Plenary Symposium 1—Presidential Symposium

Newer, Novel, or Unique Cardiovascular Risk Factors: Is It Time to Expand Our Risk Assessment Models and How We Think About Cardiovascular Risk Indicators?

Breast Arterial Calcifications Found on Screening Mammography and Their Association With Cardiovascular Disease

Peter F. Schnatz, DO, FACOG, FACP, NCMP. The Reading Hospital, Reading, PA

Cardiovascular disease (CVD), especially stroke and coronary heart disease (CHD), is the leading killer in the US. The results of previous studies have shown an increased prevalence of radiographically demonstrable calcification, found in the intimal layer of large vessels, in persons with CHD and stroke. Whereas intimal calcifications are strongly associated with morbidity and mortality from CHD and common carotid artery intima-media thickness (CCA-IMT) is associated with ischemic stroke, medial arterial calcifications are thought to have unknown clinical significance. Medial arterial calcifications are characterized by diffuse, fine, and granular deposits along the circumference of small to medium-sized muscular arteries that appear as parallel lines or a ring of calcification depending on the radiographic angle. Breast arterial calcifications (BACs) are medial calcifications of the breast arteries that often appear on mammograms. The reported prevalence of BACs on mammography is 3–29.4%. A benign nature of these medial calcifications has been suggested; therefore, they are inconsistently reported on mammography despite being common findings. Whether the presence of BACs in a woman without CVD predicts her future development of coronary atherosclerosis or ischemic stroke has been questioned. The use of BAC when interpreting mammography may allow for earlier detection and preventive interventions of CHD or stroke risk. Although some screening mammography guidelines no longer recommend testing for women under the age of 50 years, this is unlikely to affect any potential role in CHD screening, as the risk of a major cardiovascular event in women age 45–54 years is only about 0.3%. During this symposium, the association between CVD and BAC will be discussed along with data from our 5 and 10-year prospective cohort study. The objective of this study was to determine whether the presence of BAC's on routine mammography predicts the development of CVD. We found that of the greater than 1,000 subjects who were still eligible for the study, and had BAC data at baseline, 10.9% were BAC positive and 89.1% were BAC negative at baseline. Of the positive group at baseline, 9.8% developed coronary artery disease (CAD) by year 10 whereas only 3.3% of the baseline negative group did (p=.001). After controlling for age, BAC positive women were 2.3 times more likely to have CAD, with a confidence interval (CI) of 1.07-5.07 (p=0.034). Similar finding were observed for stroke. Based on our results, we suggest that BACs should be routinely reported on mammograms and viewed as a marker for the development of CVD. Clinicians noting the presence of BACs on a mammogram report, during a patient encounter, should notify patients that this may be a marker of increased risk, encourage behavior modification (diet, exercise, smoking cessation, etc), and appropriately screen patients for modifiable CVD risk factors (hypertension, diabetes, hypercholesterolemia, obesity, and the metabolic syndrome). 1. Rotter MA, Schnatz PF, Currier AA Jr, O'Sullivan DM. Breast arterial calcifications (BACs) found on screening mammography and their association with cardiovascular disease. *Menopause*. 2008;15:276-81. 2. Schnatz PF, Marakovits KA and O'Sullivan DM. The association of breast arterial calcification and coronary heart disease. *Obstet Gynecol*. 2011;117(2pt1):233-41. 3. Jiang X, Clark M, Juhn A, Singh RK, Schnatz PF. Association of Breast Arterial Calcification with Stroke and Angiographically-Proven Coronary Artery Disease - A Meta-analysis. *Menopause*. 2015; Feb 22(2):136-43.

Plenary Symposium 1—Presidential Symposium

Newer, Novel, or Unique Cardiovascular Risk Factors: Is It Time to Expand Our Risk Assessment Models and How We Think About Cardiovascular Risk Indicators?

Microvascular Disease: Have We Gone as Far as We Can Go With Macrovascular Disease?

Howard N. Hodis. Keck School of Medicine, University of Southern California, Los Angeles, CA

The initial apparent discord between observational study and randomized trial data was remedied through the *timing hypothesis*. Total data show that hormone therapy (HT) initiated in women aged younger than 60 years and/or within 10 years of menopause reduces coronary heart disease (CHD) and all-cause mortality. A large focus of CHD in women has been on coronary artery disease (CAD) and that much of the reduction in CHD results from the effects of HT on large-vessel atherosclerosis. However, CHD is a complex disease resulting from several pathophysiological processes involving large vessel and coronary microvascular disease (CMVD), with and without atherosclerosis, culminating into myocardial dysfunction. The coronary microvasculature is the key regulator of myocardial blood flow, coupling myocardial oxygen supply with demand; an autoregulatory physiologic function of the coronary arterioles. CMVD is important in the pathophysiology of CHD, especially in women in whom healthy vessels, menopause, and HT appear to play important roles in the manifestation of CMVD and ischemia. Postmenopausal women who do not use HT are more likely than HT users to have CMVD. Women with chest pain more commonly manifest with normal-appearing vessels or nonobstructive diffuse atherosclerosis with physiologic vessel dysfunction; 50% of women with chest pain have normal epicardial coronary (large) arteries with myocardial ischemia. These women have physiologic evidence of CMVD manifested as inadequate vasodilator reserve or heightened sensitivity of the coronary microvasculature to vasoconstrictor stimuli. Traditional risk factors for atherosclerosis are not associated with CMVD in women with chest pain in the absence of obstructive CAD. Although there is overlap between large vessel disease and CMVD, the underlying pathophysiology of coronary microvascular ischemia has important clinical implications for women because it concerns ischemic heart disease, cardiomyopathy, and heart failure (HF). HF is a common manifestation of CMVD/ischemia occurring in approximately 2 to 3 million US women in which the 5-year and 10-year mortality rates are 50% and 90%, respectively. HF occurs primarily in the postmenopause, and early menopause is a major risk factor. Every 1-year increase in age at menopause reduces the incidence of HF by 2% to 4%. In women with established HF, HT use reduces all-cause and cardiac mortality by 30% to 40% in both ischemic and nonischemic HF. The DOPS results support the benefit of HT on HF outcome over 10 to 16 years of follow-up. Evidence for a link between menopause and HF and the potential modification of HF with HT is growing. Although data suggest that HT may have a beneficial role in preventing CMVD and in ameliorating its poor outcomes, most studies related to menopause, HT, and CVD have focused on coronary artery atherosclerosis, a late manifestation of CHD. Expansion of the scientific focus to CMVD, noncoronary myocardial disease, diastolic dysfunction, and HF in women is warranted. The major question remains whether early intervention directed at reversing CMVD/ischemia can prevent progression to obstructive CAD and other long-term outcomes. Whether CHD prevention based on the earliest possible intervention guided by physiology will provide greater benefits than current practice of treating traditional risk factors remains open. Current data suggest that earlier intervention with HT based on the physiologic health of the vessel will more greatly benefit the long-term chronic manifestations of CMVD/ischemia relative to delaying prevention until overt anatomical obstructive atherosclerosis manifests much later in life.

Plenary Symposium 1—Presidential Symposium

Newer, Novel, or Unique Cardiovascular Risk Factors: Is It Time to Expand Our Risk Assessment Models and How We Think About Cardiovascular Risk Indicators?

Cardiovascular Disease Risk Factors and Risk Assessment Tools: What Do We Currently Use, and Is It Time to Add Newer Risk Indicators or Change Our Approach to Risk Assessment?

Anita M. Kelsey, MD, FACC, FASE. St. Francis Hospital and Medical Center, Hartford, CT

Assessment of risk for cardiovascular disease (CVD) is essential to make meaningful impact on reducing cardiovascular event rates, the leading cause of death in women in the US. Statistically, 80% of these CVD events can be prevented. Prevention of CVD can be divided into primordial prevention (modification of lifestyle to prevent the onset of risk factors), primary prevention (management of currently present risk factors), and secondary prevention (slow the progression of established CVD to prevent future CVD events). Many tools exist to assess CV risk). Framingham was first to identify risk factors responsible for CVD and developed a risk assessment tool. This tool is used to predict 10 year risk of CVD events given the patient's age, sex, total cholesterol, HDL cholesterol, smoking status, and systolic blood pressure. It may underestimate risk in women since it does not include family history, pregnancy-related problems such as preeclampsia and other emerging risk factors. The Reynolds Risk Score attempted to improve on the Framingham score by adding family history, hemoglobin A1C in diabetics and one inflammatory marker hs-CRP. In 2013 the ACC/AHA published a CVD risk assessment tool as part of the new guidelines to treat blood cholesterol. This risk score includes age, sex, BP, tobacco use, cholesterol, race, and diabetes mellitus status. It was developed with pooled cohort data from several large cohort studies including both black and white, men and women. All of these tools assist in the calculation of risk and aid in the decisions about prevention and treatment of CVD. Unfortunately providers tend to underestimate risk in women, regardless of which tool is used. New tools are necessary because most poorly predict risk for other nonwhite racial/ethnic groups. Novel techniques are emerging to assess risk including breast arterial calcifcation (BAC) on digital mammography. BAC has been found to correlate with coronary CT calcium scoring, be superior to standard CVD risk factors, and equivalent to both Framingham risk and pooled cohort data for identification of high risk women and is additive when women with established CVD are included. This tool provides a unique opportunity to take advantage of routinely performed imaging to further enhance our ability to identify high risk women simply by an additional analysis of a broadly utilized screening tool. Further studies are necessary to demonstrate if use of BAC is the key to uniformly identifying risk in all racial/ethnic groups. All women need primordial prevention: eat a healthy diet, maintain healthy body weight, and participate in aerobic physical activity a minimum of 5 days a week. Women with established CVD (cardiac, peripheral, or carotid artery disease) need secondary prevention: maximal reduction of risk factors and appropriate therapies shown to reduce CV events. Women have substantially worse outcomes than men after CVD events and require aggressive medical management, cardiac rehabilitation, and strict adherence to heart healthy lifestyle. Women are undertreated for known CVD risk factors. Women also benefit from treatment of guideline recommended endpoints including referral to cardiac rehabilitation after a CV event. In women without documented disease, risk assessment should be performed. During this symposium you will become more familiar with these CVD risk assessment tools and where we go from here. Sanghavi M, Gulati M. Cardiovascular Disease in Women: Primary and Secondary Cardiovascular Disease Prevention. *Obstetrics and Gynecology Clinics*, 2016-06-01, Volume 43, Issue 2, Pages 265-285. Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science: A Scientific Statement from the American Heart Association. *Circulation,* 2016; 133: 1-30. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Redue Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *JACC*, Volume 63, No. 25, 2014, Pages 2889-2934. Digital Mammography and Screening for Coronary Artery Disease. Margolies L, Salvatore M, Hecht HS, Kotkin S, Yip R, Baber U, Bishay V, Narula J, Yankelevitz D, Henschke C, *J Am Coll Cardiol Img*. 2016; 9(4):350-360.

Keynote Address

The Evolution of Desire: Strategies of Human Mating

The Evolution of Desire: Strategies of Human Mating

David M. Buss, PhD. University of Texas at Austin, Austin, TX

Modern humans have evolved multiple mating strategies. These include long-term mating, short-term mating, extra-pair mating, mate poaching, and mate guarding. This talk presents empirical evidence supporting evolution-based hypotheses about the complexities of these mating strategies. Since men and women historically confronted different adaptive problems in the mating domain, the sexes differ profoundly in evolved strategic solutions. These differences include possessing different mate preferences, different desires for short-term mating, and differences in the triggers that evoke sexual jealousy. Contexts such as the mating system (monogamy, polygamy), personal mate value, and phase of ovulation cycle influence various aspects of mating psychology and behavior. The talk draws conclusions about the complex repertoire of human mating strategies and their gender-dependent and context-dependent nature.

Plenary Symposium 2

The Natural History of Menopause Symptoms

Vasomotor and Other Symptoms of the Menopause Transition: Prevalence and Risk Factors, Including Racial/Ethnic Differences

Ellen B. Gold, PhD. University of California, Davis, Davis, CA

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 U01NR004061, U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH, or the NIH. The prevalences or vasomotor symptoms (VMS, hot flashes and night sweats), sleep difficulties and vaginal dryness increase in women during the menopause transition (MT), while the prevalence of urinary incontinence (UI) tends to decline through the MT. Based on results from the Study of Women's Health Across the Nation (SWAN) and other longitudinal data, VMS affect 50-80% of women in the MT; urinary incontinence (UI) affects about half; sleep disturbances are reported by 15-40% and vaginal dryness by 20-30% of midlife women. SWAN is a community-based, longitudinal cohort study of women who at baseline were aged 42-52 years, had an intact uterus and at least one ovary, had no current exogenous hormone use, and were not pregnant or lactating. SWAN has a 75% follow-up rate after about 13 years. VMS affect quality of life, result in increased outpatient visits, cost hundreds of millions of dollars for health care and have been associated with cardiovascular risk factors and lower bone density. The prevalence of VMS increases in early perimenopause, peaking in late perimenopause, and is higher in African American and lower in Asian than in white women. In SWAN, the median duration of VMS is 7.5 years, 10 years in women who first reported VMS in early perimenopause, but 4-5.5 years in women who first reported VMS in late perimenopause or postmenopause, and was negatively associated with age at first report of VMS, having a college education, and having greater symptom sensitivity and stress scores. Duration of VMS was longest, 9-10 years, in Hispanics and African Americans but 5-6 years in Asians. In addition to menopause status, higher body mass index (BMI) is a risk factor for VMS in pre- and early perimenopause, but negatively related in late peri- and postmenopause ($p < 0.0001$ for interaction with menopause status for any VMS). Thus, change in weight might have preventive implications, but in SWAN, change in weight was not associated with VMS in pre- and early perimenopause and had an *inverse* U-shape in late peri- and postmenopause (though interaction with menopause status was only significant, $p=0.004$, for frequent VMS), which did not improve prediction of incident VMS beyond that of concurrent BMI. Smoking and prior increased anxiety scores also were significantly associated with increased reporting of VMS and have preventive implications. The incidence of UI tends to decline with progression to postmenopause. Type of UI reported differed somewhat by race/ethnicity: urge UI was reported by more African American and fewer Asian and Hispanic than white women but was more likely to become more frequent in Hispanic than white women and was not associated with menopause status in SWAN. The prevalences of sleep difficulties and vaginal dryness tend to increase with progression through the MT and have been associated with declines in estrogen levels. In summary: VMS, sleep difficulties and vaginal dryness tend to increase with progression through the MT, but UI may decline over this time. The duration of VMS is longer than previously reported with a median of 7.5 years but varies by menopause status and age at the onset of VMS. The prevalence of most of these symptoms differs by race/ethnicity with VMS and urge UI being more prevalent in African American and less prevalent in Asian women, adjusting for socioeconomic and other risk factors; and increased BMI tends to be related to many of these symptoms. These differences in prevalence, duration and risk factors are important for assessing women clinically and for advising them about potential methods for reducing symptoms, eg, maintenance of a healthy weight, and about the anticipated duration and likely natural course of some symptoms over the MT.

Plenary Symposium 2
The Natural History of Menopause Symptoms

Cross-Cultural Menopause Symptoms

Lynnette L. Sievert, BSN, PhD. Department of Anthropology, University of Massachusetts, Amherst, Amherst, MA

The frequency of symptoms associated with menopause varies within and across populations. In-depth cultural ethnographies have documented variation in the meaning and experience of menopause. Investigators using semi-structured questionnaires have asked the same questions in the same way to make careful comparisons of symptom frequencies across multiple countries; across ethnic groups within the same country; and between migrants, their new neighbors, and women still residing in their country of origin. These studies demonstrate the importance of language by showing how the use of different words (e.g., for hot flashes) results in different symptom frequencies even within the same population. The use of ambulatory hot flash monitors along with semi-structured questionnaires has found that some cross-population variation in hot flash frequencies is due to differences in sensing, noting, and/or reporting symptoms rather than differences in underlying physiology. By studying symptoms associated with menopause across multiple contexts, it is possible to identify the universals associated with hormonal changes at midlife as well as cross-population differences. For example, there is some evidence that the pattern of diurnal variation in hot flashes changes with latitude. Temperature and humidity may explain a smaller than expected proportion of the variation in hot flash report. Cultural differences in women's clothing are associated with where hot flashes are felt on the body and the frequency of hot flashes. Religion influences how women dress, as well as the cultural significance of symptoms. For example, heavy menstruation and urinary incontinence interfere with prayer – a necessary personal and public demonstration of faith in many Muslim countries. Postmenopausal sexuality also has religious connotations. Some differences in symptom frequencies across populations are due to characteristics that vary by culture, such as norms related to women's smoking habits, alcohol intake, or physical activity; diet and weight; access to birth control and reproductive history; level of education and socioeconomic status; and sources of stress. These sociocultural variables can modify the underlying biology of menopause. Factor analyses of symptom frequencies have shown variation in symptom clusters across countries, such that emotional and somatic symptoms are intertwined in some countries but clearly distinct in others. In addition, there is variation in attitudes toward menopause, the particular physical or emotional phenomena believed to be associated with menopause, and what women think is culturally appropriate to discuss with clinicians. Clinicians should also keep in mind cohort effects and differences in generation of migration when considering variation in menopause symptoms.

Plenary Symposium 3

Current Controversies in the Medical Management of Ductal Carcinoma in Situ

DCIS: Surgical Treatment

Monica Morrow, MD. Memorial Sloan Kettering Cancer Center, New York, NY

The incidence of DCIS has increased substantially with the widespread uptake of screening mammography, yet incidence of invasive carcinoma has not declined in parallel. This coupled with several studies from the SEER registry documenting breast cancer specific survival rates greater than 95% regardless of the type of surgical therapy used for DCIS have caused some to question whether surgical treatment is necessary for all cases of DCIS. This is pure speculation since it is unclear that a good outcome with treatment translates into a good outcome without treatment. Current surgical management approaches to DCIS include mastectomy, lumpectomy and radiotherapy (RT) and lumpectomy alone. A compelling argument for surgery in DCIS is to exclude the presence of invasive cancer. Overall, 26% of lesions diagnosed on core biopsy as DCIS will contain invasive carcinoma, and even in low risk lesions (size ≤2cm, non high grade), 20% have invasive cancer. Recent prospective studies examining the outcome of management of pre-defined low risk subsets of DCIS treated with excision alone demonstrate a substantial risk of recurrence and invasive cancer development. In the ECOG E5134 trial, patients with low or intermediate grade DCIS 2.5cm or less in size (n=561) and those with high grade DCIS ≤1cm in size (n=104) were treated with excision to margins ≥3mm and have now been followed a median 12.3 years. The 12 year rates of local recurrence were 14.4% and 24.6% respectively, and 50% of recurrences were invasive. In contrast, in a cohort with the same non-high grade characteristics randomized to lumpectomy alone or lumpectomy and RT, the 8yr rate of local recurrence in the RT arm was 0.9%. A subset of patients with DCIS who do not benefit from radiotherapy has not been identified in randomized trials. It is clear that mortality is a poor metric for judging DCIS treatment outcomes since it is low regardless of treatment choice. However, rates of local recurrence at 10 years range from 2.6% after mastectomy to 25.5% after lumpectomy alone, with 50% being invasive. Invasive local recurrence has been shown in randomized trials of DCIS treatment to increase breast cancer mortality. Although critics of current DCIS therapy are calling for less treatment, studies of factors influencing patient treatment choices in DCIS and invasive breast cancer have shown that avoidance of recurrence of any kind is the most important influence on their decision. Mastectomy rates are highly correlated with the patient being the primary decision maker, increasing from 5% when the surgeon selects therapy to 16% when the decision is shared and 26% when the patient is the primary decision maker. The role of the surgeon in managing DCIS is to determine when mastectomy is medically necessary due to extent of DCIS in the breast or inability to receive radiotherapy. The risk of local recurrence and breast cancer death with lumpectomy alone, lumpectomy and radiotherapy and mastectomy should be discussed and competing causes of mortality considered. For the majority of women with DCIS, personal preference is a major factor in the choice of therapy. At this time, observation without surgery is not a standard approach outside of a clinical trial except in patients with severe co-morbidity.

DCIS—Conservative Nonsurgical Management—The Problem of Overdiagnosis: What Is the Path Forward?

E. S. Hwang, MD, MPH. Duke University Medical Center, Durham, NC

The term "overdiagnosis" has been used to define those conditions that appear to be early cancer, but may not be destined to cause symptoms or death during a patient's lifetime. This is an emerging issue in many cancers for which population based screening has been adopted, including prostate, thyroid, and breast cancer. The burden of overdiagnosis that stems from mammographic screening has been estimated to be as high as 1 in 4 patients diagnosed with breast cancer; one study estimates that the annual national expenditure incurred by DCIS overtreatment may be as high as $240 million. Ductal Carcinoma In Situ (DCIS) was once an uncommon breast lesion but now comprises 20-30% of new mammographically detected breast cancer. In the United States over 50,000 patients are diagnosed with DCIS annually. This is in large part due to the widespread implementation of screening mammography, where DCIS most commonly presents as microcalcifications in the absence of other clinical findings. DCIS has been traditionally considered as a precursor to invasive disease; however this paradigm has been challenged due to the fact that although the incidence and treatment of DCIS has risen there has not been a concomitant decline in the incidence of invasive breast cancer. Although some lesions will likely remain clinically insignificant over an individual's lifetime, there are more aggressive lesions with invasive components that require urgent intervention. The clinical and molecular discriminants between DCIS that is low-risk, compared to those at high-risk is a topic of active investigation. Models of clinical, pathological and molecular prognostic factors are currently being explored and validated. Ideally, better risk stratification would allow patients with low-risk DCIS to be treated with a more minimalistic approach, including omission of radiation or surgery in favor of active surveillance. Aggressive treatment would then be limited to those individuals with high-risk disease. In addition to the added morbidity that can be avoided from omitting surgery/radiotherapy in low-risk DCIS, the cost of overtreatment to the health care system in the United States from such a risk-driven approach could be reduced. The change in the management of DCIS will require better decision support tools and evaluation of tradeoffs, as are in common use for management of men with early stage prostate cancer. Clear communication of choices and possible treatment outcomes are essential to a shift from "treatment" to "management" of preinvasive conditions. Research to advance imaging and surveillance, risk stratification and decision support are ongoing, and clinical trials have been launched to provide evidence on which to base future treatment decisions for DCIS, with the end goal to optimize patient health and minimize disease morbidity.

Plenary Symposium 4

NAMS 2016 Hormone Therapy and 2015 Nonhormonal Management Position Statements

Hormone Therapy: 2016 NAMS Position Statement

JoAnn V. Pinkerton, MD, NCMP[2,1]. [1]The University of Virginia Health System, Charlottesville, VA; [2]The North American Menopause Society, Pepper Pike, OH

The NAMS 2016 Hormone Therapy (HT) Position Statement Advisory Panel comprised more than 20 experts in menopausal women's health and HT who reviewed the literature on HT since the publication of NAMS' 2012 HT Position Statement. Over a 9-month period, the panel developed evidence-based clinical guidelines for the use of HT in postmenopausal women using levels of evidence to identify strength of recommendations and quality of evidence. The position statement was written through at-times controversial consensus-seeking because the panel often held widely disparate views on the importance and significance of the findings from clinical trials. The clearest benefit for HT for treatment of hot flashes and prevention of bone loss was found to be for those aged younger than 60 years and within 10 years of menopause. Sections include effects of HT on bone, cardiovascular disease, mortality, cancers, mood, and cognition. Effects on primary ovarian insufficiency (POI), oophorectomy, *BRCA* cancer risk, estrogen-sensitive cancers, extended duration, and risk stratification are also reviewed. **FDA-Approved Indications** 1. Vasomotor symptoms (VMS): HT is recommended as first-line therapy for VMS in women without contraindications. (Level 1) 2. Prevention of bone loss: HT may be considered as a primary therapy for prevention of bone loss and fracture in postmenopausal women at elevated risk, primarily for women aged younger than 60 years or within 10 years of menopause. (Level 1) 3. For women with hypoestrogenism caused by hypogonadism, POI, or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause (52 y). (Level II) 4. Genitourinary syndrome of menopause (GSM)/Vulvovaginal atrophy: When isolated genitourinary symptoms caused by menopause are present, low-dose vaginal estrogen is recommended as first-line therapy. (Level 1) **Special Populations** 1. Early menopause: For women with POI or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause. Observational studies suggest that benefits appear to outweigh the risks for effects on bone, heart, cognition, GSM, sexual function, and mood. (Level II) 2. Family history of breast cancer: Observational evidence suggests that use of HT does not alter the risk for breast cancer in women with family history of breast cancer, although family history is one risk, among many, that should be assessed. (Level II) *3. BRCA*-positive women without breast cancer: *BRCA*-positive women without breast cancer are at higher genetic risk of breast cancer, primarily estrogen-receptor negative. For those who have undergone surgical menopause (oophorectomy), benefits of estrogen to decrease health risks caused by premature loss of estrogen need to be considered. (Level II) After appropriate counseling in women without contraindications, systemic HT may be offered until at least the median age of menopause; discussions about longer use should be individualized. (Level II) 4. Extended use: The recommendation using the Beers criteria to routinely discontinue systemic HT after age 65 is not supported by data. Decisions regarding whether to continue HT beyond the age of 60 should be made on an individual basis. (Level III) **Overall Benefit-Risk Ratio** 1. HT is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture. 2. Risks of HT differ for women, depending on type, dose, duration, route of administration, and timing of initiation and whether a progestogen is needed. Treatment should be individualized to maximize benefits and minimize risks, with periodic reevaluation. 3. For women who are aged younger than 60 years or within 10 years of menopause and have no contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for those at elevated risk of bone loss or fracture. Longer duration is more favorable for estrogen therapy (ET) than for estrogen-progestin therapy. For women who initiate HT more than 10 years from menopause or aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater risks of coronary heart disease, stroke, venous thromboembolism, and dementia.

Plenary Symposium 4

NAMS 2016 Hormone Therapy and 2015 Nonhormonal Management Position Statements

Nonhormonal Management of Menopause–Associated Vasomotor Symptoms: 2015 NAMS Position Statement

Janet S. Carpenter, PhD, RN, FAAN. Indianan University School of Nursing, Indianapolis, IN

Vasomotor symptoms (VMS) are the cardinal symptom of menopause. The mainstay of treatment has been hormone therapy but other options are needed because hormone therapy may not be the treatment of choice due to personal preference or medical contraindications. Surveys suggest 50%-80% of midlife women use nonhormonal therapies for VMS management. NAMS last issued a VMS management position statement in 2004 that required updating due to significant advances in the field over the past decade. To create the new position statement, NAMS enlisted clinical and research experts in the field and a reference librarian to identify, review, and summarize available evidence. The librarian used five different electronic search engines to cull relevant literature: Academic Search Premier, Embase, Family and Society Studies Worldwide, PsychInfo, and PubMed. Using 340 original research articles and 105 systematic reviews, the majority of which were published post-issuance of the prior position statement, experts created a document for final approval by the NAMS Board of Trustees. Based on evidence, experts grouped the therapies into 3 categories: recommend, recommend with caution, and do not recommend at this time. Recommend: Studies show cognitive-behavioral therapy and, to a lesser extent, clinical hypnosis to be effective in reducing VMS. Paroxetine salt is the only nonhormonal medication approved by the US Food and Drug Administration for VMS management. Other selective serotonin reuptake/norepinephrine reuptake inhibitors, gabapentinoids, and clonidine show evidence of efficacy. Recommend with caution: Therapies that may be beneficial for alleviating VMS include weight loss, mindfulness-based stress reduction, the S-equol derivatives of soy isoflavones, and stellate ganglion block, but additional studies of these therapies are warranted. Do not recommend at this time: There are negative, insufficient, or inconclusive data suggesting the following should not be recommended as proven therapies for managing VMS: cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, over-the-counter supplements and herbal therapies, acupuncture, calibration of neural oscillations, and chiropractic interventions. Once the position statement was published, there was extensive press coverage of during fall of 2015. By increasing awareness of and incorporating the available evidence into clinical practice, health care providers can help ensure that women receive evidence-based and timely recommendations and appropriate cautions regarding VMS therapies.

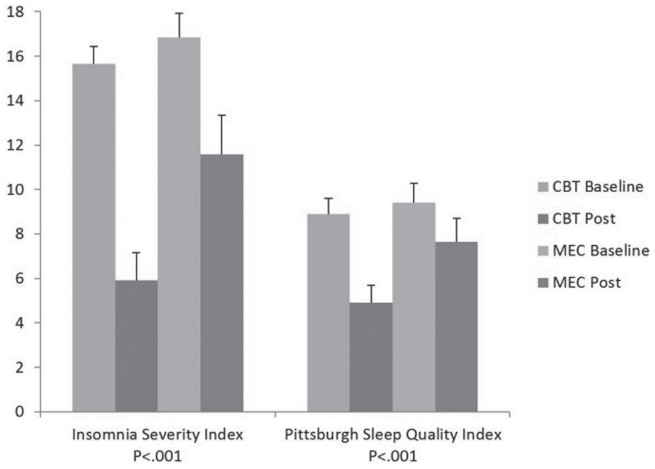
Plenary Symposium 5

Improving Sleep and Vaginal Health in Symptomatic Midlife Women—Evidence From the MsFLASH Trials

Improving Sleep and Vaginal Health in Symptomatic Midlife Women–Evidence From the MsFLASH Trials

Susan M. McCurry, PhD[1], Andrea Z. LaCroix, PhD[2], Caroline Mitchell, MD, MPH[3]. [1]University of Washington, Seattle, WA; [2]University of California, San Diego, San Diego, CA; [3]Massachusetts General Hospital, Boston, MA

Background: The Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) Clinical Trials network was established in 2009. By the end of 2015, the network completed 4 clinical trials testing 7 interventions in approximately 1000 women ages 40-62 with vasomotor (VMS) and other menopause symptoms. The network was refunded in August 2015 to conduct a trial to evaluate vaginal health and sexual function (currently enrolling). We focus this MsFLASH update on 2 areas: 1) findings from the 4th RCT, showing the effects of a telephone-delivered cognitive behavioral intervention on sleep, mood and quality of life, and 2) novel findings from pilot data on the association of vaginal glycogen, serum estrogen metabolites and the vaginal microbiome. Methods: 1) We evaluated treatment efficacy of 8 weeks of telephone-based cognitive behavioral therapy for insomnia (CBT-I) versus menopause education control (MEC). Women, aged 45-60, reporting at least moderate insomnia symptoms (Insomnia Severity Index [ISI] ≥12) and 2 or more daily hot flashes, were followed for 24 weeks. The primary outcome was change in the ISI (baseline to 8 weeks). The secondary outcome was change in the Pittsburgh Sleep Quality Index (PSQI) (baseline to 8 weeks). Exploratory vasomotor, mood and quality of life outcomes were also collected; and 2) Post-menopausal women age 40-62 enrolled in a hot flash treatment trial answered questions about vaginal symptoms (itch, burn, pain, discharge, dryness), provided vaginal swabs and a blood sample at enrollment. Bacterial communities were determined using 16S rRNA PCR and deep sequencing targeting the V3-V4 region, and results clustered by dominant taxa. Glycogen was measured fluorometrically in swab eluate. Total (T) and unconjugated (Un) serum estradiol (E2) and estrone (E1) were measured in blood by ultra-sensitive liquid chromatography/ mass spectrometry. Between group contrasts were assessed via Kruskal-Wallis or Fisher's exact test. Associations between individual taxa, glycogen and estrogen were evaluated by linear regression, and with symptoms by Wilcoxon signed-rank test, both adjusted for multiple comparisons. Results: The CBTI RCT enrolled 106 women. From baseline to 8 weeks, ISI decreased 9.9 points in women receiving CBT-I and 4.7 points in women receiving MEC (P<0.001). Significant group differences were sustained at 24 weeks. Analyses on mood and quality of life are in progress. We will present new analyses examining predictors of sleep outcomes and the effects of the CBTI intervention on the total Menopause-related Quality of Life and its subscales (Vasomotor, Psychosocial, Physical and Sexual Function). The vaginal health pilot study enrolled 88 women of whom 47 (53%) reported ≥ 1 vaginal symptom, mostly mild-moderate in severity. A vaginal microbial community dominated by *Lactobacillus* spp. was associated with a higher serum concentration of estrone (p=0.02), but not estradiol, and was not associated with higher vaginal glycogen. Vaginal itching was associated with the presence of BVAB1 (p<0.01). Conclusions: 1) Telephone-delivered CBT-I was effective for improving sleep in peri- and postmenopausal women with insomnia and hot flashes; and 2) Unlike premenopausal populations, vaginal glycogen and estradiol do not appear to be associated with lactobacilli in the postmenopausal vagina; and symptoms, such as itching, may be associated with BV related bacteria in postmenopausal women.



NAMS/Pfizer Wulf H Utian Endowed Lecture

The History and Basic Science Development of Soy Isoflavones

The History and Basic Science Development of Soy Isoflavones

Kenneth D. Setchell, PhD. University of Cincinnati College of Medicine, Cincinnati, OH

It was our serendipitous discovery of the bacterially derived soy isoflavone metabolite *S*-(-)equol, initially thought to be a new estrogen, in human urine and plasma in the early 1980s that led to a renaissance of interest in the potential role of soy isoflavones for the prevention and treatment of hormone-dependent conditions[1]. Isoflavones are non-steroidal estrogens found in many plants but soybeans and red clover are the richest source of isoflavones. Intestinal bacteria play a crucial role in their metabolism, influencing their biological activity and bioavailability. Estrogen Receptor (ER) binding studies show that isoflavones and the key metabolite *S*-(-)equol, unlike estradiol, have selective affinity for ERb, and based upon the conformational binding to the ER-complex, isoflavones align closely with SERMs such as raloxifene, rather than estrogens[2]. Isoflavones have a broad spectrum of non-hormonal properties, which include antioxidant activity, antiinflammatory actions, the ability to influence signal transduction pathways and to alter gene expression, suggesting a role for these bioactive compounds in many conditions, including those associated with menopause. When consuming modest amounts of soy foods, concentrations of daidzein and genistein, the 2 predominant soy isoflavones attain peak plasma concentrations that far exceed the levels of endogenous estrogens. The metabolite *S*-(-)equol is produced from daidzein by the action of specific species of intestinal bacteria. These bacteria are not present or active in all adults, which led to the hypothesis of the there being distinct phenotypes of 'equol-producers' and 'non-equol producers' that will exhibit differing physiological effects when consuming soy foods[3]. Key areas where soy foods, isoflavones and *S*-(-)equol have potential value in menopause include, managing vasomotor symptomology, cardiovascular disease, breast cancer and skin. Isoflavones have been exploited for their potential to treat hot flushes associated with menopause and while not as effective as estrogen for managing this symptomology, isoflavones can offer some benefit, with responses seemingly associated with the genistein content. The dietary intake of soy and its constituent isoflavones is associated with decreased risk for CVD, the leading cause of death. Data now supports significant beneficial of isoflavones on a number of surrogate markers of CVD risk. Furthermore, sub-analysis according to 'equol-producer' status has unraveled differing responses, even at the level of gene expression, with greater benefits linked to those adults capable of making *S*-(-)equol. The most contentious issue related to soy has been the potential risk isoflavones pose to women newly diagnosed with breast cancer, or those with a family history of breast cancer. Two well-established animal models of breast cancer yield conflicting and opposite conclusions regarding soy isoflavones and breast cancer, yet agreement with regard to the metabolite *S*-(-)equol. Data from these studies fuelled an unjustifiably negative view of soy, linking isoflavones with estrogen without cautioning on the limitations of these animal models. Clinical and epidemiological studies now convincing support the benefits of soy-based isoflavone-rich diets in terms of reducing risk of disease recurrence and mortality in breast cancer survivors. Finally, the antioxidant properties of isoflavones suggest potential benefits for skin. Significant deterioration in skin is associated with estrogen loss after menopause. Isoflavones, and in particularly *S*-(-)equol alters the skin metabolome and influences gene expression in a manner that is beneficial and consistent with anti-aging.

References: 1. Setchell KDR, et al. Non-steroidal estrogens of dietary origin: possible roles in hormone-dependent disease. *Am J Clin Nutr* 1984;40:569-78. 2. Setchell KDR, et al. S-equol, a potent ligand for estrogen receptor-beta, is the exclusive enantiomeric form of the soy isoflavone metabolite produced by human intestinal bacterial flora. *Am J Clin Nutr* 2005;81:1072-9. 3. Setchell KDR, et al. The clinical importance of the metabolite equol - A clue to the effectiveness of soy and its isoflavones. *J Nutr* 2002;132:3577-84.

Plenary Symposium 6

Osteoporosis

Supported in part by grant funding from Merck & Co., Inc.

A Bone to Pick—Osteoporosis Risk Assessment

Carolyn J. Crandall, MD, MS, NCMP. University of California, Los Angeles, Los Angeles, CA

One in two postmenopausal women will have an osteoporosis-related fracture in their lifetimes. Because of the aging of the U.S. population, the number of hip fractures in the U.S. will double or triple by 2040. 54 million older U.S. adults have osteoporosis or low bone mass at the femoral neck or lumbar spine. Osteoporosis is a disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. We will discuss several osteoporosis screening and risk assessment strategies and their application in routine clinical practice. The current United States Preventive Services Task Force (USPSTF) guidelines recommend screening for osteoporosis in women aged 65 years or older as well as women <65 years old who have a 10-year risk of osteoporotic fracture that is greater than or equal to that of a 65-year-old white woman who has no additional risk factors. We will review how the 10-year risk of osteoporotic fractures can be assessed, as well as the evidence that exists regarding USPSTF screening strategy. The National Osteoporosis Foundation (NOF) guidelines recommend screening for osteoporosis in women 65 years or older, but for postmenopausal women ages 50-64, the NOF recommends screening women who have experienced a fracture during adulthood, or a condition (e.g. rheumatoid arthritis) or medication associated with low bone mass or bone loss. We will review and compare the fracture risk assessment tools (e.g. The WHO Fracture Risk Assessment Tool, [FRAX], the Garvan fracture risk calculator). We will offer recommendations regarding the use of FRAX in clinical practice and caveats regarding the use of FRAX. We will review the older, simple tools designed to predict low bone mass—the Osteoporosis Self-Assessment Tool (OST) and the Simple Calculated Osteoporosis Risk Estimation Tool (SCORE). We will discuss how the USPSTF screening strategy compares with these other tools to identify women who will experience future fracture and to identify of women with low bone density. Several osteoporosis screening technologies are available, and we will discuss why dual-energy x-ray absorptiometry remains the standard test for osteoporosis screening. The optimal frequency of screening is unknown and we will discuss recent research that helps to inform decisions about screening frequency. We will review the thresholds that are recommended for treatment of osteoporosis and offer important reminders for how to implement these risk assessment guidelines into routine clinical practice.

Plenary Symposium 6

Osteoporosis

Supported in part by grant funding from Merck & Co., Inc.

The Clinical Decision Tree—Options for Treating Osteoporosis

Tobias J. de Villiers, MD, FRCOG. Department of Gynaecology, Stellenbosch University, Cape Town, South Africa

Postmenopausal osteoporosis is a common condition that leads to an increased risk of fracture. It can be diagnosed by dual x-ray absorptiometry in at risk women and treated before any fracture occurs. All treatment options should be complemented by bone-friendly lifestyle changes. A diet containing 1000-1200 mg of elemental calcium daily is recommended. Calcium supplementation is reserved for the correction of a dietary shortfall. Vitamin D supplementation of 600-800 IU daily is recommended in deficient women. Daily protein intake of 1 mg per kilogram is recommended. Adults should be doing 30 minutes of moderate-intensity physical activity at least five days a week and physical activity to improve muscle strength on at least two days a week. Older adults who are at risk of falls should also incorporate specific exercises to improve balance and coordination on at least two days a week and reduce the amount of time spent being sedentary for extended periods. Measures to prevent falls should be implemented. Bone toxic medications should be avoided. Smoking should be stopped and the intake of alcohol should be limited. NAMS recommends consideration of bone-specific medication in women with osteoporosis or low bone mass who have either a 10-year probability of a hip fracture of 3% or higher or a 10-year probability of a major osteoporosis-related fracture of 20% or higher, based on the US-adapted World Health Organization algorithm (FRAX®). Current FDA-approved pharmacologic options for the prevention of postmenopausal osteoporosis are menopausal hormone therapy, a combination of conjugated estrogens and bazedoxifene, raloxifene, and bisphosphonates. Pharmacologic options approved for the treatment of postmenopausal osteoporosis include bisphosphonates, raloxifene, denosumab, and teriparatide. There are no prospective studies comparing these drugs for antifracture efficacy. Healthcare providers should individualize treatment based on an assessment of the potential benefits and risks of therapy for the individual woman and the effectiveness of a given osteoporosis treatment on reduction of vertebral and non-vertebral fractures. In theory these therapies should reduce vertebral fractures by 50%-70% and non-vertebral fractures by 20%-50%. This is unlikely to be achieved in the real world. Many patients at high risk of fracture are still not offered treatment. Compliance to osteoporosis medication is poor and maybe related to inconvenient dosing schedules, high costs and side effects. The ideal combination of inhibition of bone resorption and stimulation of bone formation, either concomitant or in sequential fashion has not been established The ideal duration of treatment is also not known. Future success will depend on the development of more efficient drugs with fewer side effects.

Plenary Symposium 7

Vaginal and Vulvar Health in Midlife Women

Supported in part by grant funding from EndoCeutics Inc., Shionogi Inc., and TherapeuticsMD

Genitourinary Syndrome of Menopause: Novel Term for Common Conditions

Risa Kagan, MD, FACOG, CCD, NCMP. Department of Obstetrics, Gynecology, and Reproductive Sciences, UCSF, East Bay Physicians Medical Group, Berkeley, CA

In 2013, The North American Menopause Society (NAMS) and the International Society for the Study of Women's Sexual Health (ISSWSH) held a consensus conference to discuss finding a more accurate term to describe the postmenopausal hypoestrogenic state of the genitourinary tract. They agreed that the terms *vulvovaginal atrophy* (VVA) and *atrophic vaginitis* were inadequate to describe the physical signs and symptoms of the vulva, vagina, and lower urinary tract that occur from the decline in estrogen. There was also concern that the term VVA was offensive to many women and that the public use of the word *vagina* was not acceptable. The goal was that the new term would raise awareness among the public and provide a consistent description for research, teaching, and medical care. In 2014, the term *genitourinary syndrome of menopause* (GSM) was formally accepted by both societies and is gradually appearing in the scientific literature. GSM includes symptoms of vulvar or vaginal dryness, discharge, itching, and dyspareunia occurring because of the loss of superficial epithelial cells; reduced collagen and elastin, leading to thinning of the tissue; and loss of vaginal rugae and elasticity, resulting in a narrowing and shortening of the vagina that is a direct result of the decline in estrogen and other sex steroids. The vaginal epithelium can become pale and friable, leading to tears and bleeding. The labia majora can lose subcutaneous fat, resulting in a narrowing of the introitus, fusion of the labia, and shrinkage of the labia and clitoris. There is often reduced blood flow and increased pH, which can lead to the loss of lactobacilli and a marked change in the microbiome. GSM also includes lower urinary tract symptoms such as frequency, urgency, dysuria, nocturia, and recurrent urinary tract infections (UTIs). The urethral meatus often becomes prominent as the introitus shrinks, increasing the risk of infection and irritation. The urethra and bladder trigone are embryologically derived from the estrogen-receptor urogenital sinus tissue, which is also the origin of the vulva, vestibule, and lower portion of the vagina. Because GSM includes symptomatic VVA as well as lower urinary tract symptoms, it is a more comprehensive term. Unlike vasomotor symptoms, which are often pronounced early during the menopause transition and improve over time, the signs and symptoms of GSM are chronic and progressive and will generally not resolve without a therapeutic intervention. GSM has been reported to affect approximately 50% of women, but many women are unaware that these symptoms are the result of a decline in estrogen and that there are proven treatment options available. Published surveys from postmenopausal women have shown that these symptoms negatively affect sexual health, interpersonal relationships, and quality of life (QOL). Even in women who are not sexually active, these symptoms have been reported to affect self-esteem and reduce QOL. Nonhormone water or silicon-based vaginal lubricants and moisturizers may temporarily alleviate symptoms, but they do not alter the underlying physiologic changes responsible for the symptoms. For symptomatic women who do not respond to these remedies, local low-dose vaginal estrogen therapy (ET) in creams, a tablet, and a ring have been approved for the treatment of VVA. Conjugated equine estrogen cream also has the specific indication for dyspareunia. A Cochrane review of 19 randomized trials with 4,162 women reports that all were equally effective in relieving symptoms of VVA. This review also found no increased risk of hyperplasia with local therapy; therefore, the addition of progestogen is not generally needed (however, no study has exceeded 1 y). Local vaginal ET has been reported to help bladder symptoms and reduce the risk of UTIs. The low-dose estradiol ring has also been approved for the treatment of dysuria and urgency. Although systemic ET is approved for VVA, low-dose vaginal ET is recommended if GSM is the sole symptom. In 2013, ospemifene, an oral SERM with agonistic vaginal effects, was approved for moderate to severe dyspareunia. Personal preference and formulary issues are key factors in the shared decision with the patient in initiating therapy for GSM.

Plenary Symposium 7

Vaginal and Vulvar Health in Midlife Women

Supported in part by grant funding from EndoCeutics Inc., Shionogi Inc., and TherapeuticsMD

Itchy and Scratchy: Vulvar Dermatology

Lynette J. Margesson, MD, FRCPC. Geisel School of Medicine at Dartmouth, Manchester, NH

Vulvar itching is a very common and distressing problem, caused by a wide spectrum of conditions. Itching is a sensation that results in scratching and rubbing, often perpetuating the problem. This presentation will focus on the common causes, recognition, and management. Diagnosis of the causative disorder can be difficult because the genital skin is moist, altering the classic skin patterns. Often there are two, three, or four concurrent conditions to sort out. For example, lichen sclerosus, contact dermatitis, candidiasis, and estrogen deficiency may co-exist. **Vulvovaginal atrophy** due solely to low estrogen often causes vulvar itch and burn. When present, it also compounds and confuses all other vulvar diagnoses. Topical estrogen treatment re-establishes barrier function. **Candidiasis**, the most common genital disease, is not as common in menopause and perimenopause but is an important consideration for patients on supplemental patch or topical estrogen, or who are immunosuppressed, diabetic, or using topical corticosteroids. **Contact dermatitis** is the most common cause of itching and irritation. This is usually due to hygiene habits, especially use of irritating cleansers, wipes and excessive friction from rubbing. It must be considered and eliminated in all itchy patients. When itching is overwhelming patients may choose to use caustic and irritating local anesthetics, resulting in more itch and a chemical burn. History is very important. Those not responding to standard treatment must be investigated for allergic contact dermatitis. Accurate customized patch testing will be needed. All the lichens will be discussed as they all are variably itchy. **Lichen simplex chronicus (LSC)** is most important. It is the end stage of the itch-scratch-itch cycle in which relentless itching and resulting scratching results in thick indurated (lichenified) vulvar skin. It is often associated with other skin conditions such as psoriasis and irritant contact dermatitis. Management of LSC is the prototype for managing all vulvar pruritus. Treatment requires hydration, re-establishment of skin barrier function, control of infection, and stopping of all promoting factors. Topical or systemic corticosteroids are needed. Scratching is sometimes called 'itching' by patients. "I *itch* it" means "I *scratch* it." This must be stopped with appropriate early and concurrent psychotropic agents. **Lichen sclerosus (LS)**, the most common cause of chronic vulvar disease and scarring, is also itchy. This can be severe. It is recognized by the classic pattern of whiteness and scarring. Long-term (indeed lifelong) treatment with corticosteroid ointments is imperative. **Lichen planus (LP)** is ten times less common than LS and usually 'burns' or 'scalds' but can be extremely itchy. Recognition can be difficult. Usually there is a variable picture of combined erosions and scarring. Biopsies are often nonspecific. **Psoriasis** is often missed on the vulva because the morphology is atypical. It involves the hairy areas and the skinfolds in an atypical pattern which will be discussed. A commonly missed problem causing pruritus is **cancer**. Intraepithelial or invasive squamous cell carcinoma in some cases can be disproportionately itchy. **Neuropathic pruritus** presents with itch in normal skin. As in neuropathic pain there may be compression or degeneration of itch-sensing nerves. Trauma, radiculopathy or even central nervous system lesions like stroke or multiple sclerosis may be at fault. There may be a history of trauma to pelvis, back or hips. Often it is a diagnosis of exclusion. Treatment requires gabapentin, tricyclics and/or cognitive behavioral therapy. Think multiple diagnoses, think mixtures of yeast and bacteria, think avoidance of chemicals and irritants, think hydration, think nerve damage, think ointments not creams. Think cancer.

Plenary Symposium 8
Menopause and the Brain

Stress and Hypogonadism—A Double-Hit on Executive Function
C. N. Epperson, MD. Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA

Lifetime exposure to stress and adversity has been implicated in sub-optimal cognitive aging. Early life stress (ELS), in particular, impacts the central nervous system at a time when structures critical to executive function (EF) and affect regulation are developing. The potential for ELS to have enduring effects on brain health must be considered in the context of the ovarian hormone fluctuations across the lifespan. The prefrontal cortex and hippocampus, critical to learning, memory, and executive functions, are profoundly impacted by estradiol, progesterone and its metabolites in addition to the stress hormone cortisol. Research suggests that ELS programs the developing central nervous system in such a manner to lead to risk or resilience in the context of future stressors and hormonal changes. It is well established that women are at increased risk for depression during the menopause transition, even if they have no previous psychiatric history. The evidence that menopause-related fluctuations in hormones with natural menopause and abrupt hypogonadism with surgical menopause negatively impacts cognition in a subset of women is rapidly growing. Abrupt or early hypogonadism such as that which occurs with cancer risk reduction salpingoophorectomy (RRSO) or other forms of premature menopause have been associated with significant cognitive decline, particularly if estradiol is not supplemented until the average age of menopause (52 years old). Similarly, women who undergo a premature menopause, defined as prior to age 40, and do not use hormone therapy are at greater risk for dementia in their 8th and 9th decades of life. These data are concerning given that RRSO before the age of 40 is a standard recommendation for the millions of women who are at genetic risk for breast and ovarian cancer. The mechanism by which loss of estradiol unmasks risk for mood and cognitive changes is not fully elucidated. However, evidence from our group and others suggests childhood adversity has enduring effects on neural targets that are also modulated by reproductive hormones. Childhood adversity may "get under the skin" and contribute to risk for EF difficulties, particularly during the transition to menopause, through heightening inflammation. Other evidence suggests that enduring effects of ELS on neurotransmitter systems such as serotonin and glutamate contribute to risk during periods of hypogonadism. This growing literature is complex, but decipherable for the clinician who wishes to be better informed regarding the impact of stress and adversity on cognitive health. A more nuanced understanding of risk factors for sub-optimal cognitive function during periods of hypogonadism will enable clinicians to conduct a risk benefit assessment that takes into consideration the impact of procedures and treatments on brain health.

Plenary Symposium 8
Menopause and the Brain

Depression in the Menopause Transition: Role of Female Reproductive Hormones, Hot Flashes, and Sleep
Hadine Joffe, MD, MSc. Harvard Medical School, Boston, MA

The menopause transition is a period of increased risk for subsyndromal depressive symptoms and, to a lesser extent, to major depression. Reproductive aging related changes in reproductive hormones, hot flashes, and sleep disturbance are menopause-specific factors that have each been associated with an increased risk of mood disturbance. However, the relative contribution of these factors to milder depressive symptoms and to clinically significant depression during the menopause transition has not women has not been as well characterized. In this presentation, we will report findings from clinical and epidemiologic studies that will elucidate the importance of menopause-specific risk factors as predictors of and symptoms that co-occur with perimenopausal mood disturbance. Results of these studies provide important insights into the biological basis of depression in midlife women whose brains are exposed to highly variable changes in female reproductive hormones and whose well-being is highly influenced by hot flashes and associated sleep disruption. Study results will be linked to relevant therapeutic decisions in the management of mood disturbance among this at-risk population of women.

NAMS/Kenneth W Kleinman Endowed Lecture

Considering the Role of Sex and Gender in Biomedical Research

Considering the Role of Sex and Gender in Biomedical Research

Stacie Geller. Center for Research on Women and Gender, University of Illinois at Chicago, Chicago, IL

Despite some advances in gender equality in the biomedical sciences, significant inequalities persist in two general areas. Not only are biological sex and gender insufficiently reported within research studies, but women are also underrepresented as basic and clinical researchers in academic medicine. While these issues may seem unrelated, addressing both will diversify knowledge and interdisciplinary research teams, as well as improve the value of the science produced and ultimately the quality of health care provided. In 1986, the National Institutes of Health (NIH) instituted a policy urging the inclusion of women as subjects in clinical trials. This policy was made into law when Congress passed the NIH Revitalization Act of 1993, which requires that NIH-supported clinical research include women and minorities as subjects. {National Institutes of Health, 1994 #901} The Office of Research on Women's Health (ORWH), with the NIH Office of Extramural Research and Office of Intramural Research, has played a critical role in funding basic research and clinical trials to study women's health and explore the role of sex and gender differences in health outcomes. Despite these initiatives, evidence suggests that sex is still not sufficiently considered as a biologic variable in federally funded research, and studies oftentimes fail to account for the cultural and societal influences of gender in health outcomes. In 2007, women comprised 61.8% of clinical trial participants, yet 75% of federally funded studies published in 2009 failed to report any outcomes by sex/gender. Recent events, such as the FDA's updated Ambien dosage recommendation for men versus women, demonstrate the harmful effects of failing to account for sex as a biologic variable. In recognition of the slow progress, the NIH required that research grants submitted after January 25, 2016, address biologic sex within their research design and added reviewer criteria related to its inclusion. Ensuring enhanced inclusion, analysis, and reporting of sex and gender goes beyond NIH policy, also entailing the efforts of NIH to enforce requirements, journal editors to add review criteria related to sex and gender, and researchers themselves. In addition, increasing consideration of sex and gender requires expanding the proportion of women leading research programs. Latest data from AAMC (2013-2014) shows that although 47% of medical school students are female, only 21% of full professors, 15% of department chairs, and 16% of U.S. Medical School Deans are women. Studies have found that gender diversity within academic research teams improves research quality. The ORWH has implemented various programs to diversify the sciences; however, change has been less than desired. Studies indicate that females have lower publication rates throughout their careers, and are less likely to receive an R01 than men, despite reporting equal likelihood of applying for R01 awards. Additionally, the intra-organizational and network reach of female scientists is smaller than that of men, hindering opportunities for collaboration and publication. Even in the instance of equally qualified men and women conducting comparable work, studies find differential pay between male and female researchers as well as promotion to leadership positions. These factors, both in part caused by and in part exasperated by unconscious interpersonal and institutional biases, lead to higher female attrition within the sciences and academia. Addressing disparities and promoting greater inclusion includes focusing on unconscious bias and putting greater efforts toward mentoring and leadership initiatives for women. Only by partnering efforts to increase inclusion of sex/gender within research design with efforts to diversify the biomedical workforce can we adequately consider the role of sex and gender in biomedical research.

Supported in part by grant funding from Pharmavite LLC

Alternate-Day Fasting
Krista Varady, PhD. Department of Kinesiology and Nutrition, University of Illinois, Chicago, Chicago, IL

Background: Alternate day fasting (ADF) is a novel diet therapy that reduces body weight, but its effect on bone metabolism remains unknown. Objective: This study examined the impact of ADF on markers of bone turnover in a 6-month randomized controlled trial. The effect of ADF versus a conventional diet therapy, daily calorie restriction (CR), was also examined. Methods: Obese subjects (n = 100) were randomized to 1 of 3 groups for 6 months: 1) ADF (25% energy intake fast day, alternated with 125% intake feast day; 2) CR (75% intake every day); 3) control (ad libitum intake every day). Results: Body weight decreased ($P < 0.001$) by ADF (-7.8 ± 1.2%) and CR (-8.8 ± 1.5%), relative to controls (-1.0 ± 0.7%). Fat mass was reduced ($P < 0.01$) by ADF and CR, versus controls. Lean mass remained unchanged in all groups. Circulating osteocalcin and bone alkaline phosphatase did not change in any group. Leptin decreased ($P < 0.05$) by 50 ± 20% and insulin like growth factor-1 (IGF-1) increased ($P < 0.05$) by 11 ± 8% in the CR group versus controls. Leptin and IGF-1 remained unchanged in the ADF group, relative to controls. C-terminal telopeptide type I collagen (CTX) did not change in any group. Total bone mineral density remained unchanged in all groups. Conclusion: These preliminary findings suggest that 6 months of ADF does not have any deleterious impact markers of bone turnover or total bone mineral density in obese adults with moderate weight loss.

Plenary Symposium 9

Nutritional Needs for the Midlife Woman

Supported in part by grant funding from Pharmavite LLC

Vitamin D and Calcium in Midlife Women

JoAnn Manson, MD, DrPH. Harvard Medical School, Boston, MA

Both vitamin D and calcium are essential for bone and musculoskeletal health, but their benefits for non-skeletal outcomes remain controversial. Guidelines for intake of these nutrients have evolved over time. The currently recommended dietary allowance (RDA) is 600-800 IU daily for vitamin D and 1200 mg daily for calcium among midlife women. However, many professional societies recommend higher-dose supplementation for vitamin D, even amounts above 2000 IU daily. Routine high-dose supplementation is not supported by the Institute of Medicine or the US Preventive Services Task Force. Vitamin D has been widely promoted to have benefits beyond bone health, including a role in preventing cardiovascular disease, cancer, cognitive decline, depressive disorders, and autoimmune diseases. However, most of the favorable findings have derived from observational studies, with often discrepant findings from randomized clinical trials. Although low vitamin D levels have been associated with numerous chronic diseases, it remains unknown if there is a cause-and-effect relationship. Observational studies are not able to control fully for confounding factors, such as outdoor physical activity (increased sunlight exposure), general nutritional status, or medical conditions that affect vitamin D levels and metabolism. Several recent studies have implicated calcium supplements in causing an increased risk of heart disease, but these associations remain inconclusive. Overall, "more is not necessarily better" when it comes to intake of these nutrients, and excessive intake should be avoided due to the potential for adverse effects including hypercalciuria, hypercalcemia, kidney stones, and calcium deposits in the arteries or soft tissues. Several large-scale randomized clinical trials of vitamin D, including the *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL), are in progress and will help to provide conclusive answers within the next few years on the role of moderate-to-high dose supplementation.

Plenary Symposium 10

Pharmacologic Agents for Hypoactive Sexual Desire Disorder in Premenopausal Women

Supported in part by grant funding from Valeant Pharmaceuticals North America LLC and Palatin Technologies, Inc.

Data and Women's Preferences Should Inform the Treatment of Hypoactive Sexual Desire Disorder—The Case for Pharmacologic Agents

Sheryl A. Kingsberg, PhD. MacDonald Women's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH

Most sexual problems, have multiple contributing factors—psychological, cultural, and physiological. Therefore, having treatment options that address each component is logical and certainly is the approach we take with men who present with sexual problems or people with depression. While no pill would ever fix a relationship problem, no matter how skilled a therapist, rarely does talk therapy cure a biological one. Recent research has indicated that hypoactive sexual desire disorder (HSDD) may arise from an imbalance of the excitatory and inhibitory neurobiological pathways that regulate sexual desire. Neuromodulators for excitatory pathways include norepinephrine, oxytocin, dopamine, and melanocortins. Serotonin, opioids, and endocannabinoids are neuromodulators for inhibitory pathways. A review of the pivotal trials of flibanserin, the first FDA approved treatment of HSDD, demonstrates that a pharmacologic agent safely and effectively treats HSDD. Flibanserin is a non-hormonal agent approved for use in premenopausal women with HSDD at a dose of 100 mg at bedtime. It is a postsynaptic 5-HT1A agonist and 5-HT2A antagonist. Based on the observed effects of flibanserin on neurotransmitters involved in sexual excitation and inhibition, a mechanism of action for flibanserin has been proposed that involves normalization of CNS neurotransmitter levels to enhance sexual desire. The clinical efficacy and safety of flibanserin in premenopausal women has been reported in 3 large, phase 3, randomized, placebo-controlled trials involving 3548 HSDD subjects (2310 treated with flibanserin and 1238 with placebo). Statistically and clinically significant improvement compared with placebo was demonstrated after 24 weeks of treatment with flibanserin on the number of satisfying sexual events (SSEs), level of sexual desire measured by the Female Sexual Function Index (FSFI) desire domain, and reduction of distress. Up to 60% of women in the clinical trials were deemed responders to flibanserin. Although not approved in postmenopausal women, studies have evaluated the efficacy of flibanserin in this population. A 24-week, randomized, double-blind, placebo-controlled trial with 947 postmenopausal women with HSDD demonstrated efficacy results similar to those in premenopausal women. The most common adverse events in trials were dizziness, somnolence, nausea, fatigue, and insomnia with fewer adverse events seen with bedtime dosing. Additional pharmacologic treatments under investigation will provide more options for women suffering with HSDD. Bremelanotide is an MC4 receptor agonist theorized to have downstream CNS effects that increase arousal and desire. A Phase 2b placebo-controlled, double-blind dose-ranging study of the, on-demand, subcutaneous formulation in 327 premenopausal women with HSDD demonstrated its safety and efficacy. When taken approximately 45 minutes prior to anticipated sexual activity, the 1.75 mg dose showed a statistically significant increase over placebo in SSEs, desire, and decreased distress. The most common adverse events were nausea, flushing, and headache. Two large phase 3 trials have recently been completed using the 1.75 dose in premenopausal women with HSDD. There are also two different drugs under investigation for the treatment of HSDD that combine testosterone with other agents. One combines testosterone with sildenafil (50 mg), a phosphodiesterase type 5 (PDE5) inhibitor and the other combines testosterone with buspirone, a serotonin 5-HT1A partial agonist. The rationale for these combination drugs is that testosterone is thought to increase the brain's response to sexual cues, while the other drug is thought to either enhance genital sexual response (PDE5 inhibitor) or reduce the inhibitory response to sexual cues (serotonin 5-HT1A partial agonist). Psychotherapy and pharmacotherapy both have key roles in treating HSDD. However, a lack of understanding of how CNS trial outcome measures are evaluated perpetuates confusion for some clinicians. High placebo response rates are common among drugs that rely heavily on patient reported outcomes like depression and sexual dysfunction. Demonstrating consistent improvement above placebo is a clear indication that a drug is efficacious.