PLENARY SYMPOSIUM #1

The Neurochemistry of Sexual Desire and Sexual Pleasure

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Although sexual desire and pleasure have been difficult to define objectively, they have behavioral, attentional, and learned components that reliably reflect an individual's trajectory toward interacting with sex-related cues. Sexual desire is thus controlled by brain systems involved in sexual excitation and inhibition. Well over 50 years of pharmacological study has revealed a highly conserved set of excitatory and inhibitory systems in the brains of mammals that link sexual desire and sexual pleasure. This review merges data from the human and animal literatures, focusing on the effects of drugs and conditions that stimulate sexual arousal and desire (excitatory systems) versus those involved in the stimulation of sexual pleasure and reward, sedation, and satiety (inhibitory systems). Brain dopamine systems that link the hypothalamus and limbic system appear to form the core of the excitatory system. This system also includes melanocortins, oxytocin, and noradrenaline in the stimulation of components of sexual desire. Brain opioid, endocannabinoid, and serotonin systems are activated during periods of sexual pleasure that also underlie sexual inhibition or refractoriness and blunt the ability of excitatory systems to be further activated by sexual incentives. Notably, despite the fact that opioid activation during sexual pleasure leads to a short-term sexual inhibition, this activation also sensitizes dopamine release in response to sex-related cues, forming a basis for learned associations, expectations, and a focusing of attention on particular sexual cues when individuals are "horny." Hormones, drugs, or situational events that elevate dopamine, or that blunt serotonin, release and/or postsynaptic binding, appear to be effective in stimulating sexual desire in all mammals.

Sex & Drugs & Rock & Roll

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Sexual desire enhances our lives and has been the focus of research for longer than most midlife women have been alive. In fact, even pharmacologic manipulation of sexual function has an ancient history. Although research and scientific advances have moved in parallel with societal changes, deliberate, clinical manipulation of sexual function, particularly female desire, has not yet achieved widespread acceptance. This presentation will describe the elements of the history of pharmacologic manipulation of sexual function as a means of placing modern interventions in perspective. Likewise, the evolution of Rock and Roll often marks the advancement of our modern understanding of sexual function and desire, and we examine the emerging acceptance of sexual freedom through rock and roll. Ultimately, modern pharmacologic manipulation is better studied and more precise than historical interventions, but has often clinically met disproportionate suspicion and skepticism. Pharmacologic interventions of sexuality should be considered objectively in light of known evidence, clinical need, and under informed consent.

KEYNOTE ADDRESS

Healthy Longevity and Telomeres: What Does Sex Have To Do With It?

Elissa Epel, PhD. Department of Psychiatry, University of California, San Francisco, San Francisco, CA

The telomere/telomerase maintenance system is important in healthy longevity. Shorter telomeres provides a crude measure of biological aging, which specifically is the cell's proliferative potential (time to replicative senescence). Short immune cell telomere length predicts tends to predict longer healthspan (delayed disease onset) in older age and later mortality in some studies. This presentation will review the evidence to date how telomere health is implicated in healthspan, and factors that modulate telomere length, which special emphasis on women's reproductive health factors. Converging research suggests sex and hormone effects on telomere length. Telomeres are longer in women, starting from birth. Telomere length appears to be associated with certain reproductive factors related to higher exposure to estrogen, although not all findings are consistent across studies and require further examination. Longer telomeres are associated with a longer reproductive period, later menopause, and later childbearing. Experimental studies suggest estrogen exposure increases telomerase activity throughout the body, the enzyme that can protect and elongate telomeres. Countering the protective effects of sex hormones, stress mediators such as glucocorticoids, oxidative stress, and inflammation appear to shorten telomere length. Chronic or childhood psychological adversity shorten telomeres prematurely. Life History Theory may help explain the links between early adversity, early puberty, and faster telomere shortening. We will discuss the implications for slowing telomere attrition and aging related conditions.

PLENARY SYMPOSIUM #2

Who Needs Genetic Testing for Breast Cancer?

Holly J. Pederson, MD. Case Comprehensive Cancer Center, Cleveland Clinic, Cleveland, OH

Advances in cancer genetics are rapidly changing how clinicians assess an individual's risk for breast cancer. As patients with a hereditary predisposition to breast cancer are at higher risk and are younger at diagnosis, it is imperative to identify them early so they can benefit from enhanced surveillance, preventive medications, and discussions regarding risk-reducing surgeries. Given increasing demands, limited time, and the abundance of information to be discussed with patients, physicians may find it challenging to assess breast cancer risk, consider genetics testing for appropriate individuals, and counsel patients about risk management options. The process has become even more complex given the expansion in genetics knowledge and the advent of multigene panel testing. Not only is risk assessment crucial, but a delay in diagnosing and treating breast cancer in patients with hereditary and familial cancer risks may represent a worrisome new trend in medical litigation. The American Cancer Society (ACS) estimated that 252,710 cases of breast cancer would be diagnosed in 2017, leading to 40,610 deaths. 12-14% of breast cancers are thought to be related to hereditary cancer predisposition syndromes. This means that, every year, almost 35,000 cases of breast cancer are attributable to hereditary risk. These cases can be detected early with enhanced surveillance, and early detection carries the highest chance for cure. Certain medications can be recommended to reduce risk and breast cancer can be largely prevented with risk-reducing surgery in patients identified with a pathogenic/likely pathogenic variant. **Asking a few key questions can help in stratifying risk** (In taking family history, maternal and paternal family histories are equally important). ● Have you or anyone in your family had cancer? What type, and at what age? If breast cancer, did it involve both breasts or was it triple-negative? ● Is there a family history of ovarian cancer, male breast cancer, metastatic prostate cancer or pancreatic cancer? ● Are you of Ashkenazi Jewish ethnicity? ● Have you or anyone in your family ever had genetics testing for cancer? The hallmarks of hereditary cancer are multiple cancers in an individual or family; young age at diagnosis; and ovarian, pancreatic, or another rare cancer. Metastatic prostate cancer was added as a red flag for hereditary risk after a recent large series found that 11.8% of men with metastatic prostate cancer harbor germline mutations, and similarly, 2-5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA* 1/2 pathogenic/likely pathogenic variant. When possible, genetic testing should be performed first on an affected family member. It is encouraged that testing be done in commercial or academic labs that are clinically approved and validated. If patients are concerned about the cost of genetics testing, they can be reassured that the Patient Protection and Affordable Care Act identifies *BRCA* testing as a preventive service. Medicare provides coverage for affected patients with a qualifying personal history. 97% of commercial insurers and most state Medicaid programs provide coverage for hereditary cancer testing, and most commercial laboratories have affordability programs that may provide additional support. Over the past 10 to 20 years, other breast cancer susceptibility genes (eg, *ATM, PALB2, CHEK2*) have been identified. Next-generation sequencing has become commercially available to sequence multiple genes rapidly and in parallel, and its cost is similar to that of single-syndrome testing. When more than one gene can explain an inherited cancer syndrome, multigene panel testing may be more efficient and cost-effective. Use of multigene panel testing is supported in guidelines issued by the National Comprehensive Cancer Network, the American College of Obstetricians and Gynecologists, and other medical societies. There is an increased likelihood of finding variants of unknown significance when testing for pathogenic/likely pathogenic variants in multiple genes. It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling. If a patient is found to carry a pathogenic/likely pathogenic variant in a gene associated with hereditary cancer, each child would have a 50% chance of having inherited the variant.

Point-of-Care Management of GSM in Women With or at High Risk for Breast Cancer

Stephanie S. Faubion, MD, FACP, NCMP, IF. Office of Women's Health, Mayo Clinic, Rochester, MN

The recommendations from The North American Menopause Society (NAMS) and The International Society for the Study of Women's Sexual Health (ISSWSH) were developed to provide clinicians with an approach to management of genitourinary syndrome of menopause (GSM) in women with or at high risk for breast cancer. GSM is more prevalent in survivors of breast cancer than in the general population and may have an early onset due to cancer treatment or preventive strategies. Given the prevalence of GSM, clinicians should query all women with or those at high risk for breast cancer who are using risk-reducing strategies such as aromatase inhibitors (AI) or risk-reducing bilateral salpingo-oophorectomy about genitourinary symptoms, including vulvovaginal dryness, burning, or irritation; dyspareunia; and urinary symptoms of urgency, dysuria, or recurrent urinary tract infection. The lack of data regarding safety of vaginal hormone treatments for GSM in women with or at high risk for breast cancer specifically has led to avoidance of treatment, potentially adversely affecting quality of life (QOL) and partner relationships. Decision making regarding the type of treatment for GSM includes balancing risk of cancer recurrence (impacted by stage, grade, presence of invasive disease, hormone receptor status, use of endocrine therapy, time since diagnosis) with the severity of symptoms and impact on QOL. Based on consensus in the absence of definitive data, women with lower risk of recurrence vs higher risk; hormone receptor negative disease vs hormone receptor positive disease; use of tamoxifen vs AI who are experiencing severe symptoms, impairment of QOL, and have failed nonhormone options, may be more attractive candidates for vaginal hormone therapy. Counseling women with or at high risk for breast cancer about management options for GSM includes a shared decision-making approach and, when hormone-based treatments are considered, consultation with the woman's oncology team. Nonpharmacologic treatments, including vaginal moisturizers for maintenance of vaginal moisture and vaginal lubricants for comfort with sexual activity, are generally considered initial treatment strategies, although efficacy data are limited. Dilator therapy, vibratory stimulation, and pelvic floor physical therapy may help reduce pain with vaginal penetration. Although randomized controlled clinical trial data regarding the risk of breast cancer or cancer recurrence with the use of vaginal estrogen are lacking, observational data support the relative safety of local estrogen. Intravaginal dehydroepiandrosterone (DHEA) approved

by the FDA has not been studied in survivors of breast cancer, nor have there been studies directly comparing it to vaginal estrogen in terms of efficacy or hormone levels. As such, no recommendation can be made that DHEA is a safer option than vaginal estrogen for women with or at high risk for breast cancer. Despite its antiestrogenic effects on the breast in preclinical trials, the selective estrogen receptor modulator ospemifene has not been studied in women with or at high risk for breast cancer and is not FDA approved for use in these populations. Topical lidocaine is a nonhormone pharmacologic option that has been shown to relieve insertional dyspareunia in survivors of breast cancer. Preliminary data suggest vaginal lasers have the potential to alleviate GSM symptoms without the use of hormones, although longer-term, sham- or placebo-controlled trials and additional economic analyses are needed. Specific populations of women are addressed and include women at high risk for breast cancer; women with estrogen receptor positive breast cancer; women with triple negative breast cancer; and women with metastatic disease. Treatment should be individualized, taking into account recurrence risk, severity of symptoms and impact on QOL, and personal preferences, with nonhormone options offered as first line therapies for symptom management. Consensus-based recommendations offer clinicians caring for this population of women some guidance regarding therapeutic decision making in the absence of clinical trial data. Additional research evaluating the safety and efficacy of existing therapies, including vaginal estrogen, DHEA, ospemifene, and laser therapies is needed.

PLENARY SYMPOSIUM #3

Perimenopause as a Neurological Transition State: Emergence of Vulnerabilities to Neurodegenerative Disease

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Worldwide, >850 million women are 40-60 years of age during which the endocrine transitions of perimenopause, menopause, and postmenopause will occur. Alzheimer's disease (AD) prevalence is greatest in postmenopausal women and is proceeded by 10-20 year preclinical/prodromal period. The ~20-year separation between average of menopause and age of AD diagnosis is a critical transition period for identifying initiating mechanisms of AD and therapeutic targets to prevent, delay, and reverse AD prodromal endophenotype. To identify key drivers of Alzheimer's risk in women, we conducted preclinical and clinical analyses. Transcriptomic, metabolomic, electrophysiological, ^{18}FDG-PET and 7T-MRI analyses were conducted in rodent models of human endocrine and chronological aging. Bioinformatic pathway analyses was followed by hierarchical clustering to identify activated gene networks and interactions between enriched pathways. Mechanistic discovery outcomes served as the framework for clinical analyses in pre, peri, and postmenopausal women. For comparison, men were matched in age. Women and men, 40-60 years of age, underwent volumetric MRI, ^{18}FDG–PET and PIB–PET (bamyloid (Ab) deposition) brain imaging. Cytochrome c oxidase activity (COX) was determined in platelet derived mitochondria. Two distinct aging programs emerged: chronological and endocrine. Early endocrine aging transition was characterized by decline in bioenergetic gene expression which was confirmed by deficits in ^{18}FDGPET, mitochondrial function, and long-term potentiation. Bioinformatic analysis predicted insulin/insulin like growth factor-1 and AMPK/PGC1a signaling pathways as upstream regulators. Later endocrine aging transition was accompanied by rise in genes required for fatty acid metabolism, inflammation, and mitochondrial function. An increase in fatty acids and fatty acid metabolism was coincident with rise in brain ketone bodies linking bioenergetic deficits early in aging with later age development of white matter degeneration. Bioinformatic pathway analyses indicated association of bioenergetic pathway decline with rise in genes involved in AD. Mechanistic outcomes were paralleled in human brain imaging analyses indicating that compared premenopausal, perimenopausal and menopausal women across endocrine aging and to age matched men. During endocrine aging, women exhibited increased indicators of AD endophenotype, including hypometabolism, increased Ab deposition, and reduced gray and white matter volumes in AD vulnerable regions. AD biomarker abnormalities were greatest in menopausal women, intermediate in perimenopausal women, and lowest in control women and men. Ab deposition was exacerbated in APOE4 positive menopausal women. Collectively, these findings indicate that endocrine and chronological aging transitions are critical periods for women during which vulnerability for later life risk of Alzheimer's and other age-associated neurological disease can emerge. *Research supported by National Institute on Aging P01-AG026572; R37AG053589 and The Women's Alzheimer's Movement*

A Scientific Update on Alzheimer Disease: Etiology, Diagnosis, and Treatment

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We will summarily review recently published criteria for the diagnosis of dementia due to Alzheimer's disease (AD) (McKhann et al, 2011, *Alzheimer's & Dementia*), mild cognitive impairment due to AD (Albert et al, 2011, *Alzheimer's & Dementia*), and Preclinical AD (Sperling et al, 2011, *Alzheimer's & Dementia*). Pivotal to each of these revised criteria, we will discuss the role of biomarkers in the diagnostic process, compare the relative value of biomarkers alongside cognition in predicting progression to dementia, and discuss when and whether biomarkers are helpful in this process. In 2010, the National Institute on Aging and Alzheimer's Association convened workgroups to revise the three-decades-old criteria for the diagnosis of AD (McKhann et al 1984). In addition, they convened two additional workgroups on establishing diagnoses for MCI as well as research criteria for the diagnosis of preclinical Alzheimer's disease. With the publication of these recent work groups' recommendations, it is clear we have entered an era increasingly focused on the role of biomarkers in disease detection, diagnosis, and predicting clinical outcome. We will review the value of biomarkers in the early detection and summarize how they are increasingly used in clinical trials on treatment and prevention. Seeking to refine diagnostic and prediction models, in a series of studies we have compared two methods of diagnosing MCI: conventional Petersen/Winblad criteria and an actuarial neuropsychological method we have put forward. Results from these studies suggest that the conventional method is susceptible to diagnostic errors, whereas actuarial neuropsychological criteria yields dissociable cognitive subtypes (eg, amnestic, dysnomic, dysexecutive), significant AD biomarker associations, more stable diagnoses, and greater percentages who progress to dementia than conventional MCI diagnostic criteria. Findings support refining MCI diagnoses by incorporating more comprehensive neuropsychological methods, with resulting gains in characterization of specific cognitive subtypes, biomarker associations, diagnostic stability, and prediction of outcomes. Additional developments have called into question the specific uses of the biomarker strategies identified in these criteria, and we may be in the midst of a paradigm shift in our understanding of the development of AD. For the prior decade or more the amyloid cascade hypothesis (see Musiek & Holtzman 2015) has predominated research, drug discovery, clinical trials, and provided the framework underlying the revisions to diagnostic criteria. However, many biomarker studies do not conform to its temporal sequence, in which amyloid accumulation is presumed to occur first, then tangle-based neurodegenerative changes, then cognitive and functional declines. In addition, the prior decade of clinical trials, many of which have centered on clearance of amyloid, have summarily failed. Another long-standing theory that neurofibrillary tangle (NFT) pathology proceeds along well-defined predilection sites beginning in the temporal lobe (Braak & Braak 1991) has been modified by the same author to suggest that the pathologic process instead commences with the formation of tangle material in the lower brainstem (Braak et al 2011) and spreads upward to cortex. Importantly, the time course of these initial pathological accumulations in brainstem and its projections to cortex appear to begin well before amyloid accumulates (Braak & Del Tredici 2015) findings that sharply contrast with the amyloid cascade model. The notion that amyloidosis *is* Alzheimer's disease is giving way to a broader conceptualization that the preclinical phase of the disease may be driven by brainstem tauopathy and migration of this tangle pathology to cortex, most of which occurs prior to the amyloidosis associated with AD. The evidence reviewed in this seminar concludes that a multi-faceted approach that integrates biomarker and neuropsychological assessments will likely be needed to characterize the preclinical phase of AD and ends with the suggestion that neuropsychological assessment provides a central and non-interchangeable role in the diagnosis of the older adult, and that cognitive measures are among the best predictors of the initial symptomatic stages of an evolving dementia.

PLENARY SYMPOSIUM #4

KNDy Neurons, Neurokinin 3 Receptor Signaling and the Etiology of Hot Flushes

Naomi E. Rance, MD, PhD. Department of Pathologoy, University of Arizona College of Medicine, Tucson, AZ

Estrogen withdrawal in postmenopausal women leads to a rise in LH secretion from the anterior pituitary gland and dramatic cellular changes in the human hypothalamus. In postmenopausal women, there is hypertrophy and increased gene expression of a subpopulation of neurons that express estrogen receptor alpha.[1,2] These neurons are called KNDy neurons based on the co-expression of kisspeptin, neurokinin B (NKB) and dynorphin. The importance of KNDy neurons in reproduction is underscored by the discovery that patients with mutations in the genes encoding NKB or kisspeptin are infertile and do not go through puberty. A consensus is emerging that KNDy neurons play an important role in regulating pulsatile secretion of GnRH. Because KNDy neurons hypertrophy in postmenopausal women in response to estrogen withdrawal, we hypothesized that they could play a role in the generation of hot flushes.[1,3,4] Hot flushes are characterized by the activation of the physiological effectors that dissipate heat, including skin vasodilation, sweating, and cold-seeking behavior. Therefore, understanding the relationship between KNDy neurons and the neural circuits that regulate heat defense could provide clues to the mechanism of flushes. Our experiments in rodents provided evidence that KNDy neurons modulate cutaneous vasodilation (flushing) via projections to NK3 receptor-expressing neurons in the preoptic hypothalamus. A dual function for KNDy neurons in modulating LH pulses and thermoregulatory vasodilation explains why in humans, LH pulses are timed with hot flushes. Recent clinical trials have shown that NK3 receptor antagonists effectively reduce the number and severity of hot flushes, thus providing strong support for our hypothesis.[5] Notably, NK3 receptors are located both on KNDy neurons and in the preoptic area providing two CNS sites for NK3 receptor antagonists to influence thermoregulation. These studies illustrate how basic research on the mechanism of flushes could lead to the development of targeted therapies. References 1. Rance NE, Young WS, III. Hypertrophy and increased gene expression of neurons containing neurokinin-B and substance-P messenger ribonucleic acids in the hypothalami of postmenopausal women. *Endocrinology* 128:2239-2247, 1991. 2. Rometo AM, Krajewski SJ, Voytko ML, Rance NE. Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys. *J Clin Endocrinol Metab* 92:2744-2750, 2007. 3. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, McMullen NT, Rance NE. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. *Proc Natl Acad Sci USA* 109:19846-19851, 2012. 4. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA,

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Recent Advances in the Treatment of Vasomotor Symptoms: KNDy May Be the New Sweet Spot

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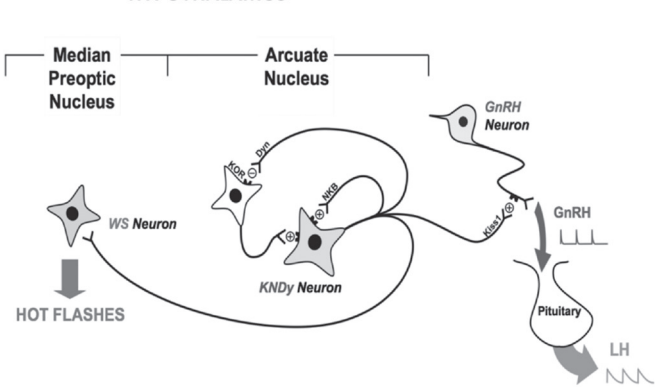
Pulsatile GnRH secretion is governed by a network of estrogen-sensitive neurons, in the hypothalamus, which express **K**isspeptin (**K**iss1), **N**eurokinin B (**N**KB), and **Dy**norphin (**Dy**). These KNDy neurons project to and are immediately adjacent to the thermoregulatory center. KNDy neurons express the key isoform of the estrogen receptor, ERα and are the primary targets for estrogen-dependent GnRH regulation. They drive the pulsatile secretion of GnRH and LH - as evidenced by the fact that blockade of kisspeptin signaling in the brain inhibits GnRH pulses. To date, there are no Federal Drug Administration (FDA) approved products for menopause directed toward the KNDy neuron complex, but drugs first developed for pain control and for mood disorders acting via KNDy are under investigation for the treatment of vasomotor symptoms in the US and Europe. Results from phase 1-2b studies show promise. This session will summarize progress on drug development targeting of the KNDy neuron complex, potential side effects of these new novel drugs and their long term potential as nonhormonal therapies for menopause symptoms.



PLENARY SYMPOSIUM #5

Vaginal Estrogen Safety and Labeling: State of the Science

Carolyn J. Crandall, MD, MS, NCMP. David Geffen School of Medicine at University of California, Los Angeles, CA

There are numerous preparations of vaginal estrogen that are available by prescription. Given the high prevalence of the genitourinary syndrome of menopause (GSM), and the substantial adverse impact of GSM on sexual function and quality of life, it is clinically relevant to assess the safety and efficacy of local vaginal estrogen use. In this presentation, we will review the timeline of availability of preparations of vaginal estrogen and vaginal dehydroepiandrosterone, their class labeling, and the evidence regarding their long-term safety. The class labeling is based on extrapolations of data from clinical trials of systemic hormone therapy which involved substantially higher levels of systemic exposure; it was not based on evidence from clinical trials of vaginal estrogen. Clinical trials regarding the long-term safety of vaginal estrogens have not been performed. However, in a recent study from the Women's Health Initiative Observational Study, we evaluated data from 32,433 postmenopausal women without a hysterectomy and 14,133 postmenopausal women with previous hysterectomy (Crandall, et al, *Menopause* 2017). In this large prospective cohort study, compared to nonusers of vaginal estrogen, postmenopausal women who used vaginal estrogen had similar risks of invasive breast cancer, stroke, colorectal cancer, endometrial cancer, and venous thromboembolism. We did not find evidence for elevated risk of coronary heart disease or death in vaginal estrogen users compared with non-users. These findings should provide reassurance to women and their health providers regarding the safety of vaginal estrogen and help to inform menopausal hormone therapy clinical decision-making.

NAMS/PFIZER WULF H UTIAN ENDOWED LECTURE

Advances in Osteoporosis in the Last 40 Years

J C. Gallagher, MD. Creighton University School of Medicine, Omaha, NE

When I started osteoporosis research in 1970, there were no drugs under study for osteoporosis. Estrogen was used but there was little known about the correct dose for preventing bone loss. In retrospect, we were using doses 5 times too high. At that time fractures were not recognized as a disease but regarded as part of normal aging. From 1970 to 2018 there have been huge advances in the osteoporosis field ranging from epidemiology of fractures to the remarkable invention of precise bone mineral density measurements. There have been major advances in therapeutic options available for patients for prevention and treatment of osteoporosis. In parallel, the advances in the laboratory helped us understand the process of bone remodeling, not only at the macroscopic level but also at the cellular level. This has led to rapid advances in translational research from cellular biology to new therapies exemplified by the development of monoclonal antibodies for treatment of osteoporosis. Further understanding will lead in the future to new small molecules for treatment and perhaps less adverse events. University-based research all over the world has been a leader in most of these advances and pharma support for phase 1-4 studies helped bring these discoveries to the patients. In the osteoporosis field alone, one sees the tremendous value of grant support for university research by national funding agencies such as the National Institutes of Health in the United States and similar agency in other countries. Advances in osteoporosis represents the innovative work of many dedicated and creative scientists during this era. There are less intellectual but formidable challenges that have to be managed. Long-term adherence and persistence with medication if we want to reduce fracture incidence long-term and the fact that following a hip fracture, which represents metabolic bone disease, less than 15 percent of patients are started on appropriate treatment. This issue cuts right across the interface between hospital surgery and primary care. Surely, we can do much better!

PLENARY SYMPOSIUM #6

Goal-directed Management of Osteoporosis

Steven R. Cummings, MD, FACP. Department of Medicine, University of California, San Francisco, San Francisco, CA

Standard current treatment of all patients to prevent fractures starts with prescription of "1st line" drug, usually alendronate. If a patient's treatment is monitored during follow-up, a BMD test may be repeated at 1 or 2 years and the patient reports fractures that have occurred. If her BMD has increased, even a little, and she has had no fracture, then the patient has "responded." What's wrong with this approach? Goal-directed treatment proposes that treatment should aim to achieve goals, such as BMD "T-score" that is at least higher than -2.5 (indicating osteoporosis) and freedom from fracture. For patients who start with a BMD T-score below -3, treatment with an oral bisphosphonate such as alendronate has a very low probability of reaching that BMD goal. Thus, patients with more severe osteoporosis and high risk of fracture, the best initial choice is a stronger agent that is more likely to improve BMD above the goal. In goal-directed treatment, follow-up focuses on progress toward achieving the goal with measurement of BMD and history of fracture – not "response" to treatment. However, response is less important than progress toward the goal. A patient may "respond" with a 2% increase in BMD but remain very far from a goal. In that case, for example, it would be warranted to switch to a more potent treatment despite the biological "response." The presentation will set out a systematic approach to initial assessment and follow-up based on treatment goals.

Bone Turnover Markers in Clinical Practice

Douglas Bauer, MD. Department of Medicine, University of California, San Francisco, San Francisco, CA

Biochemical markers of bone turnover (BTMs) are serum and urine measurements that represent an integrated picture of skeletal remodeling (the linked process of bone resorption and formation). Rates of bone turnover are elevated in some conditions, such as postmenopausal osteoporosis, and reduced in other conditions, such as hypothyroidism. In some, but not all studies, higher bone turnover is independently associated with increased fracture risk in older women, but the optimal level of bone turnover is unknown. Treatment of osteoporotic individuals with effective antiresorptive agents results in rapid and large reductions in bone turnover. A recently completed Foundation for NIH meta-analysis of patient-level data from 13 antiresorptive clinical trials with over 50,000 participants suggest that greater short-term reductions in bone turnover are associated with, on average, greater reductions in spine and non-spine fracture risk. Conversely, anabolic treatments initially increase bone turnover. There is also some evidence that BTMs may be useful to select specific treatments and to identify secondary causes of fragility. An International Federation of Clinical Chemistry and International Osteoporosis Foundation (FCC-IOF) working group recently endorsed procollagen type I N-propeptide (PINP) and C-terminal telopeptide of type I collagen (sCTX) as the preferred serum formation and resorption markers, respectively, for clinical use. However, both individual biologic and laboratory variability complicate the clinical use of BTMs. Collectively, current data suggest that BTMs may be used in certain clinical situations but several ongoing concerns continue to limit their use in routine clinical practice.

PLENARY SYMPOSIUM #7

Update on Heart Failure: Ivabradine and Sacubitril-Valsartan

Michelle M. Kittleson, MD, PhD. Heart Failure Research, Smidt Heart Institute at Cedars-Sinai, Los Angeles, CA

Current guideline-directed medical therapy for heart failure is a triumph of translation medicine where an understanding of neurohormonal activation, translated into medications to block these maladaptive systems, has culminated in improved quality of life and survival for patients with heart failure. The most effective drug therapies for chronic systolic heart failure are those that inhibit the activity of the sympathetic nervous system (SNS) and renin angiotensin aldosterone system (RAAS). These agents include the beta-blockers to inhibit SNS activity and the angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRA) to act on the RAAS pathway. Two new heart failure medications have recently been approved and represent a deepened understanding of neurohormonal mechanisms in heart failure. The first is ivabradine, which inhibits the funny current of the sinoatrial node and lowers heart rate without reducing contractility. In patients already on maximally tolerated beta-blocker dosages, ivabradine reduces the risk of heart failure hospitalization. The second medication is sacubitril combined with valsartan which takes advantage of the natriuretic peptide system and other endogenous vasoactive peptides. Sacubitril, a neprilysin inhibitor, increases vasoactive peptide levels resulting in beneficial effects in heart failure. The angiotensin receptor-neprilysin inhibitor combination sacubitril/valsartan is superior enalapril in reducing death and heart failure hospitalizations. An increased understanding of the sympathetic nervous system and breakthroughs in capitalizing on the natriuretic peptide system have resulted in two additions to the heart failure armamentarium, ivabradine and sacubitril/valsartan. Moving forward, the goal of physicians who treat heart failure patients should be to ensure that all eligible patients receive these important therapies.

Hypertension Guidelines

Martha Gulati, MD, MS, FACC, FAHA, FASPC. Cardiology, University of Arizona College of Medicine-Phoenix, Phoenix, AZ

Hypertension is a leading cause of cardiovascular morbidity and mortality nationally. Based on the most recent NHANES survey from 2011-2014, 85.7 million US adults age ≥20 have hypertension, more than half of whom are women. One in three deaths of women in the US are attributed to cardiovascular disease (CVD). Of the major modifiable CV risk factors, the complete elimination or control of hypertension resulted in the largest impact on CV mortality in women (38% and 7.3% reduction, respectively). Despite the magnitude of its societal impact, awareness, treatment and control of hypertension remain suboptimal in women. The 2017 Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults is comprehensive and is highly applicable to women. Both sex and gender differences will regarding hypertension will be discussed in this presentation, for management of one of the most modifiable risk factor in women.

PLENARY SYMPOSIUM #8

EMPOWIR Study Findings

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There are many different causes of obesity, although the ultimate cause is an imbalance between energy intake compared to energy utilization. Even very minor increases in energy intake over utilization will ultimately cause obesity. Addressing more individualized causes of the underlying problem may help people lose their excessive weight. The adverse effects of being obese is in part due to the area of fat storage. Thus, visceral fat is associated with metabolic syndrome, type 2 diabetes, and increased cardiovascular risks whereas subcutaneous fat may even be slightly beneficial. Visceral fat is also associated with insulin resistance. Therefore, addressing those individuals who have obesity, visceral fat, and insulin resistance may reduce the risks. There are genetic causes of obesity similar to ObOb mice, ie, Leptin deficiency (actually a rare cause of obesity in humans) or genetic abnormalities of the appestat (brain mechanism that causes satiety). There are environmental causes where there are plentiful sources of high caloric, fatty, and sugary foods and snacks available. These may secondarily increase people's appetite resulting in obesity in susceptible individuals. There are diseases that result in abnormalities of the normal satiety mechanisms in the brain, ie, Prader Willi syndrome (actually a genetic cause of obesity). Insulin resistance is another problem that has multiple etiologies not all of which have been identified. Obesity per se results in insulin resistance. Many are genetic with inherent (as well as inherited) insulin resistance due to changes in insulin receptor efficiency or post receptor problems. Physiological factors have also been identified. One of the most frustrating ones is that increased fat tissue itself can cause insulin resistance as summarized by Jianping in *Frontal Medicine* in 2013. Oxidative stress in fat tissue or anywhere else, from any cause, can induce insulin resistance. In fact, in susceptible individuals the insulin resistance itself causes further insulin resistance and secondarily increased intake of carbohydrates which exacerbate the problem. Our study, Enhance the Metabolic Profile of Women with Insulin Resistance (EMPOWIR) was based on Dr. Harriette Mogul's previous data that women who were obese and had insulin resistance (IR) lost weight and maintained the weight loss if treated with a carbohydrate modified diet and metformin (Mogul et al, *Heart Disease*, 2001;3:285). Based on her findings, we set-up a preliminary study as follows with funding from GlaxoSmithKline and the NIH (NCATS). Women aged 35 to 55 who had gained at least 20 pounds since age 20 and had BMI <35 were recruited for the study. After an initial evaluations with a 2-hour intervention with GTT and elevated insulin levels (>100 units under the curve done for 2 hours), there were 4-weekly nutritional workshops explaining the concepts and how to implement the diet. Thereafter, the participants were divided into diet only (D), metformin and diet (M), and metformin + rosiglitazone and diet MR group (MR) for the following 6 months. The next 6 months the diet-only group was randomized into one of the other groups. All subjects lost about 5% of their weight by 6 months (Mogul, Freeman, Nguyen, et al, *PLoS One* 2014;9 e108264). Of note, at 12 months HOMA-IR was decreased in both medication groups. Leptin stayed the same throughout. Adiponectin increased in the MR group. Ghrelin did not rise at 6 months (part of the cause of weight regain). Body composition was measured at baseline and at 12 months and showed a decrease in android fat (likely visceral fat) in all groups (Mogul, Freeman Nguyen, *Endocr Pract* 2016;22:575-586). In conclusion, an easily administered, carbohydrate modified diet and metformin can successfully help insulin resistant obese women lose weight, maintain weight loss, and improve insulin sensitivity as well as reducing visceral fat without increasing ghrelin or reducing Leptin.

NAMS/KENNETH W KLEINMAN ENDOWED LECTURE

Diagnosing American Democracy 2018: Suturing Divides with the Art of Constructive Disagreement

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Political polarization is at an all-time high and is growing with each passing election. The consequences are far-reaching and impinge on the government's ability to govern and pass laws to address the major problems of affordable healthcare, immigration, inequality, and national security. The consequences of polarization, though, are not limited to the political sphere. Polarization also affects how Americans interact with other. Increasingly, people are reluctant to interact with others holding disagreeable viewpoints. Alarmingly often, when Americans actually do interact with people who disagree with them on important matters, these interactions go quite poorly. This presentation identifies how and why polarization has spiked in recent decades leading to greater interpersonal and intergroup conflict, and then reviews research on on-going interventions that aim to promote more constructive disagreement between people on all sides of the pressing political issues.

PLENARY SYMPOSIUM #9

Sleep-circadian Rhythms and Aging in Women: A Bidirectional Relationship

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Sleep and circadian timing are fundamental biological imperatives, and are often challenged by changes in the environment, hormone transitions, unhealthy behaviors, and disease, leading to sleep deficiency. In the past decade, advances in the scientific knowledge of sleep and circadian biology, indicate that sleep and circadian disruption have a central role in the expression and development of cardiometabolic, cognitive, and mood disorders. Sleep deficiency is common in the general population, and even more prevalent in women, with only approximately 40% reporting adequate sleep. There are many factors that contribute to this high prevalence, including biological and lifestyle factors. A study by the National Sleep Foundation demonstrates that insomnia symptoms afflict women, especially older women, disproportionately. This disparity grows as men and women reach middle age and older age, particularly at menopause and perimenopause. Hot flashes, mood disorders, other sleep disorders, and normal changes that occur with aging likely contribute to poor sleep quality in perimenopausal and postmenopausal women. Age-related changes in sleep and circadian rhythm regulation may be a predisposing factor for sleep disturbances. However, with aging there is also increased comorbid medical and psychiatric conditions, which are important contributing factors for sleep disturbance. Symptoms of sleep disturbance should be differentiated from insomnia disorder and circadian rhythm sleep-wake disorders such as advanced and delayed sleep wake phase disorders and shift work. Insomnia disorder is characterized by difficulty falling and or staying asleep that is accompanied by daytime impairment in functioning for at least 3 months. Circadian rhythm disorders may present with symptoms of insomnia, but are due to changes in the circadian timing system. This lecture will review the foundational science of age-related changes and sex differences and how they contribute to sleep and circadian disturbances. In addition, discuss the consequences of sleep disturbance on metabolic and cognitive outcomes, and strategies to enhance sleep and circadian function.

Online Cognitive–Behavioral Therapy Treatment for Insomnia

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The Internet is now a vital resource to hundreds of millions of people around the world, and its uses seem limitless. However, nowhere does it seem more useful than in the healthcare field. One area, in particular, where the integration and utilization of the Internet has skyrocketed is as a tool to deliver behavioral and psycho-social based interventions. These *Internet interventions* are usually derived from effective face-to-face treatments that have been operationalized and transformed for Internet delivery. They are often highly structured, but personalized and tailored to the individual user. They can be deployed as self or semi-self-guided programs, and most are interactive

and enhanced with the multimedia capabilities of the Web. Making behavioral/psychosocial/mental health treatment and prevention programs widely available on the Internet has obvious appeal. Delivering care in this way can help overcome many of the traditional barriers to providing care, including inadequate treatment access, limited trained clinicians, poor geographical distribution of knowledgeable professionals, and expense. They clearly have promise as an efficacious, scalable, and cost effective prevention and treatment option with significant public health impact. Furthermore, interventions can be delivered in a standardized manner with fidelity across a variety of settings. Outcome trials of Internet interventions have consistently demonstrated significant changes in behavior and meaningful symptom improvements. One area that has shown particular promise is the delivery of treatment for insomnia via the Internet. Insomnia is the most common sleep complaint, with approximately 6-15% of the general population worldwide meeting diagnostic criteria. Of particular note, sleep difficulties in peri- and postmenopausal women and have been identified as a key symptom of the menopausal transition. Cognitive-behavioral therapy for insomnia (CBT-I) is an extremely effective treatment for insomnia. However, obstacles to accessing this treatment remain. As a means to overcome these barriers, a number of Internet interventions for insomnia have been developed and evaluated as part of clinical trials. This presentation will provide an overview on the use of the Internet to deliver insomnia treatment. Findings from research trials utilizing these type of programs have demonstrated compelling results, including significant changes in behavior and meaningful symptom improvements. There is strong evidence that interactive, tailored, web-based self-help approaches to addressing insomnia may have longer term impact and may offer an efficacious means to reducing the public health burden of insomnia. However, many programs and applications that are currently available have little scientific basis or empirical validity, and even fewer have been evaluated in rigorous research trials. These issues, including the availability and applicability of current applications, the science behind some of the empirically evaluated programs, and the need for more research more broadly, will be discussed.

PLENARY SYMPOSIUM #10

Four Updates on the MsFLASH Postmenopausal Vaginal Health Study: Quality of LIfe, Sexual Attitudes and Activities, Vaginal Inflammation, and the Vaginal Microbiome

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Background: Bothersome postmenopausal vaginal symptoms are prevalent and adversely affect quality of life and sexual activity. Up to 40% of postmenopausal women have vaginal symptoms presumed to be related to vaginal atrophy. Despite this high prevalence of genitourinary syndrome of menopause (GSM), evidence based information to guide treatment choices is limited. The MsFLASH Vaginal Health RCT demonstrated no significant difference in improvement in vaginal symptoms between women randomized to 1) estradiol vaginal tablet (Vagifem®) + placebo gel or 2) hydrophilic moisturizing vaginal gel (Replens®) + placebo tablet vs. placebo gel + placebo tablet. To better understand these primary results, we evaluated both impact of treatment on other measures, such as quality of life and sexual activity, and biologic characteristics of the vaginal environment. **Methods**: The MsFLASH network conducted a multicenter trial comparing popular treatments for bothersome vaginal symptoms and sexual dysfunction, and created a biorepository of specimens for translational, mechanistic research on the etiology of vaginal symptoms. Recruitment was via mass mailing and Facebook advertisements. The primary outcome was change from baseline to 12 weeks in severity of the most bothersome symptom (MBS) - dryness, itching, irritation, soreness and pain with penetration. Secondary outcomes included quality of life (using MENQOL) measured at 0, 4 and 12 weeks during the trial, frequency of sexual activity measures during the trial and baseline attitudes toward sex. Biologic markers included vaginal cytokines measured in cervicovaginal lavage fluid using MesoScale Discovery, and vaginal microbiota characterized by metagenomic sequencing from vaginal swabs. A subset of 144 women (45 estradiol, 48 moisturizer, 51 dual placebo) with complete sample sets were selected for analysis of cytokines at 0, 4 and 12 weeks. From the larger MsFLASH biorepository, 65 White and 44 Black women were selected. **Results:** Women were randomly assigned to receive Vagifem (N=102), Replens (N=100) or placebo (N=100). Study continuation was high: 293 women provided week 12 data (95% Vagifem, 99% Replens, 97% placebo). No meaningful differences in baseline characteristics were observed between treatment groups. Mean age was 61 (SD 4) years and 88% were white. The mean MBS score was 2.5 (SD 0.6): pain with sexual activity 61%, vaginal dryness 21%, vulvar or vaginal itching 7%, vulvar or vaginal irritation 6%, and vulvar or vaginal pain or soreness 5%. The mean (SD) baseline MENQOL score was 3.3 (3.1) and mean number of days with sexual acts in the first week of the trial was 0.6. The symposium will present results on baseline attitudes toward sex and results for change in menopause quality of life, sexual activity, and vaginal cytokines over the trial. We will present the metagenomic characterization of the vaginal microbiome, any racial differences in these findings and any associations with vaginal symptoms. **Conclusions:** The MsFLASH Vaginal Health Trial assessing hormonal and nonhormonal products has provided valuable evidence to guide treatment decisions for women with GSM. Among women with bothersome vaginal symptoms, a better understanding of quality of life, sexual activity and attitudes, vaginal inflammation and the vaginal microbiome will help guide development of future therapies.