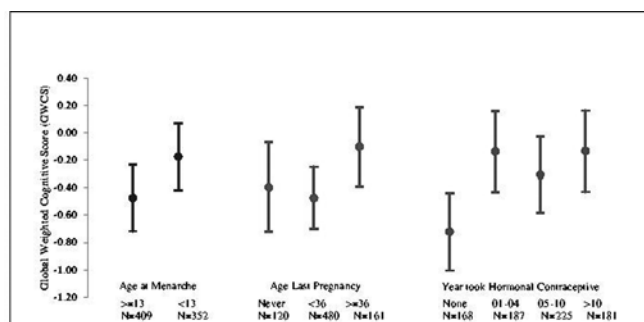


Figure 1: Adjusted means (95% CL) of GWCS for significant factors

P-40.

Consistency of Hot Flashes across a 72-hour Monitoring Session: Self-Reported vs. Objectively Recorded Hot Flashes

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Objective: Hot flashes are the most commonly reported menopausal symptom in the U.S. and have been associated with sleep disturbance, depressive symptoms, cardiovascular disease, and memory problems. Sternal skin conductance monitors allow for the objective measurement of hot flashes. Typically these monitoring sessions are conducted across a 24-hour period; however, the use of lithium ion batteries allows data collection for 72 hours. This study aimed to investigate the reliability of subjectively and objectively measured hot flashes across each of the three days of monitoring. We predicted that measures would be reliable across the three monitoring days. **Design:** Participants included 49 midlife women (40 to 60 years-old) who were enrolled in an observational study of the relationship between hot flashes and cognition. Two groups of midlife women were recruited: women who reported frequent hot flashes (>30 per week) and women with infrequent hot flashes (<7 per week). Each participant completed a two-week screening diary and then wore an ambulatory sternal skin conductance monitor (Biolog Model 3991x/2-HFI) for 72 hours in their typical daily environment. Objective hot flashes (i.e., > 2 micromho increase in skin conductance within 30 sec) and subjective hot flashes (daily diary and monitor event mark) were recorded. Totals and daily averages were calculated for objective and subject hot flash frequency. Analyses were stratified on the basis of low versus high hot flash frequency. **Results:** Five participants were not included in analysis due to incomplete objective hot flash data, leaving a final sample of 44 women (20 low HF frequency; 24 high HF frequency). There was a high correlation between the frequency of objective hot flashes on Days 1 and 2, 2 and 3, and 1 and 3 ($p < .001$), and between the frequency of subjective hot flashes on each of those three days ($p < .001$). **Conclusion:** These data suggest that monitoring hot flashes for a period of 72 hours results in reliable measures across each test day. Generally, these data indicate that a 24-hour estimate of hot flash frequency is a reliable indicator of hot flash frequency over a 3-day period.

P-41.

AGING AND REPRODUCTIVE HORMONES: TRANSITIONS OF THE MENOPAUSE

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Objective: Aging is associated with a decrease in sex hormones in both males and females. This decline is gradual in the male but is precipitous in the female during premenopause. A similar age-related decline occurs in IGF-I levels in both males and females however, the relationship between IGF-I levels and menopause has not been fully examined. **Design:** We have examined IGF-I, estradiol, and FSH levels in a cohort of women (60 women) whose ages span the menopause transition and extend into the geripause (aged 65 on) through the postmenopause. **Results:** We identify a potential relationship between estradiol and IGF-I during the menopause transition. Surprisingly, IGF-I levels were inversely correlated with estradiol levels. An analysis of a subset of the cohort suggests that an increase in IGF-I levels in women approaching menopause is the major source for the correlation. It appears that IGF-I levels may rise in a manner similar to FSH levels during the menopause transition but that IGF-I levels decline at an earlier age than FSH levels following menopause onset. **Conclusion:** These results suggest that another transition, between estrogen and the hypothalamic-pituitary axis, occurs during the postmenopause. This involves IGF-I in addition to FSH on postmenopause and estrogen resolution. This novel geripause transition (about age 65) leads to aging dominance and chronic clinical problems. Further investigations to demonstrate sources for clinical modification continue.

P-42.

Clinical findings of a new fractional CO2 laser-assisted treatment for vaginal atrophy

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Objective: genital atrophy affects sexual function as well as quality of life. Estrogen therapy has a special place in treatment of vaginal atrophy (VA), but is increasingly being used less. Both, estrogen security as the desire of patients significantly decreased use of hormone therapy for atrophic vaginitis. Monalisa Touch™ is an innovative fractional CO2 laser-assisted procedure performed to treat vaginal atrophy. Is a physical alternative, by restoring the pre-menopausal structure of vaginal tissue. The procedure can make some remarks on the restoration of trophism of the vaginal mucosa, which leads to an increase glycogen levels and can support the colonization of vaginal lactobacilli as well as vaginal acidity. The trial objective was to evidence clinical effects of fractional CO2 laser on vaginal mucosa through comparison of vaginal health index (VHI) before and after treatment **Design:** a prospective and analytical trial was performed. In Maracaibo-Venezuela, 24 patients were included after clinical and laboratory selection (with VA/hypoestrogenism). All women consent their participation in this investigation. The trial excluded patients who received hormone therapy in the last 90 days. Patients with diabetes, POP-Q ≥ II, or leak pressure (urodynamics) ≤ 90 cm H2O were also excluded. Women were to applying the laser procedure between October 2012 to February 2013, and underwent evaluated before and 55-70 days after laser sessions with a validated test. Media ± standard deviations were compared using a parametric test (paired Student t); the difference was considered statistically significant when $p < 0.05$ **Results:** 24 hypoestrogenic patients between 39 – 62 years old (52.08 ± 5.54), BMI 28.74 ± 3.34 Kg/m2. FSH 57 ± 15.13 mUI/L and E2 12.75 ± 7.17 pg/dL were the hormones serum values found. About clinical findings: genital itching/burning 83%, dysuria 45%, dyspareunia 75% (only 1/3 was sexually active), vaginal discharge 20%. Seven patients showed POP-Q I (anterior vaginal wall), only 3 patients reported stress urinary incontinence (always leak pressure over 90 cm H2O). VHI increased 11.16 ± 1.68 to 15.91 ± 2.62 after laser sessions ($p < 0.0001$), at the expense of fluids (2.16 ± 0.48 vs. 3.41 ± 1.13), vaginal pH (2.04 ± 0.46 vs. 3.25 ± 0.94) and moisture (2.16 ± 0.96 vs. 3.54 ± 0.97) mostly. There was not any complication or side effect during/after laser treatment **Conclusion:** Monalisa Touch™ is a CO2 laser-assisted effective and secure treatment for vaginal atrophy. With this non hormonal option, it is possible to recover the functionality that the vaginal mucosa has lost due to the ageing process

P-43.

Need for Nonhormonal Menopause Therapy: NAMS Survey Results from Professionals

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Objective: To gauge menopause professionals' perceived need for nonhormonal prescription therapy for menopausal symptoms in preparation for a presentation to the Food and Drug Administration Advisory Committee on Reproductive Health. Although several medications already on the market for other purposes had been shown to reduce vasomotor symptoms (VMS), none had yet been approved to treat VMS, despite the growing need. An increasing number of women are either not candidates for hormone therapy or choose not to use it. Many of these women seek nonprescription options, most of which are not effective. **Design:** The North American Menopause Society (NAMS) invited members (2,010) by email to link to an online survey regarding the need for nonhormonal prescription therapy for menopausal symptoms. Responses were tabulated. **Results:** Responders included 384 members (19% response rate), 89% of whom were clinicians. A large majority of respondents (94%) indicated there was a need for a nonhormonal prescription therapy. Of these respondents, 72% thought the need was strong or very strong, but 56% estimated that fewer than 50% of their patients would prefer or need such a therapy. While 96% of members prescribed hormone therapy, 83% prescribed nonhormonal therapies off label. **Conclusion:** The majority of a group of clinicians involved in providing care for menopausal women expressed a strong need for nonhormonal prescription therapy for their symptomatic patients. A large percentage of these clinicians prescribe nonhormonal therapies off label.

P-44.

Impact of Discontinuing Hormone Therapy on Sexual Activity and Vaginal Symptoms in Postmenopausal Women

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Objective: To determine the impact of discontinuation of hormone therapy (HT) on sexual activity and vaginal symptoms in postmenopausal women aged 50-79 years at the time of initiating HT. **Design:** Participants in the randomized, placebo-controlled estrogen plus progestogen therapy (EPT) and estrogen therapy (ET) trials of the Women's Health

Initiative who had continued study drug until the time the intervention was stopped were invited to complete a survey 8-12 months later (EPT trial) and 7 months later (ET trial). **Results:** At the time of the survey the mean ages of the 9453 EPT group and the 4103 ET group were 70 and 72 years, respectively. Approximately 50% of the participants had partners, 12-15% fewer than at baseline across treatment assignments. Approximately 30% of the EPT group and 20% of the ET group were still sexually active. Reasons provided for no sexual activity were lack of partner (~50%), partner not able (~23%) versus participant not able (~2%), and participant not interested (~28%) versus partner not interested (6%-7%). Vaginal complaints of dryness, irritation, itching, and bleeding were reported by <10%, but all were statistically significantly higher among women who had received EPT ($P<.001$) compared with placebo. The vaginal symptom reported most commonly was dryness at 9.9% in former EPT users vs 5.4% in placebo users. Reports of vaginal symptoms did not differ between those who discontinued ET and placebo in the ET trial. Vaginal estrogen was used by ~7.5% of former HT users and by only 1.7%-2.6% of former placebo users ($P<.001$). **Conclusion:** More women assigned to EPT reported vaginal symptoms after stopping study drug than those assigned to placebo. Former EPT and ET users were more likely to use lubricants and vaginal estrogen than were former placebo users. The overall rate of vaginal complaints was low.

P-45.

Need for Nonhormonal Menopause Therapy: NAMS Survey Results from Consumers

Margery Gass, MD. The North American Menopause Society, Mayfield Heights, OH **Objective:** To gauge consumers' perceived need for a nonhormonal prescription therapy for menopausal symptoms in preparation for a presentation to the Food and Drug Administration Advisory Committee on Reproductive Health. Although several medications already on the market for other purposes have been shown to reduce vasomotor symptoms (VMS), none had yet been approved to treat VMS. A number of women are either not candidates for hormone therapy (HT) or choose not to use it. Many of these women seek nonprescription options, most of which are not effective. **Design:** The North American Menopause Society (NAMS) invited 18,475 women on the NAMS consumer email list to link to an online survey regarding the need for nonhormonal prescription therapy for menopausal symptoms. Responses were tabulated. **Results:** 1,569 consumers responded to the survey (8% response rate). Of these, 89% thought there was a need for nonhormonal prescription therapy. Of those answering additional questions, 88% reported they had hot flashes, with 34% reporting severe hot flashes. Of responders to the question asking why they thought there was a need for nonhormonal treatments (checking all that apply), 29% indicated they had experienced an adverse event, 37% indicated they had contraindications to hormone therapy, and 85% indicated that they were afraid of hormone therapy or felt it was unsafe. The majority of consumers had tried nonhormonal, nonprescription alternatives, including lifestyle changes (71%) and over-the-counter products (51%). Approximately 40% had used hormone therapy, 12% had tried compounded hormone therapy, 11% had tried off-label nonhormonal prescription therapies, and 12% had not tried anything. A total of 886 comments were received from respondents. **Conclusion:** The majority of the consumers who completed the survey expressed a need for nonhormonal prescription therapy for menopausal symptoms. Many had tried HT and a sizeable proportion reported side effects and contraindications, findings that may explain why they chose to complete this survey.

P-46.

Validity of self-reported vitamin D deficiency among mid-life women living in Qatar

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Objective: In Qatar, as in many Persian Gulf countries, women are at increased risk for vitamin D deficiency due to lifestyle, genetics, obesity and diet. This study evaluates the level of agreement between self-reported vitamin D deficiency and serum vitamin D level measured within a year of the self-report. **Design:** This is a cross-sectional study of 550 women aged 40-60 drawn from a general population in Qatar. Face-to-face interviews included demographic and reproductive questions as well as questions about whether women suffered from any of a list of medical conditions, including vitamin D deficiency. Documented vitamin D levels were retrieved from electronic records. The agreement between self-reported vitamin D deficiency and measured vitamin D levels were evaluated by the kappa statistic. **Results:** Mean serum 25 (OH) D was 19.7 (SD=9.1) ng/ml. The prevalence of vitamin D < 20 ng/ml was 53.3% while the prevalence of self-reported deficiency was 84.5%. Agreement of self-reported vitamin D deficiency with levels < 20 ng/ml was very low (kappa=0.025, 95% CI=-0.038-0.088). Agreement was poor for women aged 40-49 (kappa=-0.003, 95% CI=-0.094-0.088) and for women 50-60 (kappa=0.045, 95% CI=-0.042-0.132) and for women by menopausal status (all kappas <0.105). **Conclusion:** These findings indicate that most women participating in the study believe they are vitamin D deficient. Even among women having levels > 20 ng/ml, 83.3% believe they are vitamin D deficient, while 14.3% who were below <20 ng/ml did not self-report deficiency. Agreement was virtually unchanged using a cutpoint of <30 ng/ml. The results suggest that, in a country with a high prevalence of vitamin D deficiency, many women assume their level to be low, either because they do not know their vitamin D had been measured or they were not informed of their test results. The results suggest that better communication is needed between healthcare providers and patients regarding transmission of results.

P-47.

Are women ready to use a device to reduce or alleviate menopausal symptoms?

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Objective: The aim of this study was to determine if menopausal women were willing to use a device to address vaginal dryness and/or painful intercourse symptoms. **Design:** All women were directed to an on-line survey, testing six hypotheses. They were directed to a website or surveymonkey.com. All surveys were anonymous and voluntary. To date, 142 women have completed the survey. **Results:** Of the 142 women that have completed the survey to date, the average age of the respondents is 55 years old. (Two outliers, age 78, and age 28). Results of the survey: Hypothesis 1: A predominance of women nearing menopause suffer from the effects of vaginal dryness: 83% answered yes Hypothesis 2: A predominance of women nearing menopause suffer from painful sex: 65% answered yes Hypothesis 3: A predominance of woman want to improve their sex life satisfaction: 96% answered yes Hypothesis 4: A predominance of woman have concerns about side effects from estrogen use: 83% answered yes Hypothesis 5: A predominance of woman will vaginally insert a device to help with vaginal dryness: 74% answered yes Hypothesis 6: A predominance of woman will share their success stories using a vaginal device: 89% answered yes **Conclusion:** An opportunity to provide a new solution for woman suffering from vaginal dryness and/or painful intercourse seems plausible.

P-48.

Novel regimen of Hormone Replacement Therapy: Efficacy and Safety of Transdermal Estrogen plus Intermittent Progesterone

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Objective: Hormone replacement therapy (HRT) is widely used for the successful relief of moderate to severe menopausal symptoms. Traditional oral regimens of HRT are associated with decreased rates of osteoporosis, yet increased rates of vascular thrombosis. However, transdermal therapies are associated with lower risk of VTE and stroke in observational studies. Hormone effects on the breast are complicated, with different progestational agents seeming to demonstrate differing risks on the breast. It has been postulated that the medroxyprogesterone acetate component of HRT may be responsible for the increased risk of breast cancer seen in the combination arm of the WHI. With this information in mind, we proposed an optimal HRT regimen that would confer the vascular benefits of transdermal therapy, continue treatment of vasomotor symptoms, promote bone health, and have a safety profile ideal for both the breast and endometrium. Our proposed therapy consists of low dose transdermal estrogen combined with intermittent progesterone. The purpose of the study is to assess patient satisfaction with symptom control, bleeding profile, endometrial safety, and breast effects. Our goal is to ultimately expand the safety profile of hormone replacement therapy for symptomatic menopausal women. **Design:** This is a retrospective observational study. Following institutional Research Ethics Board approval, we reviewed health records of 172 post-menopausal women in a specialized menopause clinic within our tertiary health care centre. All women were using transdermal 17-B estradiol 37.5 or 25 microgram patches twice a week, and intermittent progesterone 100mg orally 4-5 times per week. We analyzed clinical data, including demographic information, significant medical or family history, age at menopause, duration of HRT use and patient satisfaction. We also reviewed available mammogram results, and transvaginal ultrasounds. **Results:** We have identified and reviewed medical records of 172 patients, each using HRT consisting of 17-B estradiol 25 or 37.5 microgram patches and progesterone 100mg capsules 4-5 times orally per week. All patients had relief of postmenopausal vasomotor symptoms. Follow up transvaginal ultrasound was done for 54.65% of patients (97/172) at least 1 year after using our low dose therapy. The average endometrial thickness was 3.81± 2.08mm. 79.4% (77/97) of patients had endometrium measuring less than 5mm in thickness. Only 5.81% (10/172) of patients had vaginal bleeding or breakthrough bleeding; all had normal endometrial biopsies. Ninety six patients (55.8%) completed a mammogram; all reports were normal. **Conclusion:** Using 17-B estradiol 25 or 37.5 microgram patches twice weekly with prometrium 100 mg capsules 4-5 days per week is effective treatment for relief of postmenopausal vasomotor symptoms. It appears to maintain endometrial and breast safety.

P-49.

Influence of menopause and stages of menopause on objective and subjective sleep parameters in an epidemiologic study in Sao Paulo

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Objective: to investigate the influence of menopausal status on sleep patterns in a representative sample of women in the city of Sao Paulo, Brazil **Design:** A population based survey adopting a probabilistic three-stage cluster sample of the City of Sao Paulo was used to represent the local population according to gender, age (20-80 years), and socio-economic status. All participants answered a sleep questionnaire, underwent polysomnographic recording (PSG) and had hormonal measures taken. They also filled out a gynecological questionnaire in order to be classified as premenopause, early postmenopause (less than 5 years of postmenopause), late postmenopause (more than 5 years of postmenopause). **Results:** A total of 1042 volunteers underwent PSG, of which 575 were women: 383 were in premenopause, 48 were in early postmenopause (less than 5 years post menopause) 133 were in late postmenopause (more than 5 years of menopause). We excluded 11 who were in menopause transition, 25 who were under hormone therapy/isoflavone. Our main findings were that despite higher daytime

somnolence as measured by ratings in the Epworth scale, women in premenopause had higher sleep efficiency and REM sleep than the group of women after the menopause. The former group had higher total sleep time and arousal index, apnea-hypopnea index (AHI), and periodic leg movements longer, and longer REM sleep latency. Women in early postmenopause had higher percentage of stage 3 while women in late postmenopause had higher AHI, periodic leg movements and arousal index. **Conclusion:** Menopause per se and stages of menopause status exert a marked influence on objective parameters of sleep.

P-50.

Mid-life Women's Health Education in US Obstetrics and Gynecology Residency Programs

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Objective: To assess the perceived clinical competency, educational gaps, and importance of mid-life and menopause-associated women's healthcare issues of Obstetrics and Gynecology residents in the US. **Design:** A survey that included both demographic information and opinions regarding mid-life women's healthcare education was sent to all ACGME-accredited Obstetrics and Gynecology residency programs in the US. SurveyMonkey, the online survey tool, was used to administer the questionnaire. Residents at all levels of training were included in the study. Residents were queried about the number of hours spent in a mid-life clinic or similar clinical setting. They were asked about instruction received, their current and future clinical competency, the importance of residency training in this clinical area, and educational gaps in regards to 35 separate menopause-related topics. **Results:** A total of 161 residents responded to the study. Eighty-seven percent of respondents were female. Residents from all 4 levels of training were represented as were members from all US ACOG districts. Fifty percent of respondents said that their residency program did not have a menopause or mid-life health clinic. Overall, respondents thought that education in menopause-associated topics was important, and most thought that they would be competent to assess and manage most of the 35 clinical topics covered in the survey. However, significant educational gaps were perceived to exist in the following subjects: evaluation and treatment of sleep disturbances, evaluation of cognitive changes, nutrition and supplemental concerns, dental and oral concerns, dermatologic concerns, and risk factors and screening for lung and skin cancer. Furthermore, topics identified by respondents as being covered in didactics but not actually seen very often in a clinical setting included complementary and alternative medicine (CAM) treatments for vasomotor symptoms, and the use of selective estrogen receptor modulators. Finally, approximately 40% of respondents agreed that they needed to supplement their education on their own regarding the use of both behavioral modification and CAM therapies for the treatment of vasomotor symptoms. **Conclusion:** Receiving training in mid-life healthcare issues is important to Obstetrics and Gynecology residents in the US. However, only half of all respondents stated that they have a mid-life or menopause clinic at their training facility. Despite this deficiency, most residents think that by the end of their 4 years of training that they will be competent to treat a wide range of mid-life healthcare issues. Nevertheless, some educational gaps still exist in many US Obstetrics and Gynecology residency programs in regards to several menopause-associated healthcare topics that are of interest to trainees.

P-51.

Hormone Replacement Therapy versus Oral Contraception for Prevention of Osteoporosis in Young Hypoestrogenic Women: a Randomized Controlled Trial

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Objective: Most attention regarding osteoporosis focuses on menopause. However, young women with chronic hypoestrogenism are also at a high risk. This includes women with untreated PCOS, premature menopause, hypothalamic anovulation, chromosomal abnormalities such as Turners Syndrome and chemotherapy after bone marrow transplant. There is no consensus whether oral contraceptives (OC) or hormone replacement therapy (HRT) provide better protection against osteoporosis in these women. The primary objective of our study was to compare the effect of a standard OC with that of a standard HRT preparation on BMD in hypoestrogenic women in the reproductive age range. The secondary objective was to compare changes in the bone markers osteocalcin and beta crosslap. **Design:** This was a prospective randomized controlled trial involving 100 women aged 16-45 years with chronic hypoestrogenism due to various medical problems. Subjects were randomized to either Microgynon 30 ED OC (ethinylestradiol 0.03mg, levonorgestrel 0.15 mg daily for 21 days with 7 days lactose tablet) or Femoston (oestradiol 2mg daily for 14 days, oestradiol 2 mg daily plus dydrogesterone 10mg daily for 14 days) for 12-24 months. There were no significant differences in baseline measurements between the two groups. Placebo was not used for ethical reasons. BMD was measured at baseline and at 12 (and in a subgroup at 24 months) using a Hologic Discovery A densitometer. **Results:** An increase in BMD with HRT compared with OC at both 12 and 24 months was found in all sites measured in both the femur and lumbar spine. At 24 months the differences were greater than at 12 months, and the differences in BMD between the two treatment groups at 24 months were statistically significant in all areas of the lumbar spine and at the neck of femur and total BMD of the hip ($p < 0.05$, $p < 0.01$). There were no significant differences in measurements of bone markers between the two groups (0 and 12 months). **Conclusion:** We have previously shown an

improvement in BMD with the OC compared with HRT over a 12 month study period. We have now extended the study to 24 months in a selected subgroup of women. The results are even more in favour of HRT at 24 months than at 12 months. To our knowledge, this is the first study to directly compare the effect of OC with that of oral HRT on BMD changes in young hypoestrogenic women. These data strongly suggest that this group of women respond better in terms of BMD change to treatment with HRT than with OC. At this preliminary stage we don't wish to speculate on the reasons for the differences, but both the type of exogenous steroids used and the dosing schedule may prove to be important. These results have the potential to change common prescribing practice for young hypoestrogenic women whatever the underlying pathology and potentially impact future treatment in countless numbers of women who fit the inclusion criteria of this study.

P-52.

Developing evidence based guidelines for gynaecological care and menopausal symptoms after stem cell transplant

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Objective: Women undergoing stem cell transplant [SCT] for the treatment of haematological malignancies will have numerous gynaecological care requirements both before and following transplantation. Considerations prior to treatment may range from: pre transplant screening, menstrual suppression, pregnancy prevention and fertility preservation. Following transplant concerns may include; management of induced menopause, genital tract graft versus host disease, risk management of secondary cancers, bone health and sexuality. There are currently no evidence based guidelines to manage gynaecological care for this growing population. **Design:** Systematic review of the literature on gynaecological care and menopause after stem cell transplant. **Results:** Menstrual suppression is advised prior to conditioning chemotherapy to reduce the risk of vaginal haemorrhage associated with thrombocytopenia. Conditioning chemotherapy prior to SCT will induce permanent ovarian failure in around 90% of premenopausal women but diagnosis of menopause may be difficult as ovulation may resume many years later. Younger women require advice regarding contraception. Venous thromboembolic events are common in these women and the safety of HRT following VTE associated with haematological malignancies is unknown. Bone density is commonly reduced and fracture risk increased 10 fold. Following autologous SCT women are at risk of genital graft vs host disease which may induce vaginal stenosis if untreated. Risks of secondary cancers includes breast (5 fold following mantle radiation), endometrial and cervical cancer. There is no international consensus on screening intervals for secondary malignancies in these women. **Conclusion:** Increasing number of women are surviving haematological malignancies and quality of life issues for survivors must be considered. Treatment will commonly induce ovarian failure. Gynaecological care following stem cell transplant should take a multidisciplinary approach. An evidence-based protocol for management will be presented

P-53.

Nature and severity of menopausal symptoms and impact on quality of life and sexual function in cancer survivors compared to women without a cancer history

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Objective: Following cancer treatment, troublesome menopausal symptoms are common but poorly understood. Using standardized instruments, we measured differences in symptom nature, severity, impact on quality of life and sexual function between cancer survivors and non-cancer participants. **Design:** The Menopausal Symptoms after Cancer (MSAC) Clinic operates within the general menopause service in a large women's hospital, providing menopause advice and management to women with menopausal symptoms and a history of cancer. Menopausal symptoms were recorded using Greene Climacteric Scale, past-week symptoms with Functional Assessment of Cancer Therapy - Breast and Endocrine Symptom Subscales, and sexual symptoms using Fallowfield's Sexual Activity Questionnaire. **Results:** Cancer survivors (N=934) and non-cancer participants (N=155) did not significantly differ by age at menopause (46 years) or age at first clinic visit (51 years). Cancer survivors were more likely than non-cancer participants to be severely troubled by vasomotor symptoms (hot flushes and night sweats, OR 1.71 95% CI 1.06-2.74), and reported more frequent (6.0 vs. 3.1 in 24 hours, $p < 0.001$) and more severe ($p = 0.008$) hot flushes. In contrast, cancer survivors were significantly less troubled by psychological and somatic symptoms and reported better quality of life than noncancer participants. Groups did not differ significantly in physical or functional wellbeing, gynecologic symptom severity, or sexual function. **Conclusion:** Cancer survivors are more troubled by vasomotor symptoms than noncancer participants, but non-cancer participants report greater psychological symptoms. Sexual function did not differ. Improved understanding of the nature and impact of menopause in cancer survivors can be used to direct patient management protocols.

P-54.

Sexuality after breast cancer: Comparison of silicon-based versus water-based lubricants to address vaginal dryness during sexual activity

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Objective: Changes to sexual wellbeing affect around 85% of women after breast cancer. The most troublesome aspect of sexual dysfunction after breast cancer is vaginal dryness. Symptoms may continue for many years and lead to significant adverse physical and emotional outcomes. Vaginal oestrogens are effective but may be absorbed systemically and are now commonly avoided after breast cancer. Non-hormonal lubricants are available but no previous studies have measured the efficacy and acceptability of these products after breast cancer or in other groups of women, so there is little evidence-based information to guide women or health care practitioners about which non-hormonal products to use. **Design:** Double blind cross-over design to compare the efficacy and acceptability of lubricants in sexually active women with symptomatic vaginal dryness after breast cancer. The silicone-based product, PJURTM (PJUR Wasserbillig, Luxembourg), and water-based product, AstroglideTM (BioFilm Inc., Vista, California), were compared since they have the largest market share for each type of product in the international market. All subjects (target N=40) used both products, one at a time, in random order. Efficacy, acceptability, sexual function, wellbeing and quality of life were measured using validated self-administered questionnaires. Participants completed a daily sexual activity diary and the Female Assessment of Sexual Function (FACT-B), Female Sexual Function Index (FSFI), Female Sexual Distress Score (FSDS), Fallowfield Sexual Activity Questionnaire (FACT-ES), Female Intervention Efficacy Index (FIES) and the Hospital Anxiety and Distress Score (HADS). Participants were also asked to evaluate the acceptability of each treatment. Participants also completed a sexual activity diary. Changes in continuous variables were assessed using repeat-measures ANOVA and multivariate linear regression modelling. **Results:** To date, 102 women have been screened and of those, 40 were ineligible. Of these women, 21/40 were partnered but ineligible because they were no longer sexually active due to pain from vaginal dryness. Most reported distress about this. Preliminary results from the FACT-B and FACT-ES indicate that vaginal dryness, pain and discomfort with intercourse, loss of interest in sex, hot flushes and night sweats are significantly increased in the study population (>1 SD below the mean). Preliminary data from FSDS indicate >3 fold higher levels of sexual distress in this population (clinically significant score = 11, median score in study population = 34), suggesting that sexual distress is high in this population. Further data will be presented. **Conclusion:** Symptomatic vaginal dryness is common after breast cancer. It may lead to a cessation of sexual activity and distress in the women and potentially in their partners. High levels of sexual distress are reported. We will present preliminary findings from the first study to compare non-hormonal lubricants in this population

P-55.

Safety of Gastroretentive Gabapentin (G-GR) in the Treatment of Menopausal Hot Flashes: Results of Combined Phase 3 Program

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Objective: To assess safety of gastroretentive gabapentin (G-GR) given in 2 dosages: 1200 mg daily (PM) and 1800 mg daily (600 mg AM, 1200 mg PM) compared with placebo for treatment of postmenopausal women with moderate-to-severe hot flashes **Design:** Three large, randomized, double-blind, placebo-controlled, multi-center studies of 12 or 24 weeks duration. The safety population included all randomized patients who took any study medication. Safety was assessed at Week 12 and Week 24 of treatment period. **Results:** A total of 1,686 patients were treated in the three G-GR studies (placebo, 655 patients; G-GR 1200 mg, 360 patients; G-GR 1800 mg, 671 patients). The majority of AEs reported were of mild or moderate intensity; <10% of AEs were severe. Dizziness and somnolence were the most common AEs, and both occurred more frequently in the G-GR groups than in the placebo group. Prevalence of these AEs was highest during the titration week (Week 1; dizziness, 14.2%; somnolence, 8.2%), and then declined rapidly, reaching sustained low levels (4% and 2%, respectively) within 5 to 6 weeks. Serious adverse events (SAEs) were reported in 13 (2.0%) placebo patients, 4 (1.1%) G-GR 1200 mg patients, and 12 (1.8%) G-GR 1800 mg patients. SAEs rates were similar between the placebo and G-GR treatment groups, except for cardiovascular SAEs (placebo, 6; G-GR, 0) and neoplasm SAEs (placebo, 0; G-GR, 5—2 in the 1200 mg group and 3 in the 1800 mg group). Of the neoplasms, 3 were diagnosed in the first 2 months of treatment, 1 was diagnosed in Month 3, and the other was diagnosed in Month 5. Given the short duration of G-GR exposure in these patients, and 4 different organs involved, these neoplasms were likely preexisting and unrelated to study drug. Two patients died during the Phase 3 program, 1 in the placebo group and one in the G-GR 1800 mg group. The placebo patient died of a hemorrhagic stroke. The G-GR patient, a 49 year-old female, died due to accidental fentanyl overdose on Study Day 43. The patient had a history of schizophrenia and bipolar disorder that were not disclosed at study entry. Toxicology results obtained at autopsy suggested opioid abuse: In addition to fentanyl, there were also detectable levels of methadone and hydrocodone. The coroner concluded that the cause of death was an accidental fentanyl overdose. Study discontinuation due to AEs were more common in the G-GR groups than in the placebo group—7.6% in the placebo group, 11.6% in the G-GR 1200 mg, and 13.2% in the G-GR 1800 mg group. The majority of discontinuations were due to nervous system disorders and were most likely to

discontinue during the titration week (Table 1). **Conclusion:** The results of this integrated safety analysis of three Phase 3 studies demonstrate that G-GR is safe for the treatment of moderate-to-severe hot flashes due to menopause.

Table 1: Adverse Events (AEs) Leading to Study Drug Discontinuations, Pooled Phase 3 Data

n (%)	Placebo (n=655)	G-GR 1200 mg (n=360)	G-GR 1800 mg (n=671)
Total	50 (7.6)	43 (11.6)	89 (13.2)
Dizziness	2 (0.3)	10 (2.8)	18 (2.7)
Somnolence	4 (0.6)	7 (1.9)	13 (1.9)
Headache	3 (0.5)	0	6 (0.9)
Nausea	1 (0.2)	0	6 (0.9)
Sedation	0	2 (0.6)	3 (0.4)
Lethargy	0	1 (0.3)	3 (0.4)
Disorientation	0	1 (0.3)	3 (0.4)
Myalgia	0	0	3 (0.4)
Vertigo	0	2 (0.6)	3 (0.4)

P-56.

Successfully removed focal adenomyosis by robot-assisted laparoscopic adenomyomectomy

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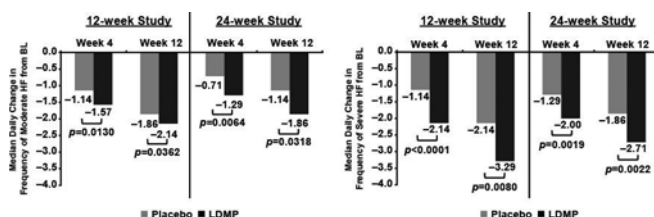
Objective: to evaluate the effects of robot-assisted laparoscopic adenomyomectomy as a minimally invasive and conservative surgical treatment option to preserve fertility for patients with focal adenomyosis and severe dysmenorrhea unresponsive to medical treatment **Design:** Retrospective analysis of 3 cases of robot-assisted laparoscopic adenomyomectomy for three patients (ages 29-37 yrs) with focal adenomyosis with severe dysmenorrhea unresponsive to NSAIDs or GnRH agonists. **Results:** Each woman had 5cm, 2cm, 4cm sized adenomyoma on posterior uterine body, respectively. These adenomyomas were removed using scissors and tenaculum forceps. All the patients were recovered without complication, and discharged within 3 days after operation. Postoperatively, symptoms of all three patients were completely resolved. **Conclusion:** For reproductive age patients suffering dysmenorrhea due to focal adenomyosis unresponsive to medical treatment but wishing future childbearing, robot-assisted laparoscopic adenomyomectomy should be considered as a treatment modality.

P-57.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Reduced Daily Frequency of Moderate Vasomotor Symptoms (VMS) and Severe VMS Due to Menopause

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Objective: LDMP 7.5 mg is an investigational low-dose, nonhormonal medication specifically developed for the treatment of VMS due to menopause. In 2 multicenter, double-blind, randomized, placebo-controlled trials, LDMP treatment reduced the frequency and severity of moderate to severe VMS and had a favorable tolerability profile. The degree to which LDMP treatment reduced the daily frequency of moderate hot flashes (HF) and severe HF was evaluated. **Design:** Postmenopausal women aged ≥40 years with moderate to severe VMS (>7-8 HF/day or 50-60 HF/week) due to menopause recorded number and severity of HFs in daily diaries during a single-blind, 12-day, placebo run-in period. Compliant patients who met eligibility criteria entered the double-blind treatment period and were randomly assigned 1:1 to receive LDMP 7.5 mg or placebo once daily for 12 or 24 weeks. In addition to the 4 co-primary efficacy endpoints (mean changes from baseline [BL] in frequency and severity of moderate to severe HF at Weeks 4 and 12), median daily changes from BL in the frequency of moderate HF and severe HF during Weeks 4 and 12 were evaluated. **Results:** Efficacy populations comprised 606 subjects in the 12-week study (LDMP, 301; placebo, 305) and 568 in the 24-week study (LDMP, 284; placebo, 284). Compared with placebo, LDMP significantly reduced the median daily frequency of moderate HF and severe HF during Weeks 4 and 12 in each study (Figure). Notably, the magnitude of HF reduction observed with LDMP was greater in women with severe HF than in those with moderate HF (range, 36% to 55% in the 2 studies). **Conclusion:** Compared with placebo, LDMP significantly reduced the daily frequency of moderate HF and severe HF. Further, patients with severe HF had a greater magnitude of benefit than those with moderate HF, suggesting LDMP may represent a potential nonhormonal treatment option for symptomatic women with VMS who have both moderate and severe HF.



P-58.

The influence on cardiovascular mortality of the metabolic syndrome in Korean postmenopausal women

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Objective: Metabolic syndrome components, insulin resistance and central obesity cause type 2 diabetes and hypertension. This will increase the risk of cardiovascular disease. In women after menopause are at increased risk of metabolic syndrome. Several researchers studied that in menopause, metabolic syndrome increased cardiac mortality. We studied the impact on cardiovascular mortality of postmenopausal women with metabolic syndrome in the Republic of Korea. **Design:** Twenty four thousand and forty postmenopausal women aged 40 years or older were enrolled at health promotion centers of national university hospital located in 18 regions during 1994–2004. Age, weights, height, body mass index(BMI), systolic blood pressure(SBP), diastolic blood pressure(DBP), fasting blood glucose(FBG), cholesterol, triglyceride(TG), high-density lipoprotein were evaluated and history taking about alcohol consumption, smoking and exercise was performed. In addition, subjects who died of cardiac disease were analyzed from January 1995 to December 2009. **Results:** Metabolic syndrome was higher in postmenopausal women with increased in age, BMI, blood pressure(BP), FBG, cholesterol, TG. Thirty cardiac deaths occurred during the observation period. Factors affecting cardiac death were age, smoking, FBG and when age and smoking were controlled. FBG was an important factor affecting cardiovascular mortality in our study. When controlling age, smoking, and alcohol consumption, metabolic syndrome caused an increased relative risk of cardiovascular mortality. Survival rate was much lower in postmenopausal women with metabolic syndrome than those without metabolic syndrome. **Conclusion:** Metabolic syndrome in Korean postmenopausal women increase cardiovascular mortality

P-59.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Reduced Daily Frequency and Severity of Vasomotor Symptoms (VMS) Due to Menopause

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Objective: Although hormone therapy is effective for VMS due to menopause, alternative treatments are needed. LDMP 7.5 mg is an investigational, once-daily, nonhormonal medicine specifically developed to treat moderate to severe VMS due to menopause. Two multicenter, double-blind, randomized, placebo-controlled Phase 3 trials demonstrated that LDMP reduced the mean weekly frequency and severity of VMS and had a favorable tolerability profile. Herein, the effect of LDMP on daily HF frequency and severity is reported. **Design:** After a single-blind, 12-day placebo run-in period, postmenopausal women ≥ 40 yrs old with moderate to severe VMS (>7 –8 hot flashes [HF]/day; 50–60/week) who were compliant with treatment were randomized 1:1 to receive LDMP 7.5 mg or placebo once daily for 12 (Study 1) or 24 weeks (Study 2). Patients recorded the number and severity of HFs in daily diaries. Median daily changes from baseline in frequency and severity of HFs were assessed. Placebo-adjusted change from baseline in HF frequency was calculated by subtracting the placebo value from the LDMP value at each time point. Severity scores were determined using a weighted calculation: $[3 \times F_s + 2 \times F_m] / [F_s + F_m]$, where F_s and F_m were the frequencies of severe and moderate HF, respectively. Missing data were not imputed. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, and clinical laboratory tests. **Results:** Modified intent-to-treat efficacy populations comprised 606 patients in the 12-week study (Study 1: LDMP, 301; placebo, 305) and 568 patients in the 24-week study (Study 2: LDMP, 284; placebo, 284). In Study 1, reductions from baseline in median daily HF frequency were significantly greater for LDMP compared with placebo at Weeks 4 ($p < 0.0001$) and 12 ($p = 0.0090$) (Table). The placebo-adjusted reduction in HF frequency was 1.2 at Week 4 and 0.9 at Week 12. Reductions from baseline in median daily HF severity were significantly greater for LDMP compared with placebo at Week 4 ($p = 0.0017$) but not at Week 12 ($p = 0.1658$). In Study 2, both HF frequency and severity were significantly reduced from baseline with LDMP compared with placebo at Weeks 4, 12, and 24 ($p \leq 0.0368$ for all comparisons). The placebo-adjusted reduction in HF frequency was 1.3 at Week 4, 1.7 at Week 12, and 1.3 at Week 24. Overall, 50.3% of LDMP-treated and 46.7% of placebo-treated patients experienced ≥ 1 TEAE; most TEAEs were mild or moderate in severity. Serious AEs were experienced by 2.4% and 1.4% of patients, respectively. TEAEs reported in $\geq 2\%$ of LDMP-treated patients and with ≥ 2 -fold higher frequency than in the placebo group were nausea (LDMP, 3.8%; placebo, 1.4%), fatigue (3.4%; 1.5%), and dizziness (2.0%; 0.8%). No clinically meaningful changes in laboratory values or vital signs were observed in either treatment group.

Conclusion: Results from these two Phase 3 studies provided substantial evidence of the efficacy and tolerability of LDMP for the treatment of moderate to severe VMS due to menopause. LDMP may be a potential nonhormonal option for women seeking treatment for menopausal VMS.

	Study 1 (12-Week Study)			Study 2 (24-Week Study)		
	LDMP	Placebo	p Value	LDMP	Placebo	p Value
Median Daily Change in Hot Flashes	(n=301)	(n=305)		(n=284)	(n=284)	
Frequency						
Baseline	10.43	10.43		9.86	9.57	
Week 4	-4.29	-3.14	< 0.0001	-3.79	-2.50	< 0.0001
Week 12	-5.93	-5.00	0.0090	-5.57	-3.86	0.0001
Week 24	—	—	—	-5.86	-4.57	0.0021
Severity						
Baseline	2.54	2.54		2.54	2.52	
Week 4	-0.05	0.00	0.0017	-0.04	-0.01	0.0368
Week 12	-0.06	-0.02	0.1658	-0.05	0.00	0.0064
Week 24	—	—	—	-0.09	-0.02	0.0320

P-60.

Decreased Bone Mineral density in Patients With Invasive Cervical Cancer

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Objective: In women, osteoporosis is a common chronic disease that induces spinal compression and femoral neck fractures, resulting in life-threatening complications. It is very important to identify risk factors in order to prevent this disorder. Bone destruction is a well-recognized complication in a variety of neoplasms without bone metastasis. Therefore, in the present study, we investigated the spinal bone mineral density (BMD) in patients with cervical cancer without bone metastases. **Design:** We measured spinal bone mineral densities by dual-photon absorptiometry in 119 patients with invasive uterine cervical cancer and compared them with measurements from 135 control women. **Results:** When adjusted for age and menopause duration, mean bone mineral density in patients with uterine cervical cancer was 13.9% lower ($p = .0003$) and age-matched percentiles were 9.2% lower ($p = .0003$) than in control women. The deficits in bone mineral density and age-matched percentiles were confined to the uterine cervical cancer patients in their fifties, ie, less than 5 years' menopause duration. **Conclusion:** Our study results suggest that patients with invasive cervical cancer have a lower BMD, resulting in an increased risk of osteoporosis.

P-61.

The Clinical Utility of Novel Genomic-Based, Gene Expression Test in a Registry Study of Women Evaluated for Symptoms Suggestive of Obstructive Coronary Artery Disease in the Ambulatory Care Setting

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Objective: Better methods for the appropriate evaluation of obstructive coronary artery disease (CAD) in women presenting to primary care physician (PCP) offices in the United States are needed, given the frequency of atypical symptoms on presentation as well as the decreased diagnostic accuracy of cardiac imaging due to breast tissue and soft tissue attenuation. The WOMEN trial, a study of optimal diagnostic strategies in women with symptoms suggestive of obstructive CAD, found that gastroesophageal reflux disease was found to be the root cause of symptoms in 40% of patients. In addition, in an evaluation of perfusion imaging in women, the American Society of Nuclear Cardiology Task Force identified non-organic causes of chest pain such as anxiety and depression may have a prevalence as high as 60%. The objective of this study was to measure the effect of a personalized, gene expression score (GES) on medical decision making by PCPs in evaluating women with symptoms of CAD. **Design:** The GES is a validated quantitative diagnostic test for non-diabetic patients that measures expression levels of 23 genes from peripheral blood to determine the likelihood of a symptomatic patient having obstructive CAD, as defined by at least one vessel with $> 50\%$ coronary artery stenosis by quantitative coronary angiography or core-lab computed tomography (CT) angiography. The test involves a routine blood draw administered in the clinician's office and does not expose patients to risks of radiation or imaging agent intolerance. The 23 gene expression measurements represent biological pathways involved in adaptive and innate immune responses to atherosclerosis, including neutrophil activation and apoptosis, neutrophil to lymphocyte ratio, NK cell activation, and B to T cell ratio. The changes in gene expression are quantified using an algorithm that is gender and age specific, which generates a score ranging from 1 – 40. The GES has a negative predictive value of 96% among low GES (≤ 15) patients. Between April 2012 to January 2013, a total of 172 stable female patients presenting with symptoms suggestive of obstructive CAD at 6 community-based PCP practices were enrolled in the Registry I study (NCT#01557855), and had a peripheral blood sample drawn, which was sent to a central reference lab and reported results to the clinician within 3 days. The primary outcome in this pre-specified, subgroup analysis was the association between GES results and referrals to noninvasive and invasive cardiac testing among women patients. **Results:** Of the 172 evaluable women in our study, the

median age was 56 years, the mean (SD) GES was 10 (± 8), and 78% of patients had low GES. Patients presented with typical and atypical symptoms (95%) or were asymptomatic with >3 risk factors (3%) or asymptomatic with <3 risk factors for CAD (2%). After adjusting for age, type of chest pain, and practice site, each 10-point decrease in the GES was associated with a significantly lower likelihood of referral to further cardiac testing (adjusted odds ratio for 10-point decrease in GES = 0.08, $p < 0.001$). Additionally, the observed rate of referrals in low GES patients was 64% lower than the referral rate seen in elevated score patients (6% in low GES vs 70% in elevated GES patients, $p < 0.001$). At 30 days of follow-up, no major adverse cardiac events were noted. **Conclusion:** The use of this novel, personalized gene expression test in medical decision making by primary care clinicians demonstrated a significant reduction in cardiac referrals for further diagnostic evaluation among low GES women. The test showed clinical utility as a rule-out test for excluding an underlying cardiac etiology of presenting symptoms suggestive of obstructive CAD and thus allows clinicians to pursue a non-cardiac cause of patients' symptoms. Because of these findings, the test may help address an important diagnostic challenge in the care of mid-life women.

P-62.

Depressive Symptoms in Perimenopausal Women with and without HIV
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Objective: Depression is more common among HIV-infected women than in those without HIV, and HIV-infected women are more likely to have elevated depressive symptoms during the perimenopause than during the premenopause. Hot flashes have been strongly linked with depressive symptoms. We have previously shown that perimenopausal HIV-infected women report greater hot flash severity and hot flash-related interference compared to perimenopausal women without HIV. Limited data are available regarding hot flash burden and depressive symptoms in perimenopausal women with HIV. The objective of the current study was to examine depressive symptoms and clinical correlates in perimenopausal HIV-infected women. We hypothesized that HIV-infected women would report more depressive symptoms compared to non-HIV-infected women, and that hot flash severity would associate with depressive symptoms. **Design:** Perimenopausal HIV-infected and non-HIV-infected women matched by age, race, and menstrual patterns were recruited as part of a longitudinal study examining metabolic, psychological and vasomotor symptoms. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), a cut off of >16 suggesting a depressive disorder. Hot flash severity was measured with the Menopause Rating Scale (MRS)-item one. Cross-sectional CES-D scores from baseline were compared between HIV-infected and non-HIV-infected women, and a multivariate linear regression model was created adjusting for HIV status and characteristics that differed between groups (i.e., hot flash severity, hot flash frequency, smoking status, recent substance use). **Results:** Among 66 women (33 HIV+, 33 HIV-), the HIV-infected women had higher CES-D scores (median 21, interquartile range [IQR] 12-29 vs. median 10, IQR 5-14, $P = 0.0006$). HIV-infected women were also more likely to have a CES-D score >16 (67% vs. 21%, $P = 0.0002$). However, a prior history of a depression diagnosis (76% vs. 64%), past treatment of depression (67% vs. 61%), and current antidepressant use (33% vs. 18%) did not differ between groups ($P > 0.05$ for all comparisons). The HIV-infected women experienced greater hot flash severity ($P = 0.03$) and were more likely to be current smokers ($P = 0.03$), and report use of illicit substances in the past 6 months ($P = 0.005$). In a multivariate analysis, hot flash severity ($P = 0.035$), HIV infection ($P = 0.049$), and smoking ($P = 0.034$) were each significantly associated with depressive symptoms ($R^2 = 0.38$). The HIV+ and HIV- groups were similar in age (median 47), race (58% non-Caucasian), and menstrual patterns (# of periods in past year, median 5.5). No associations were observed between duration of HIV, HIV viral load, or CD4 cell count and depressive symptoms. **Conclusion:** HIV-infected women report higher levels of depressive symptoms compared to non-HIV-infected women during the perimenopause, despite having a similar history of prior depression. Elevated depressive symptoms were associated with hot flash severity, HIV status, and smoking. Our findings support the need for clinicians to assess for depressive symptoms among perimenopausal HIV-infected women.

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Expression of adhesion molecules in the endometrium of women with polycystic ovary syndrome (PCOS) treated with progesterone

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Objective: Literature data indicate that the observed decrease fertility in women with polycystic ovary syndrome (PCOS) is not only attributed to anovulation, but also to endometrial dysfunction or failures of implantation. Objective: to assess the histomorphometry and immunoeexpression of the adhesion molecules $\alpha\beta 3$ integrin, MECA-79, E-cadherin and intercellular adhesion molecule 1 (ICAM-1) in the endometrium of fertile and infertile women with PCOS treated with progesterone. **Design:** Endometrial biopsies were performed in the proliferative and secretory phases of women with normal cycle (Control group, n=34) and in women with PCOS (n=36), before and after orally treatment with micronized progesterone (200 mg, per day) for 10 consecutive

days, and then, a second endometrial biopsy was performed. In the control group, biopsies were performed in the 10th and the 23th days (implantation window). **Results:** After the administration of progesterone, the endometrium of the women with PCOS exhibited a lower number of glands and thicker luminal epithelium compared to the control group in the secretory phase ($p < 0.01$). In addition, the PCOS group exhibited reduced immunoeexpression of $\alpha\beta 3$ integrin and MECA-79 compared to the control group during the secretory phase ($p < 0.01$). The expression of E-cadherin was higher in the PCOS group after treatment with progesterone ($p < 0.05$) and the expression of ICAM-1 was lower in PCOS group when compared with the control group during the proliferative phase ($p < 0.05$). **Conclusion:** Conventional doses of micronized progesterone did not correct the modifications of histomorphometric parameters and the immunoeexpression of receptive markers in the endometrium of women with PCOS.

P-64.

Prevalence of Menopausal Symptoms among Women Treated in Clinical Practice: Discordance of identification between Electronic Medical Records and Administrative Claims Data

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Objective: Few studies have used data from electronic medical records (EMR) to describe the healthcare experience of menopausal women prescribed hormonal therapy (HT). This is particularly true in terms of describing the types of menopausal symptoms experienced by this patient population, with many studies relying on data collected from surveys. EMR data may be a more robust data source for identifying menopausal symptoms compared to administrative claims data, since the latter source is limited by the availability of symptom-relevant ICD-9-CM diagnosis codes. Our study uses data from an EMR review of menopausal symptoms from women treated with HT in an integrated delivery network.

Design: A random sample of female patients was generated using data from the Reliant Medical Group, located in Worcester, Massachusetts, USA. Using an EMR database, patient-level data from the random sample were reviewed by clinical professionals until approximately 100 patients were identified who met the following study eligibility criteria: females 45 to 65 years of age; prescribed an oral or transdermal HT during the period January 1, 2006 – December 31, 2011; no history of breast cancer, venous thromboembolism, stroke, gynecological cancer, or hysterectomy; continuously eligible in the health plan for a ≥ 12 month period before and after the first observed HT prescription (this two year window constituted the "study period"). EMR data from the eligible sample were reviewed in order to assess menopause-related symptoms experienced during the study period. Menopausal symptoms included: mood disorders, major depression, anxiety, insomnia, vaginal dryness, menstrual irregularities, fatigue, vasomotor symptoms (i.e., hot flashes and night sweats), loss of sexual desire, weight gain, and hair loss. All symptoms were analyzed descriptively at both the visit and patient level, and were required to be menopause-related, defined as having menopause referenced in the physician notes of the EMR as the cause of the symptom. Provider specialty for each visit was also identified. An exploratory analysis was conducted to determine the concordance of menopausal symptom identification between EMR encounters and administrative claims data for the same patient sample and 2-year study period. Analysis was conducted at the visit level, requiring that ICD-9-CM codes for menopausal symptoms appear in the claims data within one week of the EMR encounter date to establish a match. **Results:** A total of 102 patients meeting inclusion criteria were included in the analysis. The majority of patients were between the ages of 50 – 54 years (41%), with a mean (SD) age of 54 (5). At the patient level, the most common menopausal symptoms identified during the study period were hot flashes (40%), followed by general menstrual irregularities (31%), night sweats (17%), insomnia (16%), and vaginal dryness (13%). Among the 102 patients, 163 individual visits listing menopausal symptoms were identified during the study period. Similar to the patient-level analysis, hot flashes were the most common symptom identified during visits (71 visits), followed by general menstrual irregularities (46 visits). The majority of visits with menopausal symptoms identified were provided by OB/GYN physicians (46%), followed by internal medicine physicians (36%), family practitioners (10%), and other specialties (8%). Exploratory analysis showed that only 49% of visits identifying a menopausal symptom using EMR data during the study period had a matching ICD-9-CM code in administrative claims data. **Conclusion:** Results from this analysis provide recent data on the type of menopausal symptoms experienced among mid-life women prescribed HT. Given that many menopausal symptoms do not appear to be regularly coded in administrative claims data, the EMR is an important data source for future studies for this patient population.

P-65.

Evaluating health and demographic characteristics of women presenting for care at the UCSD Menopause Health Program

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Objective: To determine the unique characteristics (demographics, menopausal symptoms and menopausal status) of women presenting for care at the UCSD Menopause Health Program and to describe patient needs evaluation. **Design:** Prospective, longitudinal, ongoing study of patients presenting for care at the UC San Diego Menopause Health Program beginning in year 2008. Prior to or upon arrival, patients completed a multi-part questionnaire assessing basic demographics, menopausal stage, symptomatology (vasomotor, mood, sexual function), preventative care and screening needs (mammography, pap), and health behaviors (diet, alcohol use, exercise). **Results:** Data

from the most recent 76 women have been analyzed. The mean age of women presenting for care was 54.6 yrs (+/- 7.9 yrs) with average age at LMP 48.3 yrs (+/- 5.2 yrs). 42% of subjects were <1 yr since LMP and 57.3% were postmenopausal. Symptom management needs varied by menopausal status. Compared to postmenopausal women, perimenopausal women were more likely to report irritability (65.6% vs. 28.6%, $p=.001$), depression (53.1% vs. 21.4%, $p=0.005$) and irregular bleeding (40.6% vs. 14.6%, $p=.012$). Depressive symptoms that were or tended to be more commonly reported in perimenopausal women include crying (32.4% peri vs. 12% post, $p=0.038$) and impaired concentration (48.4% peri vs. 26.8% post, $p=.059$). For symptoms of sexual dysfunction, compared to perimenopausal women, postmenopausal women were more likely to report vaginal dryness (66.7% vs. 25.0%, $p=.001$) and anorgasmia (20.5% vs. 3.6%, $p=.045$). Analyses of additional patients and additional available data is currently ongoing. **Conclusion:** Incorporating a structured questionnaire into the patient intake process can help ensure women's needs are understood and met by the health care team. Incorporating preventative, screening, and health behaviors assessment will help optimize the health of women at midlife.

P-66.

Development of a Multi-Dimensional Midlife Women's Program

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Objective: To describe the rationale, development and results of an innovative educational and wellness program specifically for women in midlife. **Design:** This pilot program was designed to meet the needs of women in midlife (40-65) residing within the Central Ohio area and female employees of a four hospital system. An extensive literature review was conducted and two models were selected to provide the theoretical framework for this project. The first model was the 7 Dimensions of Wellness which encompasses the domains of Physical, Intellectual, Emotional, Social, Spiritual, Environmental and Financial Well-Being. The second model was the Health Belief Model, a tool to predict general health behaviors of perceived susceptibility, severity, benefits, barriers and elements which may impact change in behavior, leading to action and promotion of self-efficacy. The program lead/primary developer met with physicians who incorporate holistic approaches into their care of midlife women and encouraged their input into the design. She also met with key stakeholders within the hospital system, held focus groups and conducted a survey through questionnaires that were distributed to clinical staff to identify suggestions for specific content. Guest program faculty and locally recognized experts in the field of women's health and wellness were identified and invited to participate in the development of the program based on their area of expertise. Initial funding for this program was provided by a grant from the hospital foundation; therefore, very few classes initially included a fee for participation. In its first quarter of program delivery (Fall 2012), 22 classes met criteria for one or more of the 7 Dimensions. During Winter 2013, the number of classes increased to 30. Concurrent curricular development focused on key issues and concerns of midlife women including: "Finding Your Path in the Second Half of Life", "Women in Midlife: Yoga and the Menopausal Years" and "Menopause: Our Current Understanding". Program satisfaction evaluations were administered for the various classes and workshops; participants were asked to identify areas of perceived need and interests. Additionally, participants completed a comprehensive survey detailing specific areas of women's health. The survey collected data from the targeted geographic population about their primary health and well-being at midlife. Anecdotal feedback shared and gathered from program speakers and participants served as an additional source of qualitative evaluative data. **Results:** Following an introductory event on "Empowering Ourselves as Women", which was attended by 103 women, 79 individuals participated in the Fall 2012 offerings. Program evaluations demonstrated high levels of satisfaction and some participants attended more than one offering. During Winter 2013, participation increased to 192 individuals with a few participants again attending more than one offering. In an effort to become a self-sufficient program, a nominal charge was included for a number of offerings. The fee did not represent a deterrent for participation in the program. In the last quarterly session of the pilot year, levels of satisfaction with the program continued to be very positive. Favorable recognition and reputation of the program as a leader in women's wellness has grown within the Central Ohio area, particularly among the targeted populations, wellness practitioners and clinicians within the health system. A consistent comment from both program faculty and participants is that the program is meeting an unmet need within the community and is addressing the complexity of issues experienced by midlife women. As the program grows, opportunities for formal study and evaluation, ideally with some longitudinal elements to assess sustained behavior change, will occur. **Conclusion:** The Women's Midlife Program has become a very successful program in a short amount of time. It has become self-sufficient and continues to grow in attendance by women in midlife. This is a model program that can easily be replicated or tailored to specific populations. The program is cost-effective, can sustain itself through a reasonable fee structure and potentially offer expansion to any adult, regardless of age or sex, as a wellness program that proactively addresses mind, body and spirit well-being.

P-67.

A study of postmenopausal women being treated for vaginal atrophy with local estrogen therapy

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Objective: To assess the effect that a local estrogen therapy applicator has on patient satisfaction and compliance with treatment. **Design:** 10,394 postmenopausal women from an online panel were contacted to participate in a quantitative online web-based study and 5,089 women accepted to participate. Inclusion criteria: US postmenopausal women

for at least one year or with a double-oophorectomy; currently being treated for 1 to 6 months for vaginal atrophy with estradiol vaginal tablets applied through a disposable applicator or with vaginal cream applied through a reusable applicator. Women employed by a health care provider (HCP), or who had a household member employed as a HCP, were excluded. Eligible participants completed 39 questions regarding vaginal symptoms, storage of vaginal medication, application time, time spent during the application, choice of position, device disposal, concerns on over-/under-dosing, and overall perception of the device. Descriptive statistics were derived for the study population and the significance of the variables was assessed with a confidence interval of 95%. **Results:** 100 cream users and 100 tablet users who met all the selection criteria and completed the survey were randomly selected and their answers were analysed. For the total users, 90 % of the women were Caucasian, 63% were 61-65 years old, mean duration of vaginal therapy use 3.48 months, 75% were married and 67% sexually active. Nearly all respondents experienced vaginal dryness since menopause and the most common symptoms reported were dyspareunia, nocturia, itchiness and urgency, 55% of users stored their vaginal medication in the bathroom and 30% in their personal bedrooms. Overall, 71% of women applied their medication at bedtime and 18% in the early morning. Cream users needed, on average, more than twice the time reported by tablet users to apply their vaginal medication (5.08 minutes and 2.48 minutes respectively). For the product administration, most of the respondents preferred to be standing with a foot raised on edge of tub or toilet or sitting on edge of toilet and dispose the applicators in the trash. Sexually active women applied their medication one day before intercourse (39%) and 37% indicated no interference of the application on intercourse. 96% of cream users reported cleaning the re-usable device after insertion and the majority use a regular soap. When washing the re-usable applicator to clear out some residual cream from the device, 61% used some kind of tool (Q-tip) and 79% indicated that a disposable device would be beneficial. 44% of women who were not using a disposable applicator indicated interest in obtaining a disposable applicator rather than washing and reusing the device. 18 % of cream users and 9% of tablet users applied their medication using their fingers. 42% of cream users used a larger amount of the dose to make it work better and faster while 60% used a lower dose to avoid messiness and leakage. Regarding privacy and discreetness of the application, participants rated the disposable device as "excellent" compared with cream users (68% and 11% respectively). Overall, a strong majority of tablet users (69%) reported to be extremely satisfied with the disposable device compared with cream users (14%). **Conclusion:** These findings should alert HCPs on women's experiences with different therapeutic formulations since all local estrogen therapies are comparable in efficacy but overall patient satisfaction may determine accurate dosing and adherence to treatment.

P-68.

HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD) IN CLIMACTERIC AFRO-DESCENDANT WOMEN

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Objective: To establish the prevalence of severe deterioration of the quality of life and sexual dysfunction in climacteric afro-descendant women with hypoactive sexual desire disorder **Design:** 861 afro-descendant women, natural and resident in municipalities of the Atlantic and Pacific coast of Colombia, were assessed by pollsters in their communities with Menopause Rating Scale (MRS) and Female Sexual Function Index (FSFI). They were women between 40 and 59 years of age and belong to the Calidad de Vida en la Menopausia y Etnias Colombianas (CAVIMEC) project. Hypoactive sexual desire disorder is defined as a score < 5 in the total sum of the 1 and 2 items of the FSFI. This research is a part of the CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas) research program. Universidad de Cartagena. Cartagena, Colombia **Results:** The average age of all population was 48.4 ± 5.5 years of age. 34.8% had hypoactive sexual desire disorder. Women with HSDD had higher presence of all menopause-related symptoms ($p<0.001$) except hot flushes ($p=0.54$). In the same way, they presented higher deterioration of the somatic, physiological, and urogenital domain and of the quality of life than women without HSDD ($p<0.001$). The prevalence of sexual dysfunction and of the deterioration of the domains and items assessed with the FSFI was higher in women with hypoactive sexual desire disorder ($p<0.001$). Of all women with HSDD, 20% presented severe deterioration of the quality of life and 96% presented sexual dysfunction. Whereas between women without HSDD, 3.6% had severe deterioration of the quality of life and 36.7% had sexual dysfunction, statistically significant differences. **Conclusion:** Afro-descendant women with HSDD have significantly worse quality of life and greater prevalence of sexual dysfunction than women without HSDD.

P-69.

SEXUAL FUNCTION AND QUALITY OF LIFE ASSESSMENT IN MIDDLE-AGED COLOMBIAN WOMEN WITH THE FEMALE SEXUAL FUNCTION INDEX AND CERVANTES SCALE*

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Objective: To assess sexual function and menopause-related quality of life in middle-aged women and to determine predictors related to socio-demographic factors and to the health status. **Design:** This research is a part of the CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas) research program. Universidad de Cartagena. Cartagena, Colombia. Cross-sectional study in which 1264 sexually active middle-aged

Colombian women filled out the 19-item version of the Female Sexual Function Index (FSFI), the 31-item Cervantes Scale (CS), and a questionnaire about socio-demographic data. A correlation between the items of the two scales and socio-demographic data was established. **Results:** Median [interquartile range] age was 47 [9] years, median of parity was 3 [2], and median of educational years was 11 [8]. 52.9% of women increased body mass index (BMI), 26.3% were in perimenopause and 35.4% were in postmenopause, 69.8% were mestizo and 30.2% were black, 6.6% were using hormone therapy, and 5.1% were currently smokers. Internal consistency (Cronbach's alpha) was high for all tools: total FSFI (0.983) and total CS (0.896). 54.7% of women obtained total FSFI scores ≤ 26.55 , which suggests sexual dysfunction. FSFI total scores were inversely correlated with total (rho = -0.137), somatic (rho = -0.354) and psychological (rho = -0.380) Cervantes Scale scores ($P < 0.001$). Collinear CS sub-domains (sexuality and partner relationships) were not included in the analysis. Multiple linear regression was used to obtain a reduced best-fit model predicting total FSFI scores (sexual function) which were positively correlated (better sexual function) to female education and parity, and inversely correlated to age, years since the menopause and both, somatic and psychological CS scores. **Conclusion:** When assessing the FSFI, the sexual function of this middle-aged sample of Colombian women was correlated with the educational level of the women, their lifestyle, and the health factors.

P-70.

PREVALENCE OF INSOMNIA, SEXUAL DYSFUNCTION AND SEVERE DETERIORATION OF THE QUALITY OF LIFE IN CLIMACTERIC WOMEN WITH ANXIETY

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Objective: To compare the prevalence of insomnia, sexual dysfunction and severe deterioration of the quality of life in Colombian climacteric women according to the presence of anxiety. **Design:** Cross sectional study carried out with Menopause Rating Scale (MRS), Athens Insomnia Scale (AIS) and Index of Female Sexual Function in abbreviated version (FSFI-6) in 945 climacteric Colombian women. They were divided in two groups according to the answer to item number six (anxiety) of the MRS. The scales and a questionnaire of socio-demographic data were applied by pollster in the same communities. Women between 40-59 years of age were included, they participated in a voluntary way. A total score of the FSFI < 26.56 is suggestive of female sexual dysfunction. A total sum > 5 in AIS indicates the presence of insomnia. More than 16 points in MRS is considered severe deterioration of the quality of life. This research is a part of the CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas) research program. Universidad de Cartagena. Cartagena. Colombia. **Results:** 550 (58.2%) women answered negatively the item number 6 (absence of anxiety). 395 (41.8%) expressed to have anxiety. Of the above mentioned, 43.8% were in postmenopause, the average of age was 49.4 ± 5.6 years of age, the average of BMI was 25.9 ± 4.1 and the average of years of study was 9.6 ± 4.7 . The prevalence of insomnia in women with anxiety was 42.0% whereas in women without anxiety it was 17.8% ($p < 0.0001$). The prevalence of sexual dysfunction in women with anxiety was 47.8% and in women without anxiety was 35.4% ($p < 0.0001$). Just like that, 26.3% of women with anxiety had higher severe deterioration of the quality of life than 1.6% of women without anxiety ($p < 0.0001$). There were significant differences in all items of the three scales just like in the somatic, psychological and urogenital domains of the MRS. In the adjusted logistic regression, there was observed: OR: 3.00 (CI95%: 2.21-4.07) for insomnia and OR: 2.07 (1.43-2.98) for sexual dysfunction. **Conclusion:** In a group of climacteric Colombian women those who presented anxiety had higher prevalence of insomnia, sexual dysfunction and severe deterioration of the quality of life when they were compared with anxious women.

P-71.

COFFEE CONSUMPTION IN COLOMBIAN WOMEN IS ASSOCIATED TO LOWER SEVERITY OF CLIMACTERIC SYMPTOMS

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Objective: To establish if there are differences in the presentation of climacteric symptoms in a group of Colombian women according to the consumption of coffee. **Design:** Cross sectional study that belongs to the research project Calidad de Vida en la Menopausia y Etnias Colombianas (CAVIMEC), which involves indigenous, afro-descendant and mestizo Colombian women from different areas of Colombia- It was carried out with Menopause Rating Scale (MRS), in Spanish version, already validated in this idiom. It was applied in an anonymous and voluntary way in the communities of residence with visit door to door. Coffee consumption was self-reported in number of cups a day. This research is a part of the CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas) research program. Universidad de Cartagena. Cartagena. Colombia **Results:** 3535 women were included and divided in two groups: 1010 women were not taking coffee and 2525 were taking coffee (1926 women were taking from 1 to 3 cups, 446 women from 4 to 6 cups and 153 women 7 or more cups). In both groups, the average age was 48.3 ± 5.5 years of age, the average age of menopause was 46.7 ± 3.0 years and the average number of years since menopause was 3.1 ± 5.7 years. There were differences between both groups regarding to BMI, ethnic group, use of hormonal therapy and smoking habit. With logistic regression when adjusting these factors, there was obtained an OR 0.22 (CI:0.11-0.42 $p < 0.000$) for total severe deterioration of the quality of life in women who consume 7 or more cups of coffee a day, and in the somatic domain OR 0.3 (CI:0.12-0.75 $p < 0.01$), psychological domain OR 0.21 (CI:0.10 - 0.42 $p < 0.001$) and

urogenital domain OR 0.18 (CI: 0.1-0.32 $p < 0.001$). **Conclusion:** Colombian women with moderate to strong consumption of coffee showed lower deterioration of the total quality of life and of the somatic, physiological and urogenital domains. There are required other studies to establish a possible beneficial effect of the consumption of coffee in the severity of the climacteric symptoms and its relationship with other effects on health

P-72.

URINARY INCONTINENCE, MENOPAUSE SYMPTOMS AND RELATED FACTORS IN MIDDLE-AGED WOMEN ASSESSED WITH MENOPAUSE RATING SCALE (MRS) AND THE INTERNATIONAL CONSULTATION ON INCONTINENCE QUESTIONNAIRE SHORT FORM (ICIQ-SF)

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Objective: Urinary problems are frequently found around menopause, in part caused by estrogens secretion. The present report aimed to analyze the data base from a middle-aged Colombian woman cohort focusing on urinary incontinence, menopausal symptoms and socio-demographic variables **Design:** Cross-sectional study in which 605 middle-aged Colombian women filled out the MRS, the ICIQ-SF and a questionnaire about socio-demographic data. A correlation between the items of the two scales and socio-demographic data was established. This research is a part of the CAVIMEC (Calidad de Vida en la Menopausia y Etnias Colombianas) research program. Universidad de Cartagena. Colombia. **Results:** Median [interquartile range] age was 47 [7] years, median parity was 1 [2], median of body mass index (BMI) was 27.3 [6.8] and median of educational years was 11 [1]. 16.4% were in perimenopause and 57.4% were in postmenopause, 12.9% had bilateral oophorectomy and 34.5% had hysterectomy, 30.9% were using menopausal hormone therapy and 1.3% were using urinary incontinence (UI) treatment. The prevalence of UI was 16.5%, 82.3% had an episiotomy, 6.0 % had perineal tears, 4.3% were alcohol users and 0.2% were currently smokers. Episiotomy was done in 82.3% of the women, 6.0% had tears, 16.5% presented UI, 8.8% had hypertension and 2.0% had diabetes. Internal consistency (Cronbach's alpha) was high for total MRS (0.92) and total ICIQ-SF (0.96). Multiple linear regression was used to obtain 2 reduced best-fit model predicting total MRS scores (adjusted $r^2 = 0.131$, $p = 0.05$) (quality of life), and ICIQ-SF (adjusted $r^2 = 0.066$, $p < 0.05$). **Conclusion:** When assessing with the ICIQ-SF, UI of this middle-aged sample was related with parity, menopausal status, hormone therapy and worse quality of life.

P-73.

Prevalence and determinants of risk for low bone mineral density and osteoporosis in a private practice population in Mexico City

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Objective: The risk of low BMD and osteoporosis in Mexico is of growing concern. Women of higher socioeconomic status may be at increased risk for osteoporosis compared to other women because they engage in lower levels of physical labor, are more likely to drive cars for transportation in the city and may be more likely to diet to stay thin. In order to assess the prevalence of risk in a population of women who are, in general, well-educated and of relatively high socioeconomic status, this study draws women from a private practice in Mexico City. **Design:** Demographic, reproductive, lifestyle, and treatment data, along with anthropometric and bone mineral density (BMD) measurements, were collected from the medical records of 511 women, aged 30 to 87 years, who had attended the Clinica de Climatorio Santa Teresa. Spine, hip and femoral neck measurements of BMD was obtained by dual-energy x-ray absorptiometry. According to menopausal status scores that were < -2.50 were classified as osteoporosis, from -2.49 to -1.00 were classified as low bone mineral density. BMD categories were examined by bivariate tests in relation to age, menopausal status, reproductive history (parity, the number of babies a woman breast fed for 4 months or more), lifestyle variables (smoking, level of exercise), health (hot flashes and depressive symptoms), use of hormone therapy and calcium supplementation, and measures of height, weight, arm muscle circumference, and percent body fat (computed by skinfold thickness). Variables significantly associated with BMD categories, and variables regarded as important in the literature, were entered into binary logistic regression models with BMD categories as the dependent variable. Variables that did not contribute to the model were removed. Because of the intercorrelation between body measurements, separate models were constructed to examine the effect of muscle area and body fat on risk of low BMD. **Results:** Participants had a mean age of 59.4 years (s.d. 10.3), a mean parity of 2.6 children (s.d. 1.5), a mean BMI of 25.6 kg/m² (s.d., 4.3), 91 were premenopausal (17.8%) and 420 postmenopausal (82.2%). Frequency of natural menopause was 51.9% with mean recalled age 49.7 years (s.d. 3.8, range 31 to 58 years, n=218). Frequency of surgical menopause was 43.8 % (n=184) with mean recalled age of 43.1 years. According to WHO's criteria for BMD and BMI; 12.32% met the criteria of osteoporosis, 3.17% of those were premenopausal and 96.83% were postmenopausal. Frequencies of low BMD were 54.01%, 13.77 % of those premenopause women and 86.23% postmenopausal. 49.4% of participants had a BMI > 25 kg/m² and 4.89% had BMI < 20 kg/m². In bivariate analyses, increasing age, post-menopausal status, and higher parity were significantly associated with low (≤ -1.0) vertebral, hip, and femoral neck BMD, as were measures of body size and fatness. With regard to spinal BMD, increasing age increased the likelihood of low BMD, while increasing height and, in separate models, muscle mass (OR 0.98, 95% CI 0.97-0.99) and BMI (OR 0.92, 95% CI 0.87-0.96) reduced the likelihood of low BMD at the spine. With regard to BMD at the hip and also at the femoral neck, increasing age increased the

likelihood of low BMD, but type of menopause and height were unrelated to the probability of low BMD. Increasing BMI and increasing muscle mass reduced the likelihood of low BMD at both the hip and at the femoral neck. **Conclusion:** It appears that increasing muscle mass is almost as protective for women at risk for low BMD as increasing BMI. Although level of exercise was not associated with BMD in this study, the results of exercise, i.e., increasing muscle area, do appear to reduce the likelihood of low BMD and exercise should be encouraged.

BMI & BMD

	Low BMI	Normal	Overweight	Obesity
Normal BMD	16%	28%	37%	45%
Low BMD	72%	55%	52%	49%
Osteoporosis	12%	17%	11%	6%

P-74.

Evaluation of Risk Factors for Falls in Early Postmenopausal Women

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Objective: Falls are a common problem observed in elderly women. Falls are associated with a high morbidity and mortality risk and may involve high-cost medical interventions. The risk of falling remains undiagnosed very often until an episode occurs; but if the risk is high, preventative measures could be introduced early. However, few studies approach young populations of postmenopausal women. The purpose of study was to evaluate the rate of falls and its association with clinical parameters in early postmenopausal women.

Design: In this cross-sectional study, 358 Brazilian women (age 45-65 years and amenorrhea ≥ 12 months) were enrolled comparing the outcome of fallers vs. non-fallers. Exclusion criteria were: neurological or musculoskeletal disorders, vestibulopathies, uncorrected visual deficits, uncontrolled hypertension and postural hypotension, or drug use (sedative and hypnotic agents) that could affect balance. A fall was identified as an unexpected position change which is unintentional and makes an individual to remain in a lower level in relation to the initial position. The history of self-reported falls during a period of 24 months as well as clinical, anthropometrics (body mass index, BMI and waist circumference, WC) and densitometric (DXA of lumbar spine and femoral neck) measures were analyzed. For statistical analysis, Chi-Square test and logistic regression method (odds ratio-OR) were calculated. **Results:** Of the 358 women, 48.0% (172/358) had a history of falls. Of these, 17.4% (30/172) had fractures resulting from falls. The fall occurred indoor (at home) in 58.7% (101/172), on the street in 32.6% (56/172) and at work in 8.7% (15/172). The mean age was 53.7 ± 6.5 years with time since menopause of 4.8 ± 3.5 , BMI 28.3 ± 4.6 kg/m² and WC 89.0 ± 11.4 cm. It was observed that 84.1% had a visual deficit with correction (wearing eyeglasses), 39.1% reported hypertension, 35.7% were hormone therapy (HT) users, 34.1% had a bone mineral density ≤ -2.0 SD by DXA, and 28.5% reported regular physical activity; no difference between the groups ($P > 0.05$). There were differences in the percentage distribution as the occurrence of smoking and diabetes, with a greater frequency among fallers vs. non-fallers, 25.6% vs. 16.1% and 12.8% vs. 5.9%, respectively ($P < 0.05$). By evaluating the risk of falls in the presence of influential variables, it was observed that the risk increased with current smoking status (OR 1.93; 95% CI 1.01-3.71) ($P < 0.05$). In contrast, HT use was associated with a significantly reduced risk of falling (OR 0.49; 95% CI 0.26-0.91) ($P < 0.05$). Other clinical, anthropometric and densitometric variables did not significantly influence this risk. **Conclusion:** Early postmenopausal women had a higher frequency of falls. Current smoking was a clinical indicator of risk for falls whereas hormone therapy use was observed to be a protective factor. With the recognition of factors for falling, preventive measures become important, as the orientation of abolishing smoking, in addition the possible beneficial effect of hormone therapy when indicated for early postmenopausal women. *Financial support by FAPESP; process no. 2011/19071-0.

P-75.

Evaluation of clinical and inflammatory markers in nonalcoholic fatty liver disease in postmenopausal women with metabolic syndrome

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Objective: The Nonalcoholic fatty liver disease (NAFLD) is considered the most common cause of chronic liver disease in Western countries. In women, the prevalence increases with age, particularly in post-menopause. NAFLD is independently associated with diabetes, hypertriglyceridemia, low HDL, abdominal obesity and insulin resistance (IR). These features are among the criteria used in the diagnosis of metabolic syndrome (MetS). NAFLD is considered the hepatic manifestation of MetS. The purpose of study was assess clinical and inflammatory markers in non-alcoholic fatty liver disease (NAFLD) in postmenopausal women with metabolic syndrome (MetS). **Design:** In this cross-sectional study, 180 women (age ≥ 45 years and amenorrhea ≥ 12 months) followed the Belo Horizonte Specialty Clinic from January 2011 to August 2012, were included. Exclusion criteria were: liver disease (hepatitis B and C, cholestatic disease, liver insufficiency and tumor); use of drugs that affect the liver metabolism; alcoholics; HIV or cancer history; and morbid obesity. MetS was diagnosed as the presence of at least three components: waist circumference (WC) ≥ 88 cm, triglycerides (TG) ≥ 150 mg/dL, HDL < 50 mg/dL; blood pressure (BP) $\geq 130/85$ mmHg; glucose ≥ 100 mg/dL. NAFLD was diagnosed by abdominal ultrasound. The participants were divided into three groups according to the presence or absence of MetS and/or NAFLD: MetS alone (n=53); MetS+NAFLD (n=67); or without NAFLD or MetS (controls, n=60). Clinic, anthropometric, and biochemical

variables were measured. Inflammatory profile included adiponectin, interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF- α). Statistical analysis employed the ANOVA, Tukey test, Chi-square test, Pearson correlation, and logistic regression (odds ratio, OR).

Results: Women with MetS + NAFLD showed obesity, greater WC, higher glucose and insulin levels, with insulin resistance (IR) when compared to MetS alone and controls ($p < 0.05$). Elevated values of IL-6 and TNF- α were observed as well as decreased adiponectin among women with MetS alone or MetS+NAFLD when compared to controls ($p < 0.05$). In multivariate analysis, the variables considered at risk for the development of NAFLD were: elevated systolic BP (OR 1.02, 95% CI 1.0-1.04); increased ALT (OR 1.03, 95% CI 1.0-1.06); higher WC (OR 1.07, 95% CI 1.01-1.13); insulin (OR 1.12, 95% CI 1.04-1.19); HOMA-IR (OR 3.81, 95% CI 2.01-7.13); and presence of MetS (OR 8.68, 95% CI 3.3-24.1). Adiponectin was considered a protective factor (OR 0.88, 95% CI 0.80-0.96). A significant negative correlation was found between adiponectin with insulin ($r = -0.29$), TG ($r = -0.30$), WC ($r = -0.24$) and HOMA-IR ($r = -0.27$) and positively correlated with HDL ($r = 0.21$) ($p < 0.05$). **Conclusion:** In postmenopausal women, the presence of MetS, abdominal obesity and insulin resistance were markers of risk for the development of Nonalcoholic fatty liver disease, and higher value of adiponectin was marker protection.

P-76.

Effect of Diet and Omega 3 Supplementation on the Metabolic and Inflammatory Markers in Postmenopausal Women with Metabolic Syndrome

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Objective: Abdominal obesity is an important characteristic in the diagnosis of metabolic syndrome (MetS). Inflammatory factors produced by adipose tissue induce insulin resistance (IR). The accumulation of abdominal fat and IR contribute to the onset of MetS. Supplementation of Omega-3 may reduce risk factors such as hypertriglyceridemia, dysglycemia, hypertension and inflammation. However, in postmenopausal women the relationship between MetS and Omega-3 supplementation is still uncertain, there is little information. The purpose of study was to evaluate the effect of diet alone or combined with omega-3 supplementation on metabolic and inflammatory markers in postmenopausal women with MetS. **Design:** In this prospective, open, randomized study, 87 women (age ≥ 45 years and amenorrhea ≥ 12 months) with MetS, seeking health care at a public outpatient center of the Botucatu Medical School-UNESP, from June 2010 to December 2011 were included. According to the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), women showing three or more diagnostic criteria were diagnosed with MetS: waist circumference (WC) ≥ 88 cm, blood pressure $\geq 130/85$ mmHg, triglycerides ≥ 150 mg/dL, HDL < 50 mg/dL and glucose ≥ 100 mg/dL. Exclusion criteria were: cardiovascular disease, insulin-dependent diabetes, cancer, autoimmune diseases and use of statins or hormone therapy. Participants were randomized to diet alone (n = 43, control) or associated with Omega-3 supplementation, 900mg/dia orally (n = 44). All women underwent individualized dietary prescription. Clinic, anthropometric (body mass index, BMI and waist circumference, WC), biochemical variables were measured. Inflammatory profile included C-reactive protein (CRP), tumor necrosis factor alpha (TNF- α) and interleukins (IL-1 β and IL-6). The intervention time was six months, with assessments at initial and final moments. Statistical analysis employed Student's t-test, ANOVA and Tukey test. **Results:** In the comparison of baseline clinical characteristics between the groups (diet alone or diet + Omega-3) no significant differences were observed, with aged 55.0 ± 7.3 vs 55.1 ± 6.6 years; duration of menopause 7.0 ± 4.9 vs 7.2 ± 4.4 years; and BMI 32.0 ± 4.6 vs 32.8 ± 4.7 kg/m², respectively ($p > 0.05$). Of the 87 women, 30 with diet alone and 33 with diet + Omega-3 completed the study. At the end, there were a significant reduction in BMI and WC in two groups ($p < 0.05$) without significant changes in body fat or muscle mass. Intervention with diet + Omega-3 was associated with significant reduction in systolic pressure (-12.2%) and diastolic (-8.2%), triglycerides (-21.4%), insulin (-11.6%) and insulin resistance (-13.1%) ($p < 0.05$). And on the inflammatory markers were observed significant reduction in the IL-6 (-28.5%) ($p = 0.034$). **Conclusion:** In postmenopausal women with MetS, dietary intervention associated with supplementation of Omega-3 had beneficial effects on metabolic risk factors (blood pressure, triglycerides, and insulin resistance), important components of MetS, and with the benefit of the inflammatory status in postmenopausal women. *Financial support by FAPESP; process no. 2009/14884-2.

P-77.

Evaluation of clinical and immune-inflammatory markers in subclinical carotid atherosclerosis in postmenopausal women

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Objective: The presence of atherosclerosis is a determinant factor in the development of coronary heart disease (CHD). The increased carotid intima-media thickness (IMT), assessed by vascular high-resolution ultrasound, is considered a marker of atherosclerotic disease, especially for premature CHD. Individual differences in the immune-inflammatory profile may modulate the severity of the atherosclerosis process. Cumulative evidence suggests that the immunological component of the atherosclerosis development may, at least in part, involve the expression of heat shock proteins (HSP). Clinical studies correlating HSP60 and HSP70 and atherosclerosis are controversial. The purpose of study was to evaluate clinical and immune-inflammatory markers in subclinical carotid atherosclerosis (ATS) in Brazilian postmenopausal women. **Design:** In this cross-sectional study, 268 women (age ≥ 45 years and amenorrhea ≥ 12 months) followed healthcare at a

public outpatient center in southeastern Brazil, from February 2011 to June 2012, were included. The exclusion criteria were history of coronary heart disease (CHD), cerebrovascular arterial disease, chronic kidney disease, liver disease, infection, chronic inflammatory disease, autoimmune diseases and cancer. Subclinical ATS was defined as either increased carotid intima-media thickness (IMT>1.0mm) and/or the presence of plaques, evaluated by carotid duplex ultrasound. Clinical, anthropometrical and biochemical evaluations were performed. The immune-inflammatory profile included the measurement of C-reactive protein (CRP), heat shock proteins (HSP) 60 and 70 as well as their antibodies, interleukins (IL) 1- β , 6 and 10, and tumor necrosis factor- α (TNF- α). As for the statistical analysis, it was used the Student's t test, Kruskal-Wallis, Chi-square, Pearson's correlation, and logistical regression (odds ratio, OR). **Results:** Of the all included women, 45.9% (123/268) presented ATS diagnosis, and 12.2% (15/123) with carotid plaques. And 54.1% (145/268) of the patients presented normal carotid ultrasound (IMT $\leq$ 1.0mm). Women with ATS were older (56.6 vs. 52.5 years) and had more years since menopause onset (6.0 vs. 4.0 years); with higher incidence of metabolic syndrome (39.0% vs. 25.5%), hypertension (52.0% vs. 30.3%), and diabetes (11.4% vs. 4.8%), and increased values of CRP and HSP60 when compared to those without disease ($p<0.05$). There was a positive correlation between IMT and anti-HSP70 ($r=0.110$, $p=0.049$) and CRP ($r=0.167$, $p=0.009$). ATS risk increased with age of menopause (OR 1.18, CI 95% 1.10-1.26); time since menopause (OR 1.12, CI 95% 1.02-1.14); and glucose (OR 2.17, CI 95% 1.12-4.20). On the other hand, HSP70 (OR 0.71, CI 95% 0.47-0.98) was associated with a lower ATS risk ($p<0.05$). **Conclusion:** In the present study the age, time since menopause, dysglycemia, and CRP and anti-HSP70 values were risk markers for subclinical carotid atherosclerosis development. On the other hand, HSP70 was a protection marker that suggested a premature immune-activation associated to atherosclerosis in postmenopausal women population of low cardiovascular risk.

P-78.

An Estimation of Mortality in Hysterectomized Women Due to Estrogen Avoidance

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Objective: The WHI Trial of estrogen therapy (ET) for women without a uterus has reported an absolute total mortality risk reduction for women age 50 to 59 receiving ET compared to the women who received placebo. However, a precipitous decline in the use of ET has occurred in the past decade following the initial WHI report for estrogen plus progestogen therapy (EPT). Millions of women who would have used ET in the past following hysterectomy are not using it. **Design:** A formula was derived to relate the excess mortality among women age 50 to 59 assigned to the placebo arm in the WHI-ET trial to the entire population of comparable women in the United States, incorporating the decline in estrogen use observed after the WHI-EPT results were published in 2002. Best point estimates were used, as were the extremes-of-reasonable-range values for purposes of sensitivity analysis. **Results:** Over a 10-year span, starting in 2002, a minimum of 18,601, and as many as 91,610 post-menopausal women died prematurely, i.e. before the age of 70, due to the avoidance of estrogen therapy. Best point estimates suggest the mortality toll is between 49,128 to 59,549. **Conclusion:** Our analysis suggests a considerable, and on-going toll of premature mortality among women post-hysterectomy age 50 to 59 since the original WHI data were published and reported in the media due to estrogen avoidance by patients and health care professionals alike. Decline in ET use continues. A conversation between these women and their health care providers about the benefits of using ET could reduce mortality.

P-79.

Examination of Nocturnal Hot Flashes, Sleep, and Interest in Behavioral Treatment in Peri- and Postmenopausal Women

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Objective: Sleep disturbance was identified as a major symptom during the transition to menopause according to a 2005 report from the NIH State-of-the-Science Conference panel on menopause-related symptoms. Approximately 26-56% of peri- and postmenopausal women experience sleep disturbance. The study aim was to test the hypothesis that menopausal women who reported nocturnal hot flashes would report greater insomnia severity and wake after sleep onset (WASO) compared to women who did not report nocturnal hot flashes and to examine interest in behavioral interventions to treat insomnia and nocturnal hot flashes. **Design:** Four hundred forty two women self-described as perimenopausal (35.9%, age range=33-58 years, $m=49.2\pm4.7$) or postmenopausal (64.1%, age range=34-75 years, $m=54.9\pm5.6$) completed an online survey about sleep and menopause, which included report of experiencing nocturnal hot flashes in the past two weeks, completion of Insomnia Severity Index (ISI), information about sleep continuity, and treatment preferences. **Results:** After controlling for treatment with hormones and use of medication for sleep in an ANCOVA, those who reported night sweats/hot flashes in the past 2 weeks reported significantly greater insomnia severity (ISI score; $m=15\pm4$, $p<0.001$) and significantly greater WASO ($m=58\text{ min}\pm46\text{ min}$), and significantly greater interest in cognitive behavioral treatment (CBT) for insomnia and nocturnal hot flashes (74%) versus those who did not report hot flashes in the past 2 weeks (ISI score $m=9\pm4$, $p<0.001$), (WASO $m=30\text{ min}\pm33\text{ min}$, $p<0.001$), and interest in CBT 37%, $p<0.001$). **Conclusion:** This study suggests that women who report nocturnal hot flashes report greater insomnia severity and report greater amount of time awake during the night. The majority of women expressed interest in receiving behavioral

treatment for their insomnia and nocturnal hot flashes and suggests that Cognitive Behavioral Therapy for Insomnia (CBT-I) may be appealing for menopause-associated insomnia, particularly among women with nocturnal hot flashes.

P-80.

Quantitative heel ultrasound as a screening tool for low bone mass in early menopausal women

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Objective: Dual X-ray absorptiometry (DXA) of the axial skeleton remains the gold standard methodology for diagnosis of skeletal fragility. Bone mass assessment by quantitative ultrasound (QUS) of peripheral skeletal sites including phalanges and the calcaneus has shown promise as a relatively simple and cost effective modality for identifying elderly individuals deemed at enhanced fracture risk; predictability of QUS for skeletal fragility in chronologically younger populations is less well studied. We aimed to determine the reliability of bone mass assessment by calcaneal QUS for predicting DXA diagnosed low bone mass (T-score<-1.0) in a subset of early menopausal women who participated in the KEEPS trial of menopausal hormone therapy (Kronos Early Estrogen Prevention Study). **Design:** Prospective study, cross-sectional design based on baseline data from KEEPS. **Results:** Early menopausal women (mean age 53 ± 2.6 , within 3 years of last menstrual period) enrolled in KEEPS at two of the 9 participating centers (Yale, CT and Albert Einstein College of Medicine, NY) ($n=135$) participated in this sub study. Institutional approvals were obtained and participants provided informed consent. All participants underwent BMD assessment by DXA at the lumbar spine (LS), left femoral neck (FN), trochanter (FT) and total body (TB). BMD at the left radius (ultra distal [UD], mid 1/3) and ribs was additionally assessed in 84 subjects enrolled at one of the two sites. BMD T-sc ≤ -2.5 defined osteoporosis. Tertiles were computed for broad band ultrasound attenuation (BUA); BUA distribution across BMD categories by DXA was compared by Kruskal Wallis Rank test and relationship between skeletal site specific BMD (g/cm²) with BUA was assessed by correlation analyses. Multivariable regression analyses assessed relationship between BUA and BMD after adjusting for age, body mass, race and race. **Results:** In early menopausal women, prevalence of low BMD was 66% with 10/135 meeting criteria for osteoporosis (7%). Women with low BMD exhibited significantly lower BUA values ($p<0.05$); conversely, BUA demonstrated positive and statistically significant correlations with DXA measured BMD at all skeletal sites ($p<0.001$). BUA was an independent predictor of BMD at all sites after adjusting for age, BMI and race; on adjusted analyses, those with BUA in the lowest tertile were 4 and 5 times more likely to have low BMD at LS and FN respectively. **Conclusion:** In a population of early postmenopausal women, calcaneal QUS was predictive of low BMD. Our data suggest that QUS may have a role as a screening tool for identifying early menopausal women who may be an increased risk for fragility fractures due to low BMD. Larger studies with long term follow up are needed to confirm this suggested relationship.

BMD	LS	FN	FT	UD Radius	1/3 Radius	Rib	Total Body
BUA	$r=0.47$, $p<0.001$	$r=0.43$, $p<0.001$	$r=0.37$, $p<0.001$	$r=0.44$, $p<0.001$	$r=0.28$, $p=0.036$	$r=0.56$, $p<0.001$	$r=0.45$, $p<0.001$

BMD: Bone mineral density by DXA

BUA: Broadband ultrasound attenuation

LS: Lumbar spine

FN: Femoral neck

FT: Femoral trochanter

UD: Ultradistal

P-81.

Pharmacokinetics of the First Combination 17 β -Estradiol/Progesterone Capsule in Clinical Development for Hormone Therapy

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Objective: Evaluate the bioavailability of the first combination 17 β -estradiol/progesterone capsule in clinical development in the U.S. versus Estrace[®] and Prometrium[®] co-administered separately. **Design:** A single-dose, randomized, 3-period, reference-replicated, crossover study compared the bioavailability of an investigational 2-mg 17 β -estradiol/200-mg progesterone combination capsule, without peanut oil, with that of co-administered 200-mg Prometrium (progesterone) and 2-mg Estrace (17 β -estradiol) tablets in healthy postmenopausal women aged 40-65 yrs ($N=66$). After consuming a high-fat, high-calorie breakfast, each woman received a single dose of the combination (Test) capsule in 1 period of the study and single doses of the co-administered products (Reference) in each of the 2 remaining periods. Plasma was collected pre-dose and at specified intervals over 48h after dosing to determine progesterone, free (unconjugated) estradiol, and free and total (conjugated+free) estrone concentrations. The primary (C_{max} , AUC_{0-48} , and $AUC_{0-\infty}$) and secondary (t_{max} , $t_{1/2}$, and K_e) PK parameters for each analyte were determined for each subject during each period by non-compartmental analyses using baseline-adjusted concentrations. Statistical analyses were conducted using the Scaled Average Bioequivalence (BE) method for highly variable drugs to determine whether the combination Test capsule had progesterone and estradiol bioavailability similar to that of the co-administered Reference products. This method is applicable when the within-subject coefficient of variation (CV) for the reference product is $\geq 30\%$. For any PK parameter with CV<30%, the BE method based on 90% CI must be used. **Results:**

All AUC and C_{max} parameters met BE criteria for all analytes, except C_{max} for total estrone (Table 1). The extent of estradiol and progesterone absorption for the Test capsule appeared to be similar to that for the Estrace and Prometrium tablets, respectively (Table 1), while the rate of estradiol absorption for the Test capsule appeared to be faster than that for Estrace, respectively (Table 2). The bioequivalent outcomes for progesterone should allow the Test capsule to bridge to the safety data for Prometrium. A bridge to the safety data for the Estrace tablet should also be viewed as having been established because the only parameter for which the Test capsule failed to meet BE criteria was the C_{max} for just 1 estradiol-related analyte (total estrone). The extent of estradiol absorption, reflecting the total amount of estradiol delivered by the Test capsule, is the most critical safety measure. **Conclusion:** The combination 17 β -estradiol/progesterone capsule demonstrated similar bioavailability of its constituents to their individual respective references of Estrace and Prometrium, when given together under fed conditions. This new capsule could represent an interesting development in hormone therapy, as no approved hormone therapy to date has been able to 1) combine natural progesterone with 17 β -estradiol as an oral formulation, and 2) provide progesterone without peanut oil, a known allergen. The efficacy and safety of this new capsule combining 17 β -estradiol with progesterone will be evaluated in phase 3 clinical trials.

Table 1. Scaled Average Bioequivalence Analyses for Each Analyte

Analyte/Parameter	Test-to-Ref Ratio	CV%	95% Upper Confidence Bound	Meets BE Criteria
Progesterone AUC(0-4) AUC(0-inf) C_{max}	1.05 0.94 1.16	122.2 116.4 173.7	-0.5422 -0.4941 -0.7850	Yes Yes Yes
Unconjugated estradiol AUC(0-4) AUC(0-inf) C_{max}	0.93 0.83 0.88	42.6 47.4 35.4	-0.0888 -0.0625 -0.0399	Yes Yes Yes
Analyte/Parameter	Test-to-Ref Ratio	CV%	90% Confidence Interval	Meets BE Criteria
Unconjugated estrone AUC(0-4) AUC(0-inf) C_{max}	0.89 0.88 0.93	18.0 26.3 23.3	0.848-0.938 0.834-0.933 0.873-0.991	Yes Yes Yes
Total estrone AUC(0-4) AUC(0-inf) C_{max}	1.06 1.06 1.75	29.7 29.7 35.9	0.982-1.115 0.985-1.114 0.3438*	Yes Yes No

*95% Upper Confidence Bound

Table 2. T_{max} for Each Analyte

Analyte	Test	Reference 1	Reference 2
Progesterone	3.00 (0.83-10.0)	3.00 (1.00-12.0)	4.00 (0.67-18.0)
Unconjugated estradiol	9.00 (0.50-36.0)	10.0 (0.50-35.1)	10.0 (0.25-36.6)
Unconjugated estrone*	5.50 (0.83-36.0)	8.00 (1.67-18.0)	10.0 (1.67-18.0)

*Uncorrected

P-82.

Bazedoxifene/Conjugated Estrogens in Minority Populations: Pooled Analysis of Phase 3 Trials

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Objective: The tissue selective estrogen complex that pairs bazedoxifene (BZA) with conjugated estrogens (CE) treats menopausal symptoms and prevents postmenopausal osteoporosis. Because hormones such as CE may affect minorities differently, this analysis compared results in minority (defined as black, Hispanic, or Asian; <1% "other" not characterized) and white populations of women given daily BZA 20 mg/CE 0.45 or 0.625 mg or PBO using pooled data from 4 phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART) clinical trials. **Design:** The SMART trials were randomized, double-blind, placebo (PBO)- and active-controlled phase 3 studies in nonhysterectomized postmenopausal women. Data were pooled from the 2-year SMART-1 (N=3397), 3-month SMART-2 (N=318), 3-month SMART-3 (N=652), and 1-year SMART-5 (N=1843) trials. Hot flashes were evaluated by daily diary at 1 and 3 months in SMART-1 and SMART-2 in women with ≥ 7 moderate-to-severe hot flashes per day. Quality of life (QOL) was evaluated using the Menopause-specific quality of life (MENQOL) questionnaire in SMART-1 (Mo 3, 12, 24), SMART-2 (Mo 3), SMART-3 (Mo 3), and SMART-5 (Mo 3, 12). Vaginal atrophy was evaluated in SMART-1 (Mo 6, 12, 18, 24) and SMART-3 (Mo 1, 3) by vaginal smear in women with $\leq 5\%$ superficial cells (Mo 3 or 12 data shown, as available); dyspareunia was evaluated in SMART-1 by daily diary over 4-week periods. Bone mineral density (BMD) was evaluated in SMART-1 (Mo 12, 24) and SMART-5 (Mo 12); responders had an increase from baseline ≥ 0 . **Results:** In both modified intent-to-treat populations (white and minority), demographics were generally balanced across treatment groups. In both populations, BZA 20 mg/CE 0.625 mg was associated with greater improvements in hot flash frequency and severity at Month 3 versus PBO (Table; $P < 0.05$ for all; similar trends at Wk 4). Similarly, in both the minority and white populations, BZA 20 mg/CE 0.45 and 0.625 mg were associated with significant improvements from baseline versus PBO in vasomotor function, sexual function, and total MENQOL score at 3 months. These increases were maintained with BZA 20 mg/CE 0.45 mg in vasomotor function and total MENQOL score at 12 and 24 months ($P < 0.05$) in both populations. At 3 months and 2 years in both populations, BZA/CE induced vaginal epithelium maturation with significant changes in parabasal cells with both BZA/CE doses versus PBO for whites only at 3 months and in both

populations at 2 years ($P < 0.05$). At Month 12, the percent of lumbar spine and total hip BMD responders was significantly increased versus PBO for BZA 20 mg/CE 0.45 and 0.625 mg in the white and minority populations; improvements were maintained at Month 24 in SMART-1 for both populations. For all variables, statistical tests for interaction between ethnicity and treatment group were not significant. **Conclusion:** In minorities, BZA/CE had positive effects on hot flashes, vulvar/vaginal atrophy, QOL, and BMD that were similar to the effects observed in whites. Although this analysis involved a small number of minority subjects and was not powered to determine significant differences between racial groups, results indicate that BZA/CE may be an effective menopause therapy across ethnicities. Future studies in a more diverse population are needed.

Table. Mean (SE) Adjusted Changes From Baseline in BZA/CE Efficacy Parameters in Pooled Minority^a and White Populations

Parameter^s	Time	Minority population			White population		
		BZA 20 mg/CE 0.45 mg (n=243)	BZA 20 mg/CE 0.625 mg (n=231)	PBO (n=206)	BZA 20 mg/CE 0.45 mg (n=1314)	BZA 20 mg/CE 0.625 mg (n=1320)	PBO (n=1012)
Number of moderate-to-severe hot flashes	Month 3	-8.16 (0.62)	-9.23 ^b (0.54)	-6.11 (0.91)	-7.80 ^b (0.43)	-8.03 ^b (0.43)	-3.84 (0.54)
Daily severity score of hot flashes	Month 3	-1.00 ^b (0.17)	-1.37 ^b (0.15)	-0.33 (0.24)	-0.91 ^b (0.08)	-1.21 ^b (0.08)	-0.25 (0.09)
MENQOL vasomotor function score	Month 3	-1.67 ^b (0.12)	-2.01 ^b (0.12)	-0.83 (0.12)	-1.74 ^b (0.05)	-2.03 ^b (0.05)	-0.81 (0.05)
MENQOL psychosocial function score	Month 3	-0.66 (0.09)	-0.77 ^b (0.10)	-0.45 (0.10)	-0.50 (0.04)	-0.56 (0.04)	-0.48 (0.04)
MENQOL physical function score	Month 3	-0.71 (0.08)	-0.76 ^b (0.08)	-0.52 (0.08)	-0.66 ^b (0.03)	-0.72 ^b (0.03)	-0.53 (0.03)
MENQOL sexual function score	Month 3	-1.30 ^b (0.11)	-1.18 ^b (0.11)	-0.73 (0.11)	-1.17 ^b (0.05)	-1.19 ^b (0.05)	-0.92 (0.05)
Total MENQOL score	Month 3	-1.11 ^b (0.07)	-1.18 ^b (0.08)	-0.63 (0.07)	-1.02 ^b (0.03)	-1.13 ^b (0.03)	-0.70 (0.03)
Percent change in superficial cells	Month 3 (SMART-3)	4.24 (2.25)	6.48 (2.35)	9.45 (3.53)	5.18 (0.84)	6.17 ^b (0.88)	2.37 (1.23)
	Month 24 (SMART-1)	-2.72 (1.80)	-1.41 ^b (2.17)	-7.15 (2.04)	-1.23 (0.61)	0.05 (0.64)	-0.40 (0.65)
Percent change in parabasal cells	Month 3 (SMART-3)	-17.10 (8.33)	-25.08 (8.49)	-11.43 (12.93)	-21.38 ^b (2.45)	-27.01 ^b (2.55)	-3.63 (3.57)
	Month 24 (SMART-1)	3.67 ^b (5.13)	-7.70 ^b (6.18)	20.18 (5.80)	-5.64 ^b (2.43)	-14.02 ^b (2.53)	5.21 (2.59)
Percent dyspareunia	Weeks 97-100	25.73 (12.25)	27.41 (11.40)	15.02 (9.57)	12.97 (3.76)	10.72 (3.10)	7.99 (3.26)
Number (%) responders in lumbar spine BMD	Month 12	52 ^b (75.36)	45 ^b (71.43)	42 (48.28)	208 ^b (67.10)	212 ^b (64.44)	102 (33.12)
Number (%) responders in total hip BMD	Month 12	49 ^b (70.00)	49 ^b (77.78)	37 (42.53)	209 ^b (67.42)	227 ^b (69.00)	116 (37.79)

^aDefined as black, Hispanic, or Asian.

^b $P < 0.05$ vs PBO.

P-83.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Improved Sleep in Women With Vasomotor Symptoms Due to Menopause

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Objective: Vasomotor symptoms (VMS), comprising hot flashes and night sweats, increase the prevalence of sleep disturbances and night-time awakenings. In 2 randomized, double-blind, placebo-controlled Phase 3 trials, LDMP reduced the mean frequency and severity of VMS due to menopause and had a favorable tolerability profile. The impact of LDMP on sleep was evaluated in a pooled analysis to increase statistical power. **Design:** Postmenopausal women aged ≥ 40 y with moderate to severe VMS ($> 7-8/d$ or $50-60/wk$) received once-daily placebo and recorded number and severity of VMS and nighttime awakenings due to VMS in daily diaries during a 12-day, single-blind, run-in period. Women who met eligibility criteria entered the double-blind treatment period and were randomized 1:1 to receive LDMP 7.5 mg or placebo once daily at bedtime for 12 or 24 wks. Co-primary efficacy endpoints were mean changes from baseline (BL) in frequency and severity of VMS at Wks 4 and 12. Prespecified sleep endpoints and components included mean change from BL in number of night-time awakenings due to VMS (primary endpoint for present analysis); mean duration of sleep; mean time to fall asleep; patient-reported sleep interference (item on the Hot Flash-Related Daily Interference Scale); difficulty sleeping (Greene Climacteric Scale subscore); and sleep-related adverse events (AEs). Rank ANCOVA was used to compare the difference between LDMP and placebo in the change from BL, with BL as the covariate. **Results:** mITT efficacy and safety populations comprised 1174 (LDMP, 585; placebo, 589) and 1175 (LDMP, 586; placebo, 589) women, respectively. Number of night-time awakenings due to VMS was reduced from BL more with LDMP than with placebo at Wks 4, 12, and 24 (Table; all $p < 0.005$). Duration of sleep increased more with LDMP than with placebo, approaching normal range. However, this difference was not explained by a reduction in time to fall asleep, which was similar in both groups. Sleep interference scores improved from BL in both groups, but a significant difference was found only at Wk 4. Proportions of women with moderate to severe difficulty sleeping decreased from BL in both groups. No differences in sedation or other sleep-related AEs were observed between treatment groups. **Conclusion:** Use of LDMP 7.5 mg/d for treatment of VMS reduced the number of night-time awakenings due to VMS and increased the duration of sleep, without increasing

sedation, reducing time to sleep onset, or increasing sleep-related AEs. These data demonstrate that LDMP improved sleep problems in postmenopausal women with VMS and suggest that this improvement was not related to increased sedation.

Sleep Endpoint	LDMP, n=585	Placebo, n=589	p Value
BL and mean daily change from BL in night-time awakenings due to VMS			
BL	3.56	3.64	—
Week 4*	-1.39	-1.01	0.0049
Week 12**	-1.91	-1.56	0.0001
Week 24**†	-2.22	-1.54	<0.0001
BL and mean change from BL in duration of sleep, minutes			
BL	375.35	385.70	—
Week 4*	+30.85	+16.44	0.0075
Week 12*	+34.52	+23.13	0.0102
Week 24*†	+36.69	+27.16	0.0336
BL and mean change from BL in time to fall asleep, minutes			
BL	51.29	50.47	—
Week 4	-7.17	-7.60	0.3509
Week 12	-11.40	-13.59	0.4875
Week 24†	-14.83	-11.58	0.1966
BL and mean change from BL in sleep interference scores (lower score better)			
BL	7.60	7.66	—
Week 4*	-2.41	-1.50	0.0068
Week 12	-3.17	-2.66	0.0663
Week 24†	-3.84	-2.89	0.2405
Proportion of women with moderate or severe difficulty in sleeping, %			
BL	56.10	57.47	—
Week 4	41.37	45.44	0.1826
Week 12	36.62	40.78	0.1928
Week 24†	34.63	40.63	0.2180

* $p<0.05$; ** $p<0.001$; †24-week study only; n=284 in each group.

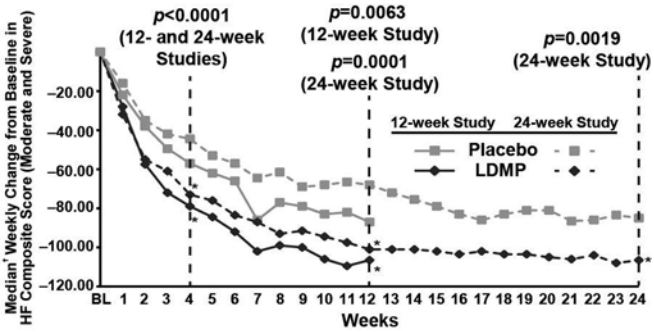
P-84.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Reduced Patient Burden of Menopausal Vasomotor Symptoms

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Objective: Vasomotor symptoms (VMS), including night sweats and hot flashes (HF), affect up to 80% of menopausal women in the United States. LDMP, an investigational, nonhormonal medication, was developed specifically for treatment of VMS due to menopause. In 2 multicenter, double-blind, randomized, placebo-controlled Phase 3 trials of postmenopausal women with moderate to severe VMS, LDMP reduced the frequency and severity of VMS and had a favorable tolerability profile. This analysis evaluated the impact of LDMP on HF composite scores, which assess patient burden of VMS. **Design:** Postmenopausal women aged ≥ 40 years who met eligibility criteria (moderate to severe VMS, $>7-8$ HF/day or $50-60$ HF/week) entered a single-blind, 12-day, run-in period, during which patients received once-daily placebo and recorded number and severity of HF in daily diaries. Compliant patients entered a double-blind treatment period and were randomly assigned 1:1 to receive LDMP 7.5 mg or placebo once daily at bedtime for 12 or 24 weeks. Co-primary efficacy endpoints were mean changes from baseline in frequency and severity of VMS at Weeks 4 and 12. HF composite scores were assessed using the formula $(2 \times F_m + 3 \times F_s)$, where F_m = frequency of moderate HF and F_s = frequency of severe HF during the study week. Treatment arms were compared using analysis of covariance on rank-transformed data with baseline values as covariates.

Results: Modified intent-to-treat efficacy populations comprised 606 patients (LDMP, 301; placebo, 305) and 568 patients (LDMP, 284; placebo, 284) in the 12- and 24-week trials, respectively. Median weekly changes in HF composite score are shown in the figure. In both trials, LDMP significantly reduced HF composite scores at Weeks 4 and 12 compared with placebo. In the 24-week study, significant reductions were maintained in the LDMP group to Week 24. **Conclusion:** LDMP significantly reduced patient burden of VMS and may be a beneficial nonhormonal treatment for women with VMS due to menopause.



12-week Study
Placebo (n=305) 305 301 298 293 289 286 285 283 280 278 276 274
LDMP (n=301) 301 296 292 289 288 281 277 275 273 268 264

24-week Study
Placebo (n=284) 284 282 279 274 267 261 256 254 252 252 250 244 239 232 231 231 227 224 219 220 218 219 218 215
LDMP (n=284) 284 279 278 276 271 268 265 262 260 258 258 257 247 248 248 244 244 236 236 234 235 234 233 234

*Median data were used because the normality assumption was not met and therefore non-parametric analyses were conducted.

P-85.

Direct and Indirect Costs for Women with Vasomotor Symptoms (VMS) Receiving Lower- versus Higher-Dose Paroxetine

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Objective: Hormone therapy (HT), an FDA-approved treatment for women with VMS, is not recommended for all women. Other medications, including paroxetine, have been used to treat VMS. In the absence of approved prescribing information to guide appropriate dosing in VMS treatment, studies evaluating the association between different dosing regimens of paroxetine and health economic outcomes are warranted. The objective of this study is to evaluate the healthcare resource use, work productivity loss, and costs in women with VMS receiving low versus high daily dose of paroxetine. **Design:** An analysis of health insurance claims (1999-2012) from 69 self-insured US companies was conducted. Adult women with ≥ 1 diagnosis for VMS (ICD-9: 627.2) continuously enrolled ≥ 6 months prior to the first lower-dose (≤ 10 mg daily) paroxetine dispensing (index date) following VMS diagnosis were matched 1:1 with a higher-dose (> 10 mg) cohort based on propensity scores. Women with pregnancy-related diagnoses were excluded. Healthcare resource utilization and work productivity loss (disability + medically-related absenteeism) were compared between cohorts using incidence rate ratios (IRRs) and conditional Poisson models. Mean per-patient-per-year (PPPY) costs were also compared between cohorts using non-parametric (bootstrap) methods. **Results:** Lower-dose and higher-dose cohorts (n=3,108 women in both) were matched and balanced with respect to age (mean=56 years), region, payer type, industry type, beneficiary status, year of index date, history of a recent hysterectomy and baseline menopause-related diagnoses. Mean total costs PPPY were similar between cohorts at baseline (lower-vs. higher-dose, \$10,001 vs. \$10,737, $p=0.310$). During follow-up, VMS women initiating lower-dose paroxetine had significantly fewer VMS-related pharmacy claims and VMS-related outpatient visits than women using higher-dose paroxetine (Table 1a). The resulting direct all-cause costs PPPY were significantly lower for women receiving lower-dose compared to higher-dose paroxetine (direct cost difference [95% CI]: -\$1,490 [-\$2,419; -\$731]; Table 1b), with VMS-related services accounting for 35% (-\$519) of the all-cause cost difference. Treatment with lower-dose paroxetine was also associated with a lower work productivity cost burden (indirect cost difference [95% CI]: -\$932 [-\$1,954; \$34]; Table 1b). **Conclusion:** The current study suggests that lower-dose paroxetine use in women with VMS is associated with a lower direct and indirect cost burden compared to higher-dose use.

Table 1a. Direct and Indirect Resource Utilization

	IRR [95% CI] Lower- relative to higher-dose paroxetine		P-value	IRR [95% CI] Lower- relative to higher-dose paroxetine		P-value
	All-cause			VMS-related		
Pharmacy claims	0.86	[0.82; 0.90]	<.0001	0.82	[0.78; 0.86]	<.0001
Outpatient visits	1.00	[0.96; 1.04]	0.9190	0.91	[0.84; 0.98]	0.0088
Emergency-room visits	1.07	[0.89; 1.28]	0.4784	0.85	[0.72; 1.01]	0.0591
Hospitalizations	0.98	[0.88; 1.10]	0.7525	0.97	[0.85; 1.10]	0.6228
Other visits	1.02	[0.93; 1.12]	0.6076	0.98	[0.87; 1.10]	0.7167
Work loss	0.87	[0.51; 1.48]	0.6086	1.29	[0.54; 3.11]	0.5703
Disability claims	0.82	[0.35; 1.94]	0.6576	1.76	[0.46; 6.71]	0.4109
Medically-related absenteeism	0.95	[0.81; 1.10]	0.4846	0.83	[0.64; 1.07]	0.1438

Table 1b. Direct and Indirect Costs

	Average Cost (PPV)		Cost Difference [95% CI]		Average Cost (PPV)		Cost Difference [95% CI]	
	Lower-dose	Higher-dose	Lower-dose	Higher-dose	Lower-dose	Higher-dose	Lower-dose	Higher-dose
Total direct costs	\$7,909	\$9,399	-\$1,490	[-2,419; -731]	\$2,588	\$3,107	-\$519	[-909; -203]
Pharmacy costs	\$2,500	\$3,131	-\$631	[-875; -386]	\$780	\$1,074	-\$295	[-382; -209]
Outpatient costs	\$3,474	\$3,760	-\$286	[-491; -35]	\$1,173	\$1,334	-\$160	[-301; -28]
Emergency-room costs	\$100	\$120	-\$20	[-42; 2]	\$31	\$48	-\$16	[-27; -4]
Hospitalization costs	\$1,553	\$2,019	-\$466	[-958; -50]	\$529	\$569	-\$40	[-220; 134]
Other visit costs	\$282	\$368	-\$86	[-218; 13]	\$74	\$82	-\$8	[-23; 7]
Total indirect costs	\$2,364	\$3,295	-\$932	[-1,954; 34]	\$835	\$1,100	-\$265	[-400; 196]
Disability costs	\$858	\$1,624	-\$766	[-1,696; 46]	\$288	\$316	-\$29	[-258; 268]
Medically-related absenteeism costs	\$1,505	\$1,671	-\$166	[-405; 140]	\$547	\$783	-\$236	[-670; 89]

P-86.

Efficacy of Oral Ospemifene 60mg: Comparison in Subpopulations

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Objective: About 50% of women experience symptoms of vulvar and vaginal atrophy (VVA) and all women will experience some degree of vaginal change associated with menopause. VVA is a chronic and progressive adverse change that does not reverse without treatment. Until the recent approval by the Federal Food and Drug Administration (FDA) of oral ospemifene, a tissue selective estrogen agonist/antagonist, prescription options for postmenopausal women with VVA were estrogen-based systemic or topical vaginal preparations. Reported here are results at 12 weeks for overall and subpopulations in placebo-controlled trials assessing the efficacy of ospemifene on the physiological vaginal epithelial changes of VVA, and on self-identified most bothersome symptoms (MBS) of dyspareunia and vaginal dryness in postmenopausal women. **Design:** Data from 4 randomized, double-blind placebo-controlled trials were analyzed for the co-primary endpoints of change in percentage of cells (superficial, parabasal) in the Maturation Index (MI) and in vaginal pH from Baseline to Week 12/LOCF. Change in severity for MBS [vaginal pain (dyspareunia) associated with sexual activity, vaginal dryness] was analyzed in the two trials which included MBS as a co-primary endpoint. To assess population effects, pooled data from the placebo-controlled trials was analyzed for age, race, prior HRT use, and uterine status of participants. Uterine status was chosen to determine whether uterine secretions contribute significantly to the efficacy response of ospemifene. Multiple doses for ospemifene were investigated; 3 trials included the 60 mg dose, a Phase 2 trial included in the pooled analysis did not. Findings for the ospemifene approved dose of 60mg from pooled analysis are reported here. **Results:** Overall, for the co-primary efficacy endpoints, changes from Baseline to Week 12 in the % of superficial cells, % of parabasal cells and vaginal pH demonstrated statistically significant improvement vs placebo in each trial. For most bothersome VVA symptoms, improvement in severity at Week 12 for dyspareunia was significant vs placebo in both trials; for vaginal dryness, significant improvement vs placebo was seen in the one trial and numerical improvement in the other. At Week 12, for both participant categories of age (< 65 years, ≥ 65 years) and race (White, Other), a numerically larger increase in superficial cells, a larger mean decrease vs increase in parabasal cells, and a numerically larger mean decrease in vaginal pH were seen in the ospemifene group than in the placebo group. All mean changes were similar within the subpopulation categories. For both MBS, ospemifene produced numerically larger mean decreases in severity than placebo; results were similar within both subpopulation categories. For participants with and without previous HRT numerical improvements for all co-primary endpoints were seen with ospemifene vs placebo at 12 weeks. Ospemifene-treated participants with and without a uterus had numerically larger mean increases in superficial cells, decreases in parabasal cells and vaginal pH than the placebo groups. Mean decreases in severity for the MBS symptoms of dyspareunia or vaginal dryness was numerically greater with ospemifene than placebo. Improvements were similar for each parameter in both uterine categories indicating that the efficacy of ospemifene is not dependent on uterine secretions. **Conclusion:** Overall, ospemifene provided significant and reproducible benefit for physiological changes and symptoms associated with VVA. The efficacy of ospemifene 60 mg was largely unaffected by subpopulation differences. Improvements in percentage of superficial and parabasal cells, vaginal pH and in participant MBS scores for dyspareunia and vaginal dryness remained consistent between and within the subpopulations of age, race, prior HRT use and uterine status. Results of these randomized, placebo-controlled trials demonstrated that oral ospemifene 60 mg is an effective treatment option for postmenopausal women with symptoms (ie, dyspareunia) of vulvar and vaginal atrophy.

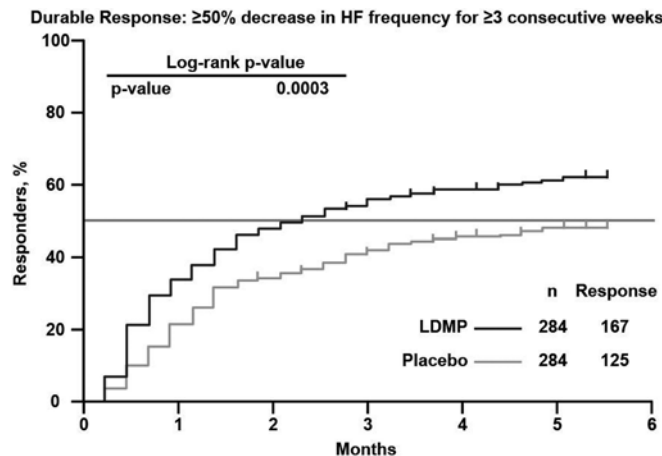
P-87.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Demonstrated Therapeutic Benefit for 24 Weeks in Women With Vasomotor Symptoms (VMS) Due to Menopause

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Objective: LDMP is an investigational, once-daily, nonhormonal medication specifically developed for the treatment of moderate to severe VMS due to menopause. Two multicenter, double-blind, randomized, placebo-controlled Phase 3 trials of 12 (Study 1) and 24 (Study 2) weeks' duration demonstrated that LDMP reduced the frequency and severity of moderate to severe VMS and had a favorable tolerability profile in postmenopausal women. Herein, we evaluate the persistence of benefit and the durability

of response with LDMP treatment in the 24-week study. **Design:** Postmenopausal women aged ≥40 yrs with moderate to severe VMS (>7-8 hot flashes [HF]/day; 50-60/week) were randomized 1:1 to receive LDMP 7.5 mg or placebo daily for 24 weeks. Co-primary endpoints were mean change from baseline (BL) to Weeks 4 and 12 in frequency and severity of moderate to severe HF. A pre-specified responder analysis was conducted to assess the persistence of benefit to Week 24 (Study 2). Responders were defined as patients achieving ≥50% reduction in frequency of moderate to severe HF from BL at Week 24. Durable response, an exploratory post-hoc analysis, was defined as patients achieving ≥50% reduction in frequency of moderate to severe HF that continued for ≥3 consecutive weeks. **Results:** The modified intent-to-treat efficacy population comprised 568 patients, 284 per arm. Significantly more patients treated with LDMP than placebo (47.5% vs 36.3%; p=0.0066) were responders at Week 24, demonstrating persistence of therapeutic benefit. Kaplan-Meier estimates of time to start durable response (Figure) indicate a significantly greater proportion of LDMP patients achieved a durable response compared with placebo. **Conclusion:** LDMP provided benefit after treatment initiation that persisted for at least 6 months of treatment. LDMP may provide a nonhormonal option for women who seek treatment for moderate to severe VMS due to menopause.

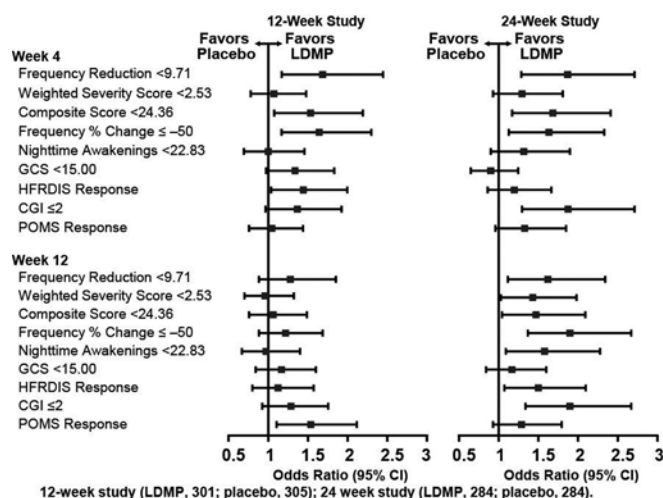


P-88.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Had Broad Clinical Benefit Across Multiple Assessments of Vasomotor Symptoms (VMS)

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Objective: LDMP is an investigational, once-daily, nonhormonal medication specifically developed for the treatment of VMS due to menopause. Two randomized, double-blind, placebo-controlled Phase 3 trials demonstrated that LDMP reduced the frequency and severity of VMS and had a favorable tolerability profile. To investigate the breadth and depth of effect that LDMP had on various assessments of VMS, odds ratio (OR) point estimates were computed for primary endpoints and relevant secondary outcomes, and multivariate global tests were performed to assess all outcomes simultaneously. **Design:** Postmenopausal women ≥40 years old with moderate to severe VMS (>7-8 hot flashes [HF]/d; 50-60 HF/wk) were randomized 1:1 to receive LDMP 7.5 mg or placebo once daily for 12 or 24 weeks. Exploratory analyses were conducted on primary endpoints (mean changes from baseline in HF frequency and severity at Week 4 and Week 12) and clinically relevant secondary outcomes, including HF composite scores; night-time awakenings due to HF/d; Greene Climacteric Scale (GCS); HF-Related Daily Interference Scale (HFRDIS); Clinical Global Improvement (CGI); and Profile of Mood States (POMS). All endpoints were dichotomized so that between-arm ORs for each endpoint could be compared; the analysis was based on the modified intent-to-treat population, with missing data imputed as "no response." For each analysis, OR estimates and exact 95% confidence intervals (CIs) were computed. Multivariate global tests using the O'Brien test procedure assessed all outcomes simultaneously so that between-outcome correlations could be taken into account. **Results:** In both studies, most OR point estimates are to the right of 1, suggesting LDMP had broad clinical benefit for multiple VMS outcomes (Figure). All multivariate global tests had p values < 0.01. **Conclusion:** These results support the consistency of LDMP effect across multiple VMS outcomes and suggest that LDMP provided broad clinical benefit for VMS due to menopause.



P-89.

Patient and Clinician Impressions of Improvement in Vasomotor Symptoms (VMS) Due to Menopause With Low-dose Mesylate Salt of Paroxetine (LDMP) Treatment

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Objective: VMS, including hot flashes (HF) and night sweats, are one of the most bothersome consequences of menopause and can negatively impact daily functioning. Hormone therapy is effective for VMS but may not be appropriate for all women; therefore, nonhormonal therapies are needed. Results from 2 multicenter, double-blind, randomized, placebo-controlled Phase 3 studies demonstrated that LDMP treatment reduced the frequency and severity of moderate to severe VMS and had a favorable tolerability profile. Patient and clinician impressions of VMS improvement during these studies were analyzed. **Design:** Postmenopausal women aged ≥40 years with moderate to severe VMS (>7–8 HF/day or 50–60 HF/week) were eligible. Patients first entered a single-blind, 12-day run-in period and received once-daily placebo. Compliant patients who met eligibility criteria entered a double-blind treatment period in which they were randomized 1:1 to receive LDMP 7.5 mg or placebo once daily at bedtime for 12 (Study 1) or 24 (Study 2) weeks. Patients recorded number and severity of HF in electronic daily diaries. Co-primary efficacy endpoints were mean change from baseline in frequency and severity of HF at Weeks 4 and 12. Secondary endpoints included the Patient Global Impression (PGI) scale (Study 1) and the Clinical Global Impression (CGI) scale (both studies). PGI was completed by patients at Weeks 4 and 12, and CGI was completed by clinicians at Weeks 4 and 12, and at Week 24 (Study 2). Improvement was scored on a scale of 1 (very much better/improved) to 7 (very much worse). Patients scoring 1, 2, or 3 were considered responders. Logit models were used to analyze proportions of responders. Additional analyses examined potential correlations between PGI/CGI perception of improvement and reduction in HF frequency. **Results:** Modified intent-to-treat efficacy populations comprised 606 patients in Study 1 (LDMP, 301; placebo, 305) and 568 patients in Study 2 (LDMP, 284; placebo, 284). In Study 1, a higher percentage of LDMP-treated patients were PGI responders at Weeks 4 and 12, with results achieving statistical significance at Week 12 (Table). In both studies and at all time points, significantly more LDMP-treated patients were CGI responders. A strong alignment of patient and clinician impressions of improvement was clearly evident at Weeks 4 and 12 in Study 1. In addition, an association between PGI improvement and HF frequency reduction was identified in Study 1: Patients with greater HF frequency reduction tended to report greater improvement in PGI. A similar association was observed with CGI in both studies at all weeks. **Conclusion:** As early as Week 4, proportions of PGI/CGI responders were significantly greater in the LDMP treatment arm than in the placebo arm. A correlation between patient- and clinician-reported outcomes and HF frequency reduction demonstrated consistent clinical benefit of LDMP in treating VMS due to menopause. LDMP may offer a nonhormonal treatment option for women who seek treatment for moderate to severe VMS due to menopause.

	Study 1 (12 weeks)			Study 2 (24 weeks)		
	LDMP (n = 301)	Placebo (n = 305)	p Values	LDMP (n = 284)	Placebo (n = 284)	p Values
PGI responders, %						
Week 4	68.21	61.75	0.1080	—	—	—
Week 12	72.82	64.60	0.0336	—	—	—
CGI responders, %						
Week 4	68.93	57.89	0.0067	67.88	53.58	0.0007
Week 12	71.88	63.92	0.0407	69.88	59.74	0.0203
Week 24	—	—	—	73.23	58.21	0.0003

P-90.

Reductions in objective vasomotor symptoms are positively associated with improvements in verbal learning: Findings from an RCT of stellate ganglion blockade for the treatment of vasomotor symptoms

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Objective: We previously reported the novel finding that verbal memory performance relates significantly to the number of objective vasomotor symptoms (VMS) women experience but not to the number of VMS they report. These findings suggest that physiological factors related to VMS, rather than psychological factors, predict poorer verbal memory function. Furthermore, these findings suggest that effective treatments for VMS will benefit verbal memory performance in women with moderate-to-severe VMS. Here we aimed to test this idea by examining changes in verbal learning and memory in relation to changes in objective VMS in the context of a randomized, sham-controlled clinical trial of stellate ganglion blockade (SGB) for the treatment of VMS. We predicted that the magnitude of reduction in objective, but not subjective, VMS would relate to improvements in verbal learning and memory but not to improvements in other cognitive domains. **Design:** In a randomized, double-blind, sham-controlled study, 36 midlife women with moderate-to-severe VMS (from a total of 40 participating in a parent study; mean age 52; 50% African-American) were randomized to undergo active intervention with fluoroscopy-guided SGB or sham control performed with saline. Participants completed measures of verbal learning and memory (primary outcomes), verbal fluency, processing speed, visuospatial abilities, visual memory, attention, and working memory at baseline and three months after treatment. Participants also wore an ambulatory sternal skin conductance monitor (Biolog Model 3991x/2-HFI) for a 24-hour period before randomization and three months after injection. Thirty-one of the 36 women had valid VMS data. Mixed effects regression analyses were conducted to examine the change in cognitive performance over time as a function of Treatment Group. Pearson correlations were conducted to examine associations between changes in cognitive performance and changes in VMS and partial correlations were conducted to examine whether these associations remained significant after controlling for changes in sleep and mood. **Results:** At baseline, there were no differences between the two treatment groups on the cognitive outcomes or on the number of VMS (objective and subjective). At baseline, the mean sensitivity (ie, subjective detection of objectively measured VMS) was 55%. The SGB group showed significant improvements in verbal learning (B=4.76, SE=1.95, p<0.05) and a trend towards improvement on delayed verbal memory (B=0.88, SE=0.49, p=0.08) from baseline to 3-months post-treatment whereas the sham control group did not show improvements on these primary outcomes. However, the interaction between treatment group and time was not significant (p's 0.13-0.20). Notably, the reductions in the frequency of objective VMS but not subjective VMS were positively associated with improvements in verbal learning (r=0.51 total; r=0.48 awake, p's<0.05). The magnitude of these associations did not change after controlling for changes in mood and sleep (r=0.53 and r=0.59, respectively, p's<0.05). **Conclusion:** As shown in previous studies, women underreport the number of VMS detected with ambulatory monitoring. Results support the hypothesis that improvements in VMS relate to improvement in verbal learning but only when VMS are measured objectively. Although the exact mechanism by which SGB improves verbal learning is not understood, ongoing studies are exploring hypothalamic-pituitary-adrenal axis function and autonomic nervous system function as possible mediators of this relationship. More generally, these findings also raise the possibility that one determinant of the effects of hormone therapy and other interventions to treat VMS on memory maybe the number of VMS a woman experiences, with memory improvements observed in relation to reductions in the number of VMS.

P-91.

Mean Score and Ranking Scale measurement on the Impact of Health Education on Behavior Change Communication of Menopausal Women in North Central Nigeria

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Objective: This study evaluate the impact of health education on behavior change communication of menopausal Nigeria women **Design:** This is an experimental study carried out in three stages; namely pre-intervention, intervention and post-intervention **Results:** Pre-intervention analysis showed that less than half of the study 87 (48.9%) and control 80 (44.4%) respondents were positive in their behavior towards menopause. The mean scores of the respondents' behavior change towards menopause were rank-ordered on the basis of selected sociodemographic variables. It was found that after health education intervention many of the groups in each variable had significant (p= 0.005) increase in behavior means score and ranking. Study respondents' knowledge and understanding of menopause increased significantly from 41 (23.0%) to 129 (73.7%). Their attitudinal behavior also changed significantly from 87 (48.9%) to 157 (89.7%). **Conclusion:** This study shows that health education intervention has significant impact on the behavioral change communication on menopausal women in north central Nigeria. Further research and regular health education on menopause by the health workers are recommended

Respondents' Knowledge Of Definition Of Final Menstrual Period (FMP)

Consecutive Period of Amenorrhea	Study Group Pre	Study Group Post	Control Group Pre	Control Group Post
6 months	26(14.6)	11(6.3)	12(6.7)	10(5.6)
9 months	46(25.8)	12(6.9)	44(24.4)	41(22.7)
12 months	41(23.0)	129(73.7)	40(22.2)	65(36.1)
2 years	52(29.3)	14(8.0)	48(26.7)	34(18.9)
3 years	13(7.3)	09(5.1)	36(20.0)	30(16.7)
Total	178(100)	175(100)	180(100)	180(100)

P value for pre/post X²=93.37 df=4 p value= 0.0000001 x²=9.18 df=4 p value 0.056853

P-92.

Vaginal estrogen usage and effect on quality of life and urogenital morbidity in menopausal women after publication of the Women's Health Initiative in New York City

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Objective: In the years following the publication of the results from the Women's Health Initiative (WHI) study in 2002, there have been a reluctance to prescribe and confusion over the duration and method of prescription of hormonal therapies to symptomatic menopausal women. The main concerns are the risks of cardiovascular events and breast cancer. However, local vaginal therapy may provide benefits without systemic effects. This study looks at the usage and the effect of vaginal estrogen therapy (VE) on the quality of life and urogenital morbidity in women who stopped systemic hormone therapy after WHI and compared them to women who continued. **Design:** We have previously reported on quality of life and hypertensive medication use with systemic therapy [1]. A retrospective cohort study was conducted. All consenting, eligible patients aged 55 to 73 in selected physicians' offices in New York City were interviewed between 2009 and 2012. Subjects included women who were postmenopausal and had used systemic hormone therapy (HT) or estrogen therapy (ET) for at least 5 years. Standardized qualities of life and menopausal and medical questionnaires were administered. Three groups were compared; Group 1: women who have remained on HT/ET, Group 2: women who have resumed HT/ET after stopping for at least 6 months, and Group 3: women who have stopped HT/ET and not resumed. **Results:** The study enrolled 310 eligible consenting women; Group 1: n = 159, Group 2: n = 43, and Group 3: n = 108. Of the women who discontinued HT/ET (Groups 2 and 3), 70.2% discontinued because of adverse media about therapy, 24.5% due to a physician's recommendation, and 16% for other reasons. Overall the ever use and present use of VE was most prevalent in women who reported dyspareunia (ever p = 0.003; present p = 0.005) and vaginal dryness (ever p = 0.001; present p = 0.004). VE use was significantly more likely for women in Group 3 compared to the other groups (Group 3 = 35.5% vs. G1 = 17.7% and G2 = 16.7%; p = 0.002). (Table 1) Women in Group 3 who used VE reported significantly higher sexual quality of life (using the sexual domain of the Utian quality of life scale), than those in Group 3 not using VE (p = 0.007). There was no difference in the incidence of urinary tract infections (UTIs) between the three groups (Group 1 = 22.9%, Group 2 = 26.3%, Group 3 = 25.5%). (Table 1) The percent of women either married, or living in a marriage-like relationship, did not differ between the three groups (Group 1 = 68.4%, Group 2 = 78.6%, Group 3 = 78.8%). (Table 1) **Conclusion:** Women who report dyspareunia and vaginal dryness are most likely to use VE. Those who do not use systemic therapy and use VE experience a significantly higher sexual quality of life over those not on VE. There were no differences in the incidence of UTIs, a difference reported by others [2, 3]. However these reports examined women with 3 or more UTIs and power was not sufficient to examine this variable. No systemic effects were noted with respect to blood pressure, weight, waist hip ratio, or use of hypertensive medications. VE improves sexual quality of life in women, particularly in those not using systemic therapy. [1] Warren, M.P., et al., Quality of life and hypertension after hormone therapy withdrawal in New York City. Menopause, 2013. [2] Raz, R. and W.E. Stamm. N Engl J Med, 1993. 329(11): p. 753-6. [3] Eriksen, B. Am J Obstet Gynecol, 1999. 180(5): p. 1072-9.

Table 1. VE Usage in Users and Non-users of Systemic HT/ET

Outcome	Group 1 [n (%)]	Group 2 [n (%)]	Group 3 [n (%)]	Significance
VE Use	28 (17.7)	7 (16.7)	38 (35.5)	0.002
UTIs in Last 3 Years	33 (22.9)	10 (26.3)	26 (25.5)	NS
Married or Marriage-like Relationship	106 (68.4)	33 (78.6)	82 (78.8)	NS

P-93.

Treatment persistence with local estrogen therapy in postmenopausal women dealing with vaginal atrophy

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Objective: To compare rates of pharmacy refill-based treatment duration and persistence in women treated with estradiol vaginal tablet versus estradiol vaginal cream in a managed care population. **Design:** The study population was comprised of treatment-naïve adult females (ages 18+) within the IMS LifeLink™PharMetrics database who filled 1+

prescription for a LET (Vagifem® 10mcg tablet, Estrace® cream, Premarin® cream) between January 1, 2010 and December 31, 2010 (although Vagifem® 10mcg was launched in late February 2010, it was also included in this analysis). Patients were assigned to one of three mutually exclusive LET treatment cohorts (Vagifem® 10mcg tablet, Estrace® cream, or Premarin® cream) based on the first observed LET fill (i.e., the index fill) on pharmacy records. Persistence was defined as the number of consecutive days of treatment of the index LET during the 10 month follow-up period. Survival analysis (Kaplan-Meier) was used to evaluate time to LET discontinuation. A Cox proportional hazards model compared the risk of discontinuation for the index LET cohorts. Multivariate logistic regression analysis was used to identify potential predictors of filling more than one prescription of the index LET. P-values < 0.05 were considered statistically significant. **Results:** A total of 7,935 women met the study selection criteria; the majority of women initiated LET with a cream formulation; 4,053 (51.1%) Premarin® (conjugated estrogen [CE] vaginal cream); 3,485 (43.9%) Estrace® (estradiol vaginal cream); and 397 (5%) Vagifem® 10 mcg vaginal estradiol tablets. Treatment was most commonly prescribed by an OB/GYN. Cohorts were comparable in terms of age (mean age overall was 56.3 years), geographic distribution and Charlson comorbidity index. During the 10-month follow-up period, 61.2%-63.2% of patients treated with vaginal creams discontinued their therapy after one prescription compared with 41.6% of tablet users (p<0.0001). A greater proportion of tablet initiators (58.4%) filled subsequent prescriptions compared with cream initiators (36.8% for CE vaginal cream users and 38.9% for estradiol vaginal cream users). A greater proportion of tablet initiators were fully (100%) persistent during the 10-month follow-up period compared with initiators of cream formulations (based on pharmacy refill records). The mean therapy duration for tablet initiators was 89.8 days compared with 41.2 days for CE vaginal cream and 43.6 days for estradiol vaginal cream (p<0.0001). After adjusting for age, geography, health plan type and comorbidities, tablet initiators were significantly more likely to fill more than one prescription than users of creams (p < 0.0001). The median time to index LET discontinuation was 30 days for patients initiating with creams compared with 142 days for tablet users (p<0.0001). Among patients who filled multiple prescriptions of the index LET, the average treatment duration among tablet users remained significantly higher compared with cream users (175.2 days vs. 121.2-123.0 days, p<0.0001). **Conclusion:** Use of estradiol vaginal tablets was associated with greater persistence versus cream-formulations in the treatment of vaginal atrophy. One possible explanation for this difference may be due to lack of metered dosing for cream formulations which could contribute to either underdosing or overdosing by patients. Additional studies using a longer follow-up period to measure gaps in therapy are warranted.

P-94.

Sexual function in post menopause woman with Metabolic Syndrome

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Objective: To assess sexual function in postmenopausal women diagnosed with MetS and compared to a control group in the same age group not carrying the syndrome. Studying what component of sexual response (desire, arousal, lubrication, orgasm, satisfaction and pain) is the most affected by the MetS and diagnostics component which is associated with sexual dysfunction. **Design:** Two hundred seventy-two postmenopausal women were interviewed (amenorrhea > 1 year and FSH > 30 mIU/mL). After applying inclusion and exclusion criteria, 77 were excluded. The remaining 195 were divided into Group I (Control) n = 87 non-carrier of Metabolic Syndrome and Group II (study) n = 108. The carriers of the syndrome were diagnosed using the criteria of ATP III. We use the questionnaire Female Sexual Function Index (FSFI) to assess sexual function. **Results:** A high prevalence of FSD in postmenopausal women with MS compared to women without this complaint (62/108 [57.4%] vs 16/87 [18.39%], p<0.001). Analyzing the two groups women with sexual dysfunction Present and relating them to variables HDL, Triglycerides, Glucose, desire, arousal, lubrication, orgasm, satisfaction and pain, we observed statistically significant differences in HDL (control group = 54.5 Group and SM = 47.5 mg / dL, p < 0.001), triglycerides (control group = 110.5 and SM Group = 182mg/dL p<0.001), plasma glucose (Control Group 89 and Group SM = 102mg/dL = p < 0.001), lubrication (Group Control Group SM = 3.3 and = 3 p < 0.016) (Mann-Whitney) and Pain (Control Group and Group SM = 3.6 = 4.8 p < 0.016). Analyzing the women with hypertension as the presence or absence of sexual dysfunction observed in the control group 20 are hypertensive (22.98%), while 16 (18.39%) have Sexual Dysfunction. In the SM Group, 82 are hypertensive (75.92%) and 62 (57.40%) have Sexual Dysfunction. Comparatively analyzing the groups we observed a significant difference both in relation to hypertension as compared to DSF (p<0.001). **Conclusion:** In our study, postmenopausal women with metabolic syndrome have more sexual dysfunction than women in the same age group not carrying the syndrome. We found that sexual function domains desire, arousal, lubrication, orgasm, and satisfaction were affected by the presence of Metabolic Syndrome. Question pain for no statistically significant difference. All the components that make up the diagnosis of Metabolic Syndrome were associated with higher rates of sexual dysfunction.

P-95.

The effect of soy isoflavones and estrogen therapy on the urethra and bladder of castrated rats

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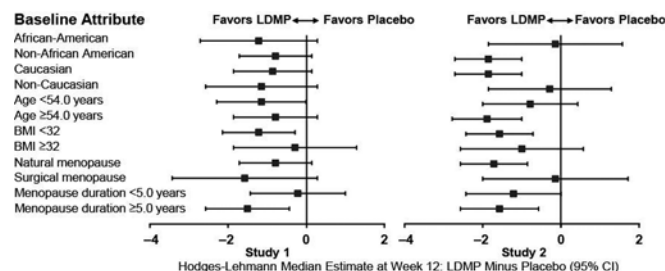
Objective: To evaluate the effect of soy isoflavones and estrogen therapy on the urethra and bladder of castrated rats. **Design:** Forty female albino rats were studied. The animals were castrated 32 days before the gavage drug administration. They were divided in four groups: Group A: control; Group B: 100 mg/kg/day of soy concentrated extract, containing 46 mg/kg/day total isoflavones; Group C: conjugated equine estrogens, 50 µg/Kg/day; Group D: conjugated equine estrogens, 50 µg/Kg/day and concentrated extract of soy, 100 mg/kg/day containing isoflavones, 46 mg/kg/day. The groups B, C and D received treatment for 32 days. All animals were sacrificed after 32 days. The bladder and urethra wall were extracted for histological analysis. We calculated the wall thicknesses at two different cuts of the same blade. The significance of results was calculated using the Student's t-test (p < 0.05). **Results:** Bladder: Group A (control) and Group B (Isoflavone) did not have any changes at the end of treatment. When we compared Group C to Group D, there was no significant difference, as well Group C to Group B. The bladder thickness in group C and D showed significant difference when compared to control Group. Urethra: Group A (control) and Group B (Isoflavone) did not have any changes at the end of treatment. When we compared Group D to Group A there were significant difference on urethra thickness. When we compared Group D to Group C showed significant difference. **Conclusion:** Oral concentrated extract of soy isoflavone treatment did not have positive trophic effect on the urethra and bladder thickness of female castrated rats. When we associated soy isoflavone to conjugated equine estrogens we observed trophic effect in both bladder and urethra thickness, but the urethra thickness was higher with conjugated equine estrogens associated with isoflavone when compared to conjugated equine estrogens alone.

P-96.

Analysis of Clinical Benefit of Low-Dose Mesylate Salt of Paroxetine (LDMP) for Vasomotor Symptoms (VMS) Across Subsets Defined by Baseline Attributes

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Objective: LDMP is an investigational, once-daily, nonhormonal medication specifically developed for the treatment of VMS due to menopause. Two randomized placebo-controlled Phase 3 trials demonstrated that LDMP reduced the frequency and severity of VMS and had a favorable tolerability profile. We examined the statistical relationship between the reduction in frequency and severity of VMS after treatment with LDMP or placebo and various baseline attributes in these studies. **Design:** Postmenopausal women ≥40 yrs old with moderate to severe VMS (>7-8 hot flashes [HF]/day; 50-60 HF/week) were randomized 1:1 to LDMP 7.5 mg or placebo once daily in multicenter, double-blind, Phase 3 trials of 12 (Study 1) and 24 (Study 2) weeks' duration. Primary endpoints were mean changes from baseline to Weeks 4 and 12 in frequency and severity of moderate to severe VMS. Effect modification analyses for HF frequency were conducted for the baseline attribute factors of race, age, body mass index (BMI), type of menopause onset, and duration of menopause. For each baseline attribute, between-arm differences in the change from baseline in median HF frequency (± confidence intervals [CIs]) were calculated for LDMP and placebo groups on the basis of available data. **Results:** In total, 614 participants were randomly assigned to Study 1, and 570 to Study 2. No evidence of bias resulted from ~10% missing data in each arm at 12 weeks. Forest graphs for median change in HF frequency (±95% CI) by study and subgroups at Week 12 are shown in the Figure. The preponderance of medians shifted to the left, suggesting that LDMP has consistent clinical benefit for VMS regardless of baseline patient attributes. Similar results were found for Week 4. **Conclusion:** These results support the consistency of LDMP effect on HF frequency across the baseline attributes analyzed and suggest that LDMP may be an effective nonhormonal treatment option for a wide range of women with VMS due to menopause.



P-97.

Comparison of Two Weighted Severity Score Calculations in Phase 3 Studies Evaluating Low-Dose Mesylate Salt of Paroxetine (LDMP) for the Treatment of Vasomotor Symptoms (VMS) Due to Menopause

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Objective: VMS due to menopause can be extremely bothersome, causing many women to seek treatment. LDMP is an investigational, nonhormonal medication specifically developed for the treatment of moderate to severe VMS due to menopause. In 2 randomized, double-blind, placebo-controlled Phase 3 trials, LDMP 7.5 mg/day reduced the frequency and severity of moderate to severe VMS due to menopause and had a favorable tolerability profile. Herein, we present 2 methods of calculating weighted average severity score—one that includes moderate and severe hot flashes (HF) (Calculation 1, the prespecified weighted average severity score calculation), and one that includes mild, moderate, and severe HF (Calculation 2). Both formulas have been used to support approved hormone treatments for VMS. **Design:** Patients were postmenopausal women ≥40 years of age with moderate to severe VMS (>7.8 HF/day; 50-60 HF/week). After a single-blind, 12-day placebo run-in period, patients were randomized 1:1 to receive LDMP or placebo once daily for 12 (Study 1) or 24 (Study 2) weeks. Primary endpoints were mean weekly change from baseline (BL) to Weeks 4 and 12 in frequency and severity of moderate to severe VMS. HF severity levels were defined as mild (a sensation of heat without sweating); moderate (a sensation of heat with sweating and ability to continue with activity); and severe (a sensation of heat with sweating causing cessation of activity). To derive the severity scores, mild HF were weighted as 1, moderate HF as 2, and severe HF as 3. Weighted average severity scores were derived using 2 equations; in the first method, only moderate or severe flashes were considered: $[3 \times F_m + 2 \times F_s] / [F_m + F_s]$, where F_m = frequency of severe HF and F_s = frequency of moderate HF. In the second method, frequency of mild HF (F_{mild}) was also considered: $[3 \times F_s + 2 \times F_m + 1 \times F_{mild}] / [F_s + F_m + F_{mild}]$. **Results:** Results of the 2 different weighted severity calculations are shown in the Table. Accounting for moderate and severe HF only, median daily change from BL in HF severity was significantly different between LDMP and placebo at Week 4 but not at Week 12 in the 12-week study and at both Weeks 4 and 12 in the 24-week study; differences remained significant at Week 24 in the latter. Accounting for mild, moderate, and severe HF, median daily change from BL in HF severity was significantly different at Weeks 4 and 12 in both studies and remained significantly different at Week 24 in the 24-week study. **Conclusion:** Weighted severity scores can be calculated with or without mild HFs. Data from both analyses show that severity scores were reduced to a greater extent with LDMP compared with placebo.

	Study 1 (12 Weeks)			Study 2 (24 Weeks)		
	LDMP	Placebo	p Value	LDMP	Placebo	p Value
	n=301	n=305		n=284	n=284	
Moderate and severe HF only (Calculation 1)						
BL	2.54	2.54		2.54	2.52	
Median daily change from BL at:						
Week 4	-0.05	0.00	0.0017	-0.04	-0.01	0.0368
Week 12	-0.06	-0.02	0.1658	-0.05	0.00	0.0064
Week 24	NA	NA	NA	-0.09	-0.02	0.0320
Mild, moderate, and severe HF (Calculation 2)						
BL	2.39	2.41		2.39	2.39	
Median daily change from BL at:						
Week 4	-0.08	0.00	0.0026	-0.05	-0.02	0.0110
Week 12	-0.12	-0.02	0.0287	-0.07	0.00	0.0034
Week 24	NA	NA	NA	-0.13	-0.02	0.0179

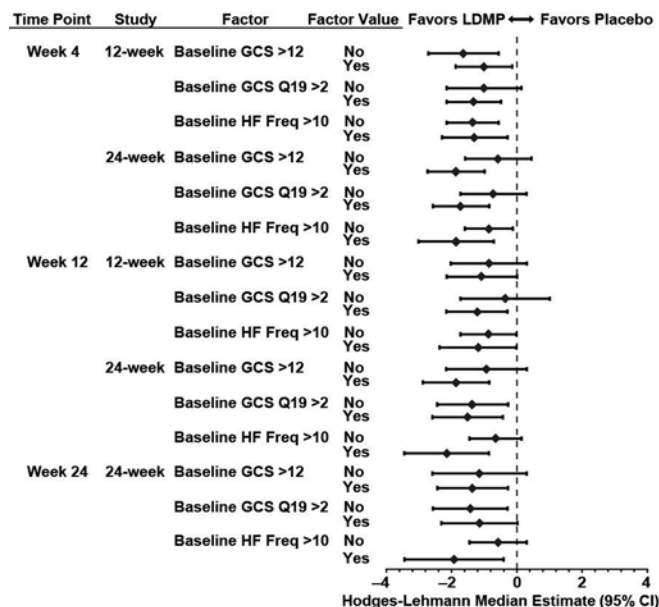
P-98.

Low-Dose Mesylate Salt of Paroxetine (LDMP) Provided Therapeutic Benefit in Women With Vasomotor Symptoms (VMS) Due to Menopause and High Baseline (BL) Symptom Burden

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Objective: Each year, millions of women in the US experience VMS due to menopause. The intensity of VMS varies, ranging from mild and tolerable to severe and debilitating. Although hormone therapy (HT) is effective for VMS, non-HT options are needed. LDMP is an investigational, once-daily, nonhormonal medication specifically developed for the treatment of moderate to severe VMS due to menopause. Two randomized, double-blind, placebo-controlled Phase 3 trials demonstrated that LDMP reduced the frequency and severity of VMS and had a favorable tolerability. The effect of LDMP treatment on women with and without high BL VMS burden was evaluated. **Design:** Patients: postmenopausal women ≥40 y; moderate to severe VMS (>7.8 hot flashes [HF]/d; 50-60 HF/wk). Study design: single-blind, 12-d placebo run-in period followed by a randomized (1:1), double-blind treatment period of 12 or 24 wks. Treatment: LDMP 7.5 mg or placebo qd. Co-primary endpoints: mean change from BL to Wks 4 and 12 in frequency and severity of HF. Analyses: an effect modification analysis assessed reduction in HF frequency in

women with high BL VMS burden (ie, Greene Climacteric Score [GCS] >12 or GCS vasomotor subscore [Q19] >2 or HF frequency >10/d). Hodges-Lehmann estimator was used to produce median point estimates (95% confidence intervals) for each parameter at Wks 4 and 12 (both studies) and Wk 24 (24-wk study only). **Results:** For women with high BL VMS symptom burden (using any of the 3 definitions), median point estimates favored LDMP at each time point (Figure). Further, women with high BL VMS burden generally had a greater magnitude of benefit than those without high BL VMS burden. **Conclusion:** LDMP treatment resulted in consistent benefit in women with and without high BL VMS burden at all time points, and women with high BL VMS burden often experienced the greatest magnitude of benefit. Thus LDMP may be a non-HT option for women with severe VMS due to menopause.



P-99.

Expression of vascular endothelial growth factor (VEGF) in the endometrium of women with polycystic ovary syndrome (PCOS)

Ricardo S. Simões, Dr¹, Gisela R. Sasso², Rinaldo Florencio-Silva², Carla C. Maganin², José M. Soares-Jr, MD, PhD^{2,1}, Maria Candida P. Baracat¹, Edmund C. Baracat¹. ¹Obstetrícia e Ginecologia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; ²Morphology and Genetics, Escola Paulista de Medicina, São Paulo, Brazil **Objective:** It is described that the vascular index (uterine Doppler) in the uterus of women with PCOS is lower when compared with the one of normal women. These data corroborate with the high prevalence of recurrent abortions, due to the presence of inappropriate endometrium in women with PCOS. As angiogenesis is one of the fundamental characteristics of tissue development, we carried out the present study. **Objective:** to evaluate the endometrial immunoreactivity of VEGF in normal women at the first phase of menstrual cycle and in women with PCOS. **Design:** This is a prospective case control study, approved by the research ethics committee of the Medicine School of the University of São Paulo (FMUSP). After patient consent assignment, it was collected and analyzed 15 endometrial samples from women with PCOS and 10 from normal women at the proliferative phase of the menstrual cycle (10th day) at the ages of 21 to 35, assisted in the ambulatory of the Discipline of Gynecology at the FMUSP. The biopsies were fixed in 10% formaldehyde solution for histological process and paraffin embedding. Sections with 5µm thick were subjected to immunohistochemistry for the detection of VEGF-A. The immunoreactivity index was evaluated by two pathologists in a light microscope linked to an image analysis system, providing numerical values (from 0 to 4) according to the degree of reactivity. Data were statistically analyzed by the t Student test (p<0.05). **Results:** Our data showed that there is VEGF immunoreactivity in all endometrial regions of both groups (superficial and glandular epithelium and in the lamina propria), being significantly higher in the PCOS group (p<0.05). Interestingly, the control group presented a low VEGF immunoreactivity. **Conclusion:** the vascular endothelial growth factor is present in higher concentration in the endometrium of women with PCOS; however, this factor may not be sufficient to maintain irrigation in this organ.

P-100.

Evaluation of the BCL-2/BAX ratio in the endometrium of women with polycystic ovary syndrome (PCOS) and in women during proliferative phase

Ricardo S. Simões, Dr¹, Gisela R. Sasso², Rinaldo Florencio-Silva², Carla C. Maganin², José M. Soares-Jr, MD, PhD¹, Maria Candida P. Baracat¹, Edmund C. Baracat¹. ¹Obstetrícia e Ginecologia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; ²Morphology and Genetics, Escola Paulista de Medicina, São Paulo, Brazil **Objective:** The process of endometrial remodeling in PCOS patients is probably regulated by the balance between apoptotic (BAX) and anti-apoptotic (BCL2) proteins. This study aimed to evaluate the immunoreactivity of BCL-2 and Bax proteins in the endometrium of PCOS women with regular menstrual cycle, during the proliferative phase. **Design:** We analyzed 15 samples of endometrium from 15 women with PCOS and 10 from women in the proliferative phase with normal menstrual cycle (Control group), at the age of 20 and 35, which as attended in the Discipline of Gynecology, of the Faculty of Medicine Hospital, at the University of São Paulo. Biopsies were performed with endometrial catheter Pipelle of Cornier (Cooper Surgical, Trumbull, CT, USA) and fixed in phosphate buffered 10% formaldehyde solution for histological processing and paraffin embedding. Sections (5-µm thick) were collected on silanized slides and submitted to immunohistochemical methods for the detection of BCL2 (clone 124 – DakoCytomation®, EUA) and Bax (policlonal – DakoCytomation®, EUA). Data were analyzed by score test. **Results:** Our data showed greater immunoreactivity of Bax in surface and glandular epithelium in the endometrium of women with PCOS and higher immunoreactivity of BCL2 in the endometrium of women from control group. **Conclusion:** Apoptosis in the superficial and glandular epithelium is more intense in the endometrium of women with PCOS than in women in the first phase of regular menstrual cycle. This process may maintain the endometrial homeostasis in PCOS patients.

P-101.

DEPRESSION AND ANXIETY OF PERIMENOPAUSAL AND POST-MENOPAUSAL NURSES AT H ADAM MALIK HOSPITAL IN MEDAN, INDONESIA

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Objective: To determine the proportion of depression and anxiety symptom in perimenopausal and post-menopausal nurses and to determine the differences between depression and anxiety symptom in both group **Design:** A cross sectional study, between perimenopausal, and post-menopausal nurses at H. Adam Malik Hospital, Tembakau Deli Hospital and Haji Mina Hospital, was conducted from 1st Juli 2011 to 31st October 2011. All participants attending this study were subjected to interviews and were recorded. Subsequently, L-MMPI scale tests were filled. Due to the self rating or subjective nature of these subjects, the validity of this study is highly affected by honesty of each respondent to fill each instrument available. If raw scores > 5, samples are instantly excluded due to dishonesty. Measuring symptoms of menopause was performed using the The Greene Climacteric Scale. This scale assesses 21 symptoms, accumulated from several symptoms that include psychological, somatic, vasomotor, and sexual dysfunction symptoms. Anxiety and depression disorders are diagnosed if questionnaires 1-6 and 7-11 are scored > 10, respectively. **Results:** During the study period, 157 women met inclusion criteria and filled out the climacteric scale. This study had mean age of perimenopausal nurses was 47 year old and post-menopausal nurses was 52 year old. The anxiety symptom in post-menopausal nurses is higher (40,3%) than perimenopausal nurses (33,8%). The depression symptom in post-menopausal nurses is higher (20,8%) than perimenopausal nurses (13,8%). **Conclusion:** There are no significant differences between depression and anxiety symptom in perimenopausal and post-menopausal nurses.

Greene Score Discrepancies between Perimenopausal and Postmenopausal Groups based psychological impacts including anxiety

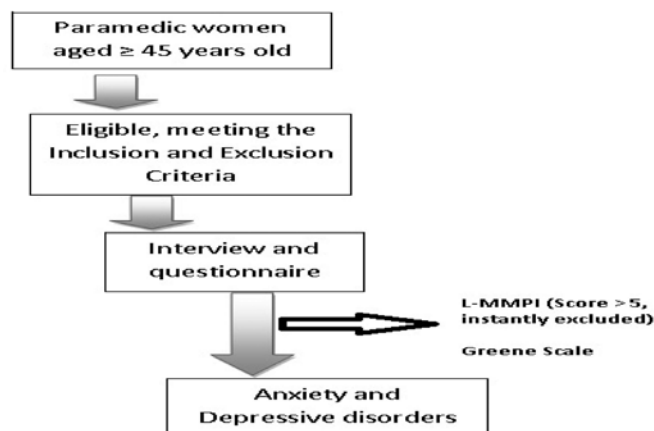
Symptoms of anxiety	Perimenopausal	Postmenopausal	Total
Anxiety	27 (33,8%)	31 (40,3%)	58 (36,9%)
Non Anxiety	53 (66,3%)	46 (59,7%)	99 (63,1%)

$$X^2 = 0.714 \quad p = 0.398$$

Greene Score Discrepancies between Perimenopausal and Postmenopausal Groups based psychological impacts including symptoms of depression

Symptoms of Depression	Perimenopausal	Postmenopausal	Total
Depressive	11 (13,8%)	16 (20,8%)	27 (17,2%)
Non depressive	69 (86,3%)	61 (79,2%)	130 (82,8%)

$$X^2 = 1,361 \quad p = 0,243$$



P-102.

The effect of Food with Isoflavones in Osteoporosis Prevention

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Objective: Isoflavones found abundantly in soybeans are structurally similar to estrogen and thus able to exert weak estrogenic effects. Fermentation of soymilk with probiotic bifidobacteria metabolises daidzein into equol. Findings from earlier clinical studies on the potential positive effects of isoflavones on cardiovascular and osteoporosis risk factors in postmenopausal women have been highly variable and inconclusive. **Aim:** The objective of this study was to examine the effects of ingesting a fermented soymilk containing viable bifidobacteria on serum lipid profiles, bone turnover markers and levels of FSH, LH and SHBG in postmenopausal women. **Design:** Thirty-six post-menopausal women were involved in a randomised, double-blind, placebo-controlled, parallel study involving a 12-week supplementation of fermented soymilk (FS), non-fermented soymilk (NFS) and casein-milk (CAS). Subjects in the FS and NFS group ingested the same dosage of isoflavone at 80 mg per day. Populations of B. animalis in fermented soymilks were 107 to 108 viable cells per mL. At baseline and endpoint, hormones, lipids, osteocalcin and β -CrossLaps were analysed in serum and deoxypyridinoline in urine. **Results:** There was no significant differences in either BMI ($P=0.24$) or bodyweight ($P=0.14$) between the three groups. After 12 weeks of milk supplementation, there was no significant change in mean bodyweight from baseline measurements for any of the groups. Supplementation of FS and NFS caused a decrease in the levels of FSH and LH ($P>0.05$). Moderate rises in SHBG were observed in the groups consuming the NFS and FS. There were no significant differences between baseline and endpoint means of total cholesterol, triglyceride and LDL-cholesterol ($P>0.05$). Ingestion of FS showed a trend toward a reduction in bone resorption, with urinary DPD decreasing by 2.4 nmol/mmol of CRE, but no significant difference was evident between baseline and endpoint means of the FS group ($P=0.16$). In contrast to the increase in DPD excretion shown by women in the NFS and CAS group (10.3% and 3.3%, respectively), women consuming fermented soymilk showed a 17.3% reduction in the urinary excretion of DPD ($P=0.05$). **Conclusion:** Preliminary findings show that FS may prevent bone loss in postmenopausal women. However, further studies with a larger number of subjects per group are required to evaluate trends showing a positive effect on hormones, bone formation and cardiovascular disease risk.

P-103.

Menopausal Experience of Exercise at Menopause

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Objective: The menopause is associated with a range of health issues, including hot flushes, urinary disorder, joint pain and psychological distress. Exercise is a well-established method of optimizing health, and a range of significant benefits. Maintaining an active lifestyle can delay the onset of most conditions associated with ageing and with menopause. **Aim:** To identify the meanings of exercise to menopausal women, and the influence of menopausal symptom severity. **Design:** Interpretative phenomenological analysis was employed as the theoretical and methodological framework in this qualitative study. Semi-structured interviews were carried out with eleven women with different levels of exercise participation and menopausal symptom severity. **Results:** Women associate various meanings with the experience of exercise during menopause. Regardless of exercise behavior and symptom severity, the participants associated exercise with both physical and physiological benefits. The women with high-severity symptoms valued the role of exercise in fighting ageing, whereas the women with low-severity symptoms associated exercise with feeling better able to cope with difficult situations. All of the participants recalled the presence of barriers to exercise. Exercisers enjoyed exercise more than non-exercisers, and exercise participation was found to have more influence in the perception of symptom severity as a barrier to exercise than symptom severity itself. **Conclusion:** Findings of this study will aid in the development of tailored interventions to enable women to overcome personal obstacles to exercise throughout menopause, regardless of the severity of their symptoms.

P-104.

Comparison of subjective menopausal symptoms between Chinese and Japanese women: A canonical correlation analysis between severity of subjective symptoms and self-efficacy scores

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Objective: Subjective menopausal symptoms reported by women vary cross-culturally. This study aimed to identify the characteristics of symptoms reported by middle-aged Japanese and Chinese women and to determine the correlation between the severity of subjective menopausal symptoms and self-efficacy. **Design:** We surveyed 329 Chinese and 310 Japanese women, ranging from 40 to 59 years of age. We used a sociodemographic questionnaire, a subjective menopausal symptoms inventory, and a general self-efficacy scale. Correlations between severity of subjective symptoms of menopause and general self-efficacy scores were analyzed by a canonical correlation analysis. **Results:** The subjective menopausal symptoms inventory had good internal consistency and the five-factor model fit the data for both Japanese and Chinese samples. Japanese women showed significantly higher severity scores than Chinese women in all factors in the pre-menopausal group [$F(1, 1645) = 97.28, P < 0.01$] and in mental condition, interpersonal anxiety, and autonomic balance factors in the post-menopausal group [$F(1, 1060) = 28.05, P < 0.01$]. The most frequently reported symptoms were fatigue (93.6%) in Japanese women and memory loss (76.6%) in Chinese women. Japanese women reported a significantly higher occurrence of 50 out of 60 symptoms than did Chinese women ($P < 0.01$). With the exception of the sexual function factor, a negative correlation was identified between menopausal symptoms and one self-efficacy factor: fear of failure. (Japan: $\lambda = 0.701, P < 0.01$, China: $\lambda = 0.458, P < 0.01$). **Conclusion:** Japanese women suffer more from menopausal symptoms than do their Chinese peers. Furthermore, in both Japanese and Chinese women, menopausal experience and self-efficacy are interrelated.

TABLE 1. The ten most frequently reported symptoms by Japanese and Chinese women

Ranking	Japanese women		Chinese women	
	Symptoms	Prevalence (%)	Symptoms	Prevalence (%)
1	Fatigue	93.6	Memory loss	76.6
2	Memory loss	92.3	Decreased frequency of sexual intercourse	71.4
3	Poor concentration	88.4	Presbyopia	68.4
4	Physical symptoms (shoulder stiffness, lower back pain, and joint aches)	88.4	Fatigue	68.4
5	Social anxiety	87.4	Low libido	68.1
6	Skin abnormalities (increased acne and blemishes, roughness, and dryness)	85.5	Irritability	67.8
7	Indecisiveness	85.5	Physical symptoms (shoulder stiffness, lower back pain, and joint aches)	66.0
8	Irritability	84.2	Dreaminess	65.7
9	Anxiety	80.3	Poor concentration	65.3
10	Low self-esteem	79.3	Skin abnormalities (increased acne and blemishes, roughness, and dryness)	65.0

TABLE 2. Comparison of the severity of subjective menopausal symptoms, the scores of self-efficacy between Japanese and Chinese women

	Pre-menopause group		Menopause-transition group		Post-menopause group	
	Japanese women	Chinese women	Japanese women	Chinese women	Japanese women	Chinese women
n	153	178	50	44	107	107
Severity scores of subjective menopausal symptoms						
Sexual function	19.58±0.73	15.04±0.67a	21.60±1.34	20.91±1.55c	21.80±1.11	22.13±1.08c
Mental condition	35.44±1.15	27.12±0.95a	36.92±1.80	35.25±2.20c	35.14±1.41	29.60±1.25a
Interpersonal anxiety	27.45±0.95	21.92±0.86a	28.14±1.63	24.39±1.58	27.34±1.18	20.79±1.02a
Autonomic balance	42.76±1.27	35.75±1.17a	41.84±2.24	43.30±2.73c	45.81±1.79	38.05±1.67a
Other subjective symptoms	39.68±1.20	33.07±1.12a	38.66±1.97	38.25±2.19	39.70±1.55	36.02±1.49
Scores on the self-efficacy scale						
Positive behavior	21.06±0.44	24.06±0.30a	20.46±0.64	22.30±0.70	20.43±0.44	24.34±0.52a
Fear of failure	17.94±0.37	18.37±0.30	17.68±0.54	16.09±0.61c	17.06±0.43	17.92±0.43
Self-perceived social ability	9.95±0.29	10.57±0.26	9.92±0.55	10.98±0.53	10.46±0.31	9.78±0.41

Mean ± S.E., Difference between Japanese and Chinese women, significant level: a $P < 0.01$; b $P < 0.05$.

Difference between three menopausal groups of Chinese women, significant level: c $P < 0.01$.

P-105.

Hormone replacement therapy and quality of life in postmenopausal women

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Objective: Menopausal symptoms decrease quality of life (QoL) of postmenopausal women, and hormone replacement therapy (HRT) reduces vasomotor symptoms. However, there are some ongoing debates about whether HRT improves health-related QoL. The purpose of this study was to examine the relationship between HRT and QoL in postmenopausal women. **Design:** We analyzed data from the 5th Korean National Health and Nutrition Examination Survey 2011. EuroQol-5 Dimension (EQ-5D) index and EuroQol-Visual Analogue Scale (EQ-VAS) were used to evaluate QoL. They are standardized measurement instruments of health status developed by the EuroQol Group. **Results:** A total of 511 postmenopausal women aged 45-59 years were included in the analysis. 426(83.45%) were the non-HRT group and 85(16.6%) were the HRT group. EQ-5D index and EQ-VAS were not significantly different between the two groups, except that the anxiety/depression dimension was poorer in the HRT group (1.26) than the non-HRT group (1.13)(p=0.02). Among the HRT group, we analysed two subgroups divided by whether they initiated HRT before or after 48 months from the onset of menopause, and there were no significant differences of EQ-5D index (p=0.3) and EQ-VAS (p=0.827). **Conclusion:** This study concludes that there is no significant association between HRT and QoL in postmenopausal women.

Comparison of demographic characteristics

Variables	non-HRT (n=426)	HRT (n=85)	P-value
Age group, n(%)			0.016
45-49	22 (7.1)	10 (16.8)	
50-54	185 (45.5)	22 (28.9)	
55-59	219 (47.4)	53 (54.3)	
Age, y	54.14 ± 0.193	53.99 ± 0.506	0.777
Education level, n(%)			0.661
Elementary school	129 (34.3)	25 (32.9)	
Middle school	94 (24.7)	21 (24.7)	
High school	142 (29.3)	31 (35.0)	
College	61 (11.7)	8 (7.3)	
Marital status, n(%)			0.637
Married	367 (85.6)	73 (86.8)	
Single	9 (1.6)	3 (2.9)	
Divorced or widowed	50 (12.8)	9 (10.3)	
BMI, kg/m ²	24.43 ± 0.196	23.44 ± 0.285	0.004
Occupation, n(%)			0.807
Yes	244 (60.2)	49 (61.7)	
No	182 (39.8)	36 (38.3)	
Age at menopause, y	50.09 ± 0.191	48.94 ± 0.424	0.010
Income, n(%)			0.909
Lowest	53 (13.8)	8 (11.6)	
Low-middle	95 (25.6)	24 (27.9)	
Middle-high	126 (31.6)	23 (28.3)	
High	150 (29.0)	30 (32.2)	

Values are presented as mean ± SE or number (%)

HRT: hormone replacement therapy, BMI: body mass index

HRT and QoL, subjective health status

	non-HRT	HRT	P-value
EQ-5D index*	0.94 (0.92-0.95)	0.91 (0.89-0.93)	0.061
Mobility	1.17 (1.13-1.22)	1.20 (1.10-1.30)	0.629
Self-care	1.04 (1.02-1.07)	1.06 (0.99-1.12)	0.705
Usual activities	1.11 (1.07-1.14)	1.10 (1.03-1.17)	0.808
Pain/discomfort	1.30 (1.24-1.36)	1.42 (1.30-1.54)	0.087
Anxiety/depression	1.13 (1.09-1.17)	1.26 (1.16-1.37)	0.020
EQ-VAS†	75.27 (73.37-77.17)	72.97 (68.48-77.45)	0.360
Subjective health status			0.741
Very good or good	136 (31.7)	23 (28.4)	
Not good	214 (49.7)	43 (49.1)	
Bad or very bad	76 (18.6)	19 (22.5)	

Values are presented as estimated value (95% confidence interval) or number (%)

HRT: hormone replacement therapy, QoL: quality of life

*Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension.

†Standard vertical 20 cm visual analogue scale (similar to a thermometer) for recording an individual's rating for their current health-related quality of life state

P-106.

Pilot study of menopause-related symptom reduction through a noninvasive EEG-based technology for auto-calibration of neural oscillations (HIRREM)

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Objective: Eighty-eight percent of peri- and postmenopausal women in the United States experience daytime hot flashes or night sweats, which often affect mood and sleep, and can decrease quality of life. Loss of ovarian steroid effects on neurotransmitters and neural circuits, changes in hypothalamic thermoregulation, and autonomic dysregulation have all been implicated as contributing to these symptoms. Since autonomic function is managed by the central nervous system, especially the left and right insular cortex, autonomic dysregulation as a contributor towards menopausal symptoms is consistent with a model that includes a common upstream neural source for diverse menopausal symptoms. High-resolution spectral electroencephalography (EEG) offers a mechanism for data-gathering and noninvasive intervention relative to the central nervous system. Increased electrical amplitudes in the high frequency (beta range) of the EEG are reported in many studies of insomnia. Increased high frequency EEG power during sleep appears to differentiate late peri- and postmenopausal women, from pre- and early perimenopausal women. Hot flash frequency appears to explain much of the relationship between menopausal status and increased high frequency EEG power. High-resolution, relational, resonance-based electroencephalic mirroring (HIRREM) is a noninvasive technology designed to support the brain to auto-calibrate its neural oscillatory dynamics by using musical tones to reflect brain frequencies in near real time. The primary objective of this pilot study is to evaluate the effect of HIRREM on hot flash symptoms, and high frequency temporal EEG power. The secondary objective is to evaluate the effect of HIRREM on symptoms of insomnia and depression. **Design:** Seven women (median age 54, range=46 to 69) were enrolled in an ongoing, open-label, single site, IRB-approved, feasibility study of HIRREM for individuals with diverse psychophysiological conditions. All reported hot flash symptoms, and completed a daily hot flash diary. EEG frequencies and amplitudes were analyzed from one minute epochs of data collected at baseline, and during the penultimate minute of the final HIRREM session. EEG power analysis focused on high frequency (23-36 hertz) EEG power at the temporal regions (sum of power at T3 and T4) due to the proximity to underlying cortical regions implicated in autonomic regulation. The primary outcomes for this analysis include the median of hot flash scores (total hot flashes multiplied by severity score, calculated daily), and serial values for high frequency EEG power at T3 and T4. Secondary outcomes include self-report insomnia (Insomnia Severity Index, ISI) and depression (Center for Epidemiologic Studies Depression, CES-D) questionnaires at baseline, and following the HIRREM intervention. **Results:** Subjects had a median of 14 (range=10 to 23) HIRREM sessions (90 minutes each) over a median of 11 (range=5 to 32) days. At baseline, the median hot flash score was 9 (range=3 to 42), with 6/7 women exhibiting decreased hot flash scores post-intervention (decreases ranging from 61% to 100% of baseline). Median total high frequency power was 11.04 microvolts at baseline and decreased by a median of -2.89 microvolts (range=-11.05 to 0.42, p=0.031) at the final HIRREM session. At baseline, participants had a median ISI score of 18 (range=4 to 27), and a median CES-D score of 12 (range=3 to 36). For both symptom inventories, scores decreased post-HIRREM, with a median decrease of -13 (range=-20 to -1, p=0.022) for the ISI, and a median decrease of -7 (range=-32 to -1, p=0.016) for the CES-D. **Conclusion:** These data suggest that menopausal symptoms, including hot flashes as well as associated insomnia and depression, may have a common upstream neural source, and that auto-calibration of neural oscillations through HIRREM may positively impact this group of symptoms. Controlled clinical trials of HIRREM as an intervention for menopausal symptoms are indicated.

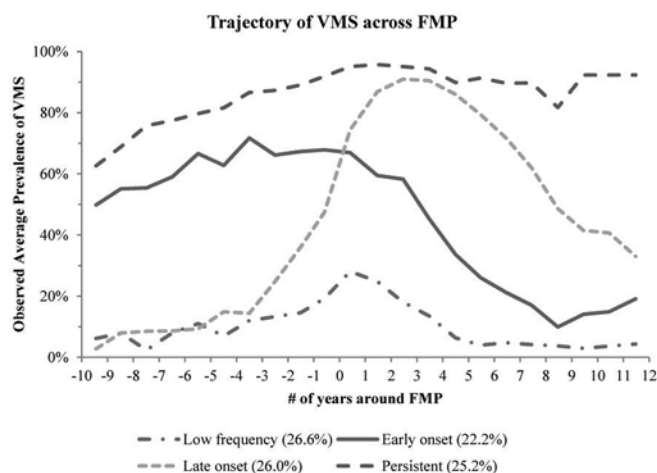
P-107.

Trajectory Patterns of Vasomotor Symptoms over the Menopausal Transition in the Study of Women's Health Across the Nation (SWAN)

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Objective: Menopause-related vasomotor symptoms (VMS) are highly prevalent. Although several studies have shown the time course of VMS over the menopausal transition (MT), these studies are based on group averages and do not consider individual variation or patterns of VMS. We aimed to identify the temporal patterns of VMS over the MT. **Design:** We studied annual self-reports of VMS (experiencing hot flashes, night sweats or cold sweats in the past 2 weeks) in SWAN, a multiethnic, multicenter longitudinal observational study. Group-based trajectory modeling was used to identify different temporal patterns of VMS prevalence across the final menstrual period (FMP) using a polynomial relationship between presence of VMS and time before and after FMP. Time stable and time-varying factors were included in the model. A total of 1591 women who experienced natural menopause with up to 13 annual visits were analyzed. **Results:** Four distinct VMS trajectories were found: early onset and decline after the FMP (early onset, 22.2%), onset near the FMP then decline (late onset, 26.0%), early onset and persistent (persistent, 25.2%), and consistently low frequency (low frequency, 26.6%). Compared to women in the early onset group (the reference group), women in the late onset group were more likely to be normal weight and to have a moderate rise in FSH over

the MT; while women in the persistent group were more likely to be African American and normal weight, and to have lower educational attainment; and women in the low frequency group were less likely to be obese and to have a moderate FSH rise over the MT. Baseline menopausal stage, overall health, depressive symptoms, symptom sensitivity, alcohol use, perceived stress and change in perceived stress over time were also significant factors associated with membership in a VMS trajectory but not estradiol trajectory over the MT, smoking, anxiety, physical activity, financial hardship or clinical site. **Conclusion:** These findings suggest that the pattern of VMS around the FMP varies among women. Distinct VMS trajectories with specific risk factors can be identified to aid in treatment decision making. Future studies can now focus on trajectories of circulating hormones that may provide additional physiological insights.



P-108.

In-home S-equal Supplement Sample Survey in Symptomatic Climacteric Women in the US and Japan

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Objective: Equol, which is an active metabolite of soy isoflavone “daidzein”, have similar structures to estrogen and exhibit certain aspects of estrogenic activity via the binding to estrogen receptors. Equol can be produced by intestinal bacteria in approximately 50% of Japanese and 20–30% of the US population. Using a lactic acid bacterium, *Lactococcus* 20-92, that metabolizes daidzein to S-equol, we successfully produced a fermented soy ingredient containing S-equol. The clinical studies have suggested that the daily 10mg S-equol supplement alleviates hot flashes and muscle stiffness of neck and shoulder in both Japanese and US women. Although vasomotor symptoms and/or muscle stiffness are primary symptoms in Japan and the US, menopausal women are various and multiple symptomatic in general and not a few women’s situations, like using hormone therapy (HT) or surviving gynecological cancers, were excluded from the clinical studies previously conducted. Thus, in these surveys, the wider range of symptomatic women was enrolled, and then they reported the self-rating menopausal symptoms to indicate their severity at each time point of the surveys. **Design:** In the survey in Japan, 1035 women, who were outpatients of 33 clinics or members of a non-profit organization for women’s health, were participated. Participants were recommended to take 10mg S-equol supplement daily for 12 wks, then reported the severity of menopausal symptoms using the Climacteric Symptom Evaluation Checklist, which is a questionnaire with 4-point rating scale, at 0, 4, 8, and 12 wks. In addition, the subjective supplement evaluation as an overall menopausal symptom relief was reported with either “improvement”, “unchanged”, or “aggravation”. In the US, 796 symptomatic women enrolled the survey with clinician’s recommendation. Self rating of the supplement satisfaction and current symptom severity, on which they indicated how much for each with a choice of prepared answers on a questionnaire, were reported at 0, 3, 7, 12 and 16wks. **Results:** Five hundred sixty-six of 1035 participants were climacteric women aged 45–55 years. In the 566 climacteric women, 46 were gynecological cancer survivors and 47 were HT users in Japanese survey. A total 60% of the climacteric women reported “improvement” in the overall symptoms. The rated score in somatic symptom was improved ($P<0.05$). In HT users, although the medical treatment did not alleviate the somatic symptoms, S-equol supplement decreased the scores ($P<0.05$). In addition, 62% of HT users were improved the overall symptoms, which was as same as that of non-HT users (57%). Fifty-five percents of gynecological (breast, endometrial, or ovarian) cancer survivors were improved the overall symptoms. The symptom scores for depression, anxiety, sleeplessness, backache and joint pain were decreased ($P<0.05$ in each symptom). In the survey of the US, approximately 80% participants reported the supplement satisfaction as “very-”, “somewhat-”, or “slightly-satisfy”. The percentage of women who selected the answer, either “extremely” or “quite a bit” in the symptom severity instead of “a little” or “not at all” were 36–82% decreased in the symptoms addressed, ie. hot flash, night sweat, sleep disturbance, fatigue, change in sexual desire or drive, memory or concentration problem, mood swing or irritability, anxiety, depression, muscle discomfort, weight gain, hair loss and heavy period, at 3 wks. The reduction of each symptom severity was similar

to the 3 wks at 7, 12 and 16wks. There are no serious adverse events reported during S-equol supplementation in both Japan and US surveys. **Conclusion:** Both in-home sample surveys suggest that S-equol supplement alleviates various climacteric symptoms more than hot flash and muscle stiffness/discomfort in Japanese and US symptomatic women, in which approximately 60% of the Japanese participants were HT users and gynecological cancer survivors. We believe these surveys have a practical significance, because S-equol supplement worked for various climacteric symptoms relief with various individual situations.

P-109.

The Effect of Hormone Therapy on Intraocular Pressure in a Randomized Hormone Trial: The Women’s Health Initiative Sight Exam Study (WHISE)

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Objective: The worldwide prevalence of glaucoma is estimated to be 3% in individuals aged 40 years and older, and women carry a higher burden of glaucoma and blindness due, in part, to longevity. Vision loss from glaucoma impairs critical independent activities of daily living, and confers substantial secondary risks to health including depression, falls, and motor vehicle accidents. Increased intraocular pressure (IOP) is a major risk factor for glaucoma, and at present reduction of IOP is the only available treatment. Previous observational, clinical studies and randomized clinical trials suggest that postmenopausal hormone therapy is associated with lower IOP. Here we report results examining the impact of hormone therapy on IOP in women participating in an ancillary study of the Women’s Health Initiative (WHI) randomized hormone trial. **Design:** This is a secondary analysis of data from the WHI-Sight Exam (WHISE), a WHI ancillary study of women aged 65 years and older in the hormone trial. It was designed to assess the impact of hormone therapy on age-related macular degeneration. An eye examination including fundus photography and an IOP measurement was performed at 5 years after the initial randomization in the main trial. Regression models were used to assess the effect of placebo compared to conjugated equine estrogen (CEE trial) or combined CEE with medroxyprogesterone acetate (CEE+MPA trial) on IOP at 5 years after randomization, adjusting for age, race, diabetes, hypertension, smoking, alcohol use, and body mass index. Of note, women in the CEE+MPA trial were not hysterectomized. Non-adherence was defined as any of the following: discontinued study medications, crossed to the placebo group or another hormone, or decreased below the 80% compliance based on pill counts at any time during follow-up. **Results:** A total of 1,585 women in the CEE trial and 2,567 women in the CEE+MPA trial were included. The participants were mostly Caucasian (84.8% Caucasian, 10.6% African American in the CEE trial, and 91.2% Caucasian, 4.7% African American in the CEE+MPA trial); an average age was 67 ± 5 years in the CEE trial and 66 ± 5 years in the CEE+MPA trial at the time of randomization. The overall non-adherence rate was 53.1% in the 2 trials combined. Mean IOP in mmHg (95% confidence interval, CI) was 15.5 (15.4, 15.7) in the right eye, 15.5 (15.4, 15.7) in left in the CEE trial, and 15.6 (15.5, 15.7) in the right eye, 15.7 (15.6, 15.8) in left in the CEE+MPA trial. After adjusting for covariates, CEE was statistically significantly associated with lower IOP by 0.5 mmHg (95% CI: -0.8, -0.1, $p = 0.0048$) in the right eye and 0.6 (95% CI: -0.9, -0.3, $p = 0.0001$) in the left; there was no significant difference in IOP between the CEE+MPA and placebo groups ($p = 0.34$ in the right eye and $p = 0.45$ in the left). **Conclusion:** This analysis suggests that postmenopausal women, treated with CEE, but not with CEE+MPA had a small, but significantly lower IOP than the placebo arm, 5 years after initiation of treatment. While this study represents the first epidemiologic analysis of the impact of hormone therapy on IOP in a large clinical trial, it has some limitations. As it was not primarily designed to assess glaucoma outcomes, data on IOP at baseline and central corneal thickness that could potentially affect the IOP measurement were not available. It is therefore not known if the randomization was well matched on IOP at baseline. Further analysis for the effect of age at hormone initiation on IOP and analysis limited to adherents is required. Basic, clinical and epidemiologic research suggests that estrogen is protective against glaucoma through an IOP reduction, increased blood flow and/or IOP-independent neuroprotection. Future studies are needed to determine if the observed magnitude of IOP-lowering effect in the CEE trial is related to a reduced incidence of glaucoma in this population.

P-110.

Cimicifuga racemosa Rhizome and Root Extract for the Management of Moderate to Severe Menopausal Symptoms in Thai Women: a Randomized Controlled Trial

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Objective: To compare the effects of black cohosh extract 40 mg/day on moderate to severe vasomotor symptoms and menopause quality of life (MENQOL) with placebo **Design:** A randomized double-blind placebo-controlled trial **Results:** Peri- and postmenopausal women age at least 40 years who Kupperman menopausal index (KI) at least 20 are randomized to receive black cohosh extract 40 mg/day or placebo. Primary efficacy endpoints are changes in Kupperman menopausal index on 4, 8 and 12 weeks. Secondary endpoints are changes in MENQOL. 27 participants are assigned to each treatment. Mean (SD) baseline KI is 32.5 (7.4). At 12 weeks, there is the trend of continue lowering KI in black cohosh group than placebo but not statistical significant ($P = 0.527$).

MENQOL between group is not significantly difference in every domains. No serious adverse events and significant changes in liver function tests report. **Conclusion:** Black cohosh extract does not significantly relieve moderate to severe menopausal symptom

Mean Kupperman index between groups at each time point (intention-to-treat analysis)

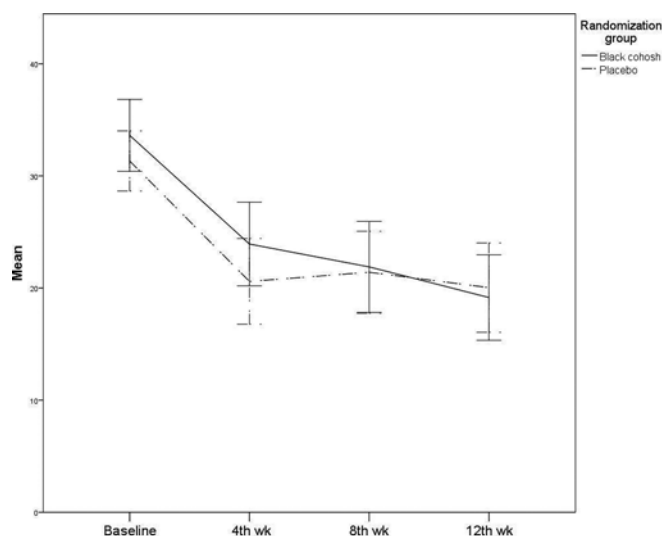
	Black cohosh (N = 27)		Placebo (N = 27)	
	Mean (SD)	P	Mean (SD)	P
Baseline	33.6 (7.9)		31.3 (6.8)	
4 weeks	23.9 (9.3)	< 0.001 ^a	20.6 (9.7)	< 0.001 ^a
8 weeks	21.9 (10.1)	< 0.001 ^a	21.4 (9.2)	< 0.001 ^a
12 weeks	19.2 (9.4)	< 0.001 ^a	20.0 (10.1)	< 0.001 ^a

^a Compared with baseline, Adjustment for multiple comparisons: Bonferroni; SD, standard deviation

Mean differences in MENQOL between black cohosh and placebo groups (intention-to-treat analysis)

	Black cohosh (N = 27)	Placebo (N = 27)	p ^a
	Mean (SD)	Mean (SD)	
Vasomotor	1.1 (1.6)	1.4 (1.9)	0.346
Psychosocial	0.9 (1.5)	0.7 (0.01)	0.675
Physical	0.7 (1.2)	0.6 (1.0)	0.556
Sexual	0.39 (1.6)	0.02 (1.8)	0.38

^a Compared with black cohosh group, ANCOVA; SD, standard deviation; MENQOL, menopause-specific quality of life questionnaire



Changes in mean Kupperman index by study group. $P = 0.527$ (repeated measures ANOVA with a Greenhouse-Geisser correction). Error bar represented 95% CI.

P-111.

Sex and Gender Women's Health Collaborative: Fostering a Sex and Gender Approach to Medical Education

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Objective: A poster presentation designed to inform participants of the need for education in sex and gender specific medicine as it applied to the healthcare needs of women **Design:** Poster Presentation and Interactive Learning Process **Results:** Gender-Specific Medicine is the study of the differences in the normal function of men and women and in their experiences of the same disease. Over the past several decades, a significant international body of research on sex and gender differences in health and illness has developed and continues to grow. This emerging discipline goes beyond women's health in that it also informs the teaching of men's health. However, too little of this information has been applied to clinical practice. Medical educators must aim to train medical students for sex and gender competency. Despite decades of progress, a 2010 IOM report, "Women's Health Research: Progress, Pitfalls, and Promise," Indicates inadequacy in the translation of sex and gender based science into practice. The Sex and Gender Women's Health Collaborative, www.sgwhc.org is a universally accessible resource for educational and teaching tools focused on sex- and gender-specific women's health for clinicians, faculty, students, and health practitioners. Created by members of leading women's health organizations, the SGWHC aims at improving women's health by recognizing and applying evidence-based medicine to the specific issues, concerns, and medical responses that affect women. The Founding members of SGWHC are the American Medical Women's Association, the American College of Women's Health Physicians, and the Society for Women's Health Research, which joined us just this Spring. The site boasts

over 200 members, 22 collaborating organizations, including educational institutions, the former Centers of Excellence in Women's Health, and International Societies of Gender Medicine. To date, it catalogues over 600 journal abstracts, curricular materials, powerpoint presentations, teaching tools, and case studies. Future projects include webinars, journal clubs, and interactive presentations. Our NAMS poster presentation will highlight the mission and vision of the SGWHC, and promote our new interactive contest, the "Wheel of Differences," which is designed to pique interest in concrete sex and gender differences which have been revealed in evidence based research. Conference participants will be asked simple S&G factoids that should be known by every healthcare provider. E.g. "Which sex has greater sensitivity to alcohol ingestion and why?" "What are the typical symptoms of MI in women as opposed to men?" "How does the recommended dose of Zolpidem differ between the sexes?" "How does serum cholesterol level vary throughout the menstrual cycle?" Participants will receive prizes for correct answers. By presenting this project, the hope is that more healthcare providers will be motivated to "Know the Differences" that an X or Y chromosome makes in the health and disease outcomes of their patients. **Conclusion:** Sex and gender differences greatly affect the clinical care and outcomes of women and should be considered in all medical and professional teaching venues

P-112.

Challenges and Positive Experiences during the Menopausal Transition: Observations from the Seattle Midlife Women's Health Study

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Objective: Despite assumptions that the menopausal transition is a stressful period in a woman's life, our prior research has indicated that the menopausal transition, itself, is not a major source of stress for most women. The purposes of these analyses were to: 1) Identify major challenges women reported retrospectively over their 15 years of participation in a longitudinal study of the menopausal transition; and 2) identify women's most positive experiences during the period of the menopausal transition and early postmenopause. **Design:** After 15 years of participation in the Seattle Midlife Women's Health Study, women were asked to describe the most challenging experiences they experienced during that time as well as the most positive experiences. A subset of women completed these open-ended questions as part of the annual health questionnaire (N=95). Data were content analyzed and grouped into categories of challenges and positive experiences. **Results:** Women described challenges that were related to family relationships, work, self, and material resources. Challenges in family relationships involved their husbands/partners, children, parents, and to a lesser extent their in-laws and siblings. The most commonly reported spouse/partner challenge was divorce followed by partner's health problems. Challenges related to children most commonly involved parenting issues, such as children moving in or out of the household or encountering developmental issues. The most common challenge women encountered related to their parents was their death, with caregiving responsibilities the next most frequent. Challenges related to work involved job stress and role overload, e.g. difficulty balancing multiple roles. Challenges related to self involved development of health problems. Only two women reported that their greatest challenge was their experience of menopause-related symptoms (bleeding and hot flashes/mood symptoms each reported by one). Self-acceptance issues were also commonly reported, e.g. accepting that some life goals would not be achieved, coming to peace with the number of healthy years of life they had left to live. The dominant challenges related to material resources involved financial problems and a debt. Lack of health insurance related to employment was mentioned by several women. The most positive experiences women reported during the study included relationships, work, and self. Relationships with children and grandchildren and spouses/partners were mentioned most often followed by positive experiences with friends and spiritual relationships, e.g. with God. Work also was an important source of positive experiences. Women mentioned job or career successes and fulfillment as well as retirement. Self development, growth in career, self confidence, making a difference, and having time for oneself were also mentioned frequently. **Conclusion:** Relationships figured prominently in sources of challenge as well as among positive experiences for women during the menopausal transition, consistent with prior studies of women's lives. Menopause was conspicuously absent among the challenges they noted.

P-113.

Low doses of oral hormone therapy decrease lipoperoxides levels in postmenopausal women

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Objective: To determinate the effect of low doses [LD] of oral hormone therapy on oxidative stress [OS] in postmenopausal women. **Design:** A randomized, double blind controlled trial was carried out. We evaluated 135 patients and were assigned to the three groups. Each group had 45 postmenopausal women. Group 1: Standard dose (SD) (0.625 mg/d of synthetic conjugated estrogens [Sixdin®] plus 5 mg/10d of medroxyprogesterone [MPA]); Group 2: Low dose (LD) (0.312 mg/d of Sixdin® plus 5 mg/10d at 6th mo. MPA); Group 3: Placebo [P]. We measured LPO by TBARS assay as OS biomarker. Tests were carried out at the beginning, 3 and 6 mo. of treatment. An alternative cut-off value of LPO ≥ 0.320 $\mu\text{mol/L}$ was defined on the basis of the 90th percentile of young healthy subjects. **Results:** Of the participants enrolled, 14 dropped out in different time, leaving 39 subjects in SD group and 41 in groups LD and P, who completed 3 assessments (basal,

3 and 6 mo.). At basal time, LPO levels were similar in all groups; at three months we saw a trend to decrease LPO in LD and SD except in P group. After 6 months of treatment, LPO levels decreased significantly in SD and in LD (0.297 ± 0.06 and 0.297 ± 0.04 $\mu\text{mol/L}$, $p < 0.0001$ and $p = 0.001$, respectively). In P group LPO did not change (Figure). We also found that women with high LPO at baseline had a 48% reduction in OS using SD; in LD group LPO diminished 44% and in P group LPO increased 6%, after 6 mo. **Conclusion:** Our findings suggest that LD of oral hormone therapy decreases LPO as an OS biomarker. Both doses have the same trend reducing OS. This work was supported by grant DGAPA-UNAM IN306111 and IN222213, sponsored by Laboratorios Senosiain SA de CV. Trial registration: COF000120.

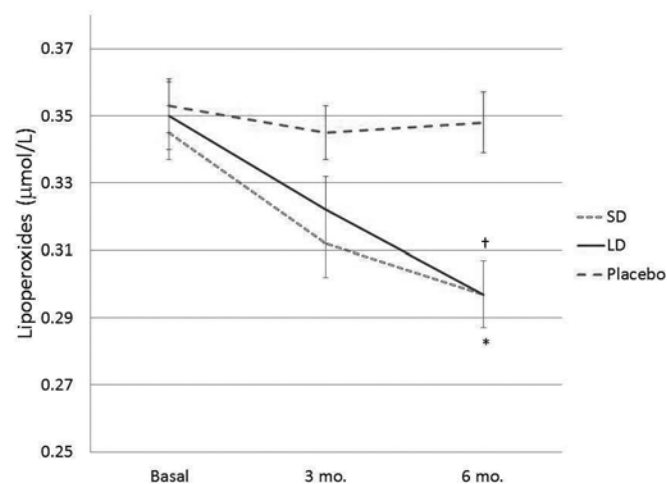


Figure. Lipoperoxides levels in postmenopausal women by treatment, basal, after 3 and 6 mo. Repeated measures ANOVA $p < 0.0001$; Dunnet test as posthoc vs. placebo, * $p < 0.01$, † $p < 0.05$. LD: low dose; SD: standard dose.