Plenary Symposium 1—Presidential Symposium

The Female Brain: Menopause and Aging

Supported in part by grant funding from Pfizer Inc.

Sex Differences in the Brain

Larry Cahill, PhD. School of Biological Sciences, University of California, Irvine, Irvine, CA

The past 20 years witnessed a remarkable proliferation of data proving that "sex matters" to brain function at all levels, from the functioning human to the molecular level. This lecture captures the enormity of this development, and discusses why the issue of sex influences on brain function is one whose time has finally come.

Plenary Symposium 1—Presidential Symposium

The Female Brain: Menopause and Aging

Supported in part by grant funding from Pfizer Inc.

Women and Brain Aging

Pauline M. Maki, PhD. College of Medicine, University of Illinois at Chicago, Chicago, IL

Alzheimer's disease (AD) is the 6th leading cause of death in the United States. Women are disproportionately affected by AD; almost two-thirds of Americans with AD are women. Age is a primary risk factor for AD. The longer average lifespan of women compared to men is a primary reason why women have a higher prevalence of AD than men. Lifelong, women show an advantage over men in their ability to learn and remember words, stories and other verbal material. During the menopausal transition, women experience a modest but significant decline in verbal memory. Initial evidence indicates that these appear to be temporary and resolve after the menopausal transition. Declines in verbal memory following bilateral oophorectomy are reversed by estrogen therapy, and the increased risk of late-life AD associated with early oophorectomy also appears to be offset by use of estrogen therapy. Later in life, deficits in verbal memory are a key indicator of an early stage of AD known as amnestic Mild Cognitive Impairment (aMCI), which paradoxically is diagnosed more often in men than women. Emerging evidence suggests that women's lifelong advantage in verbal memory might mask the underlying neuropathology of emergent AD until later stages of the disease, so that women are diagnosed later than men and decline more rapidly thereafter. Indeed, studies show a sex difference in the course of AD. After diagnosis, women decline more rapidly than men. Other than a longer lifespan, what might account for the higher rates of AD among women? The strongest genetic risk factor for late-onset AD (i.e., onset after age 65) is a greater risk factor for AD in women than men. That sex difference might be explained by higher levels of the AD biomarker, tau, in women with the genetic risk factor than men. Lifestyle factors and depression might also play a role in the higher prevalence of AD in women. Women exercise less than men and have higher rates of television viewing in adulthood. Observational studies suggest that early use of hormone therapy lowers the risk of AD in women, but this hypothesis has not been tested in a randomized trial. Hormone therapy should not be prescribed for the sole purpose of improving cognition. Midlife women with memory complaints should be advised that complaints are normal and dementia is rare at this age.

Plenary Symposium 1—Presidential Symposium

The Female Brain: Menopause and Aging

Supported in part by grant funding from Pfizer Inc.

Exercising Your Mind and Brain

Arthur F. Kramer, PhD. Beckman Institute for Advanced Science and Technology, University of Illinois, Champaign, IL

In my presentation I will review research conducted in our laboratory, and the field in general, which has examined the extent to which fitness training and physical activity enhances cognition and brain structure and function of adults. The presentation will cover both cross-sectional and intervention studies of fitness differences and fitness and physical activity training. Studies which assess cognition via both behavioral measures and non-invasive neuroimaging measures, such as magnetic resonance imaging, functional magnetic resonance imaging, event-related brain potentials, and the event-related optical signal, will be reviewed and discussed. Finally, I will explore the gaps in the human and animal literature on cognitive and brain health and the manner in which they can be addressed in future research.

Keynote Address

Why Hospitals Should Fly—The Ultimate Flight Plan to Patient Safety and Quality Care

Why Hospitals Should Fly—The Ultimate Flight Plan to Patient Safety and Quality Care

John J. Nance, JD. [1]National Patient Safety Foundation, Seattle, WA; [2]Aerospace Analyst, ABC World News, Seattle, WA

Taking the title from the book by John J. Nance, this is the premier presentation that has been so in demand in the last 6 months in Healthcare (64 presentations by Mr. Nance alone in 2009). This presentation builds on the reality that American Healthcare is, in fact, a gigantic and complex Non-System, and that to achieve real patient safety and quality of care in such a chaotic environment requires building healthcare for the first time into a coherent, interactive system. Inclusive in this revolutionary approach is the fact that the American Hospital cannot serve the patient's best interests as long as it continues in the tradition of Ben Franklin (the creator of the first American Hospital) as an institution built only for doctors, not patients. The hospital MUST become a true unified entity in which even the outside physicians consider themselves an integral and proud part of the team - rather than independent practitioners merely renting space for their patients in a farmer's market. In addition, this lecture highlights the essential role of the physician AS a leader (rather than a commander) in orchestrating the amazingly effective shift to Collegial Interactive Teamwork based on open communications, caring and trust. How the hospital board and C-suite become essential to this process of change - and how it can all be torpedoed by a chief financial officer who refuses to understand the broader human effects of each cost-cutting decision - will upend your previous understanding.

Plenary Symposium 2

Perimenopausal Contraception

Supported in part by grant funding from Bayer Healthcare and Pfizer Inc.

The Contraceptive Needs of Older Reproductive-Aged Women

Amanda Black, MD, MPH, FRCSC. [1]Shirley E. Greenberg Women's Health Centre, Ottawa, ON, Canada; [2]Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, ON, Canada

The perimenopause is a transitional period characterized by fluctuating hormone levels, irregular menstrual cycles, and the onset of vasomotor symptoms that may increase in severity as menopause approaches. With increasing age, fertility decreases but pregnancy is still possible. Pregnancy over the age of 40 is associated with increased risks of chromosomal abnormalities, miscarriage, and pregnancy complications. Hence women should be counseled that although there is a natural decline in fertility as they get older, effective contraception is still required to prevent an unintended pregnancy. Menopausal hormone therapy does not provide effective contraception. Many factors influence the choice of contraceptive method for older reproductive-aged women, including the frequency of intercourse, the natural decline in fertility, the desire/need for non-contraceptive benefits, abnormal uterine bleeding, the completion of child-bearing, and concurrent medical conditions. The odds of consistent contraceptive use in women over 40 may be lower compared to younger women, possibly due to a lower perceived risk of pregnancy. None of the available contraceptive methods are contraindicated based on age alone. For most contraceptive methods, the benefits usually outweigh the risks in women over the age of 40. However, with increasing age, women may develop incidental medical conditions that become more significant risk factors and possibly impact contraceptive choice. Methods such as IUDs, implants, and permanent contraception may be preferred for older reproductive age women because of their high effectiveness, lack of association with cardiovascular events, lack of effect on bone mineral density, and treatment of abnormal/heavy uterine bleeding (LNG-IUS). Combined hormonal contraceptives may be preferred for some women due to non-contraceptive benefits such as menstrual management, decrease in endometrial and ovarian cancers, protection against endometrial hyperplasia, and alleviation of vasomotor symptoms. Progestin-only methods are associated with a decrease in endometrial cancer and alleviation of vasomotor symptoms but this must be balanced against the effect on bone mineral density (DMPA). Barrier methods may be well suited to some women, particularly if intercourse is infrequent. Women over 40 years of age should be reminded to use condoms for protection against STIs, even after contraception is no longer required. The contraceptive needs of older reproductive age women should be re-evaluated regularly. There is limited evidence to determine when to stop particular contraceptive methods. Considerations for stopping/switching include method-associated health risks with increasing age, decreasing fecundity, alternative contraceptive methods, and menopausal status. Women should continue to use contraception until menopause is confirmed. Women who have a LNG-IUS 52 mg inserted at age 45 or later can use the device for 7 years (off label use). Women using a Cu-IUD should have it removed once menopause is confirmed. Women using a combined hormonal contraceptive method may consider switching to a progestin-only pill or non-hormonal method at the age of 50. In general, non-hormonal contraception can be stopped 1 year after the last menstrual period in women over age 50, and 2 years after the last menstrual period in women under age 50. The probability of menstruation (and possibly ovulation) after a year of amenorrhea for women over age 45 is estimated to be between 2% and 10%. Natural sterility can be assumed after age 55 in amenorrheic women. In women using contraceptive hormones, FSH levels may be used to help diagnose menopause but only in women over age 50 on progestin-only methods. It is not a reliable indicator of ovarian failure in women using combined hormonal contraceptives even if measured during the hormone-free interval. Progestins do not have a significant effect on FSH levels. If a woman is over the age of 50 and amenorrheic on the progestin-only pill, she may stop contraception one year after having elevated serum FSH levels on 2 separate occasions at least 6 weeks apart.

Plenary Symposium 2

Perimenopausal Contraception

Supported in part by grant funding from Bayer Healthcare and Pfizer Inc.

Contraceptive Options for Perimenopausal Women with Health Challenges

Anita L. Nelson, MD. David Geffen School of Medline at UCLA, Manhattan Beach, CA

Perimenopausal women face a substantially reduced risk of pregnancy, but pregnancy at that time in life may be even more impactful from a medical as well as social perspective than for younger women. However, perimenopausal women as a group have higher prevalence of medical conditions and can suffer more serious complications from those conditions. All of this present challenges for selecting contraceptive methods. The US Medical Eligibility Criteria have simplified the evaluation of women with medical problems and have liberated clinicians from the theoretical concerns perpetuated by product labeling. Despite impending menopause, top tier methods are still recommended as first line choices not only because of their low failure rates in typical use, but also their convenience and important noncontraceptive benefits. The higher dose LNG-IUD is the most effective treatment for heavy menstrual bleeding. All three LNG IUDs offer endometrial protection from unopposed estrogen during the perimenopausal years and after menopause (with or without menopausal hormone therapy). The ENG-implant may diminish risk of excessive bleeding. Copper IUDs provide hormone free top tier pregnancy protection, which is very important to women at increased risk for or with increased concern for breast cancer. DMPA is an excellent choice if amenorrhea is induced; concerns of BMD will not adversely impact longer term bone strength or fracture risk, but may add to complaints about vaginal dryness. Progestin-only pills are excellent choices from a safety stand point and can replace male condoms as a transitional method after cessation of methods that suppress or induce scheduled bleeding. Estrogen-containing products offer cycle control/elimination and vasomotor symptom relief, but are most likely to be rated as category 4 in women with serious medical conditions. Barrier methods are available, but because partner problems with erectile dysfunction or her own pelvic relaxation issues may diminish use. Fertility awareness method may be less useful in this age group. The challenge for providers is the woman who presents with multiple medical problems, such as hypertension, dyslipidemia, obesity, and prediabetes. She prefers to use St. John's Wart for her depressive symptoms. She also has heavy menstrual bleeding from her fibroids and is really worried about hormones and cancer risk. We have all met her and tried to balance her health issues, her concerns and her need for effective contraception. This session will review the tools available to clinicians trying to help perimenopausal women avoid unwanted pregnancies in the sunset of their reproductive years and guide in approaches that can help them be successful.

Plenary Symposium 2

Perimenopausal Contraception

Supported in part by grant funding from Bayer Healthcare and Pfizer Inc.

Transitioning From Contraception to Postmenopausal Hormone Therapy

Petra M. Casey, MD, NCMP. Obstetrics and Gynecology, Mayo Clinic, Rochester, MN

As a woman approaches menopause, her hormonal balance changes along with her fertility. Her risk of obstetric complications as well as spontaneous pregnancy loss increases well before fertility wanes. Unplanned pregnancy rates tend to be highest at the extremes of reproductive age including in a woman over 40 years of age. Therefore, if sexually active and pregnancy is not desired, she should consider a reliable method of contraception until age 55 years when 95% of women have reached menopause or after 12 months of continuous amenorrhea without exogenous hormonal management. If she wishes to transition to menopausal hormone therapy for treatment of vasomotor symptoms, she has several options for concurrent contraception. Any of the combined hormonal contraceptive (CHC) methods (pill, patch or ring) will provide adequate estrogen for menopausal symptoms including genitourinary syndrome of menopause (GSM) along with reliable contraception. If no contraindication to contraceptive dose estrogen exists, she can remain on a combined hormonal contraceptive until age 55 years as testing for menopause can be problematic and may require interruption of CHC and consequently contraceptive for several weeks to months in order to check a level of follicular stimulating hormone (FSH). Moreover, FSH can be quite unreliable in the perimenopause and a single elevated level should not be deemed diagnostic of menopause or an indication for discontinuation of contraception. Those women who desire lower doses of estrogen or in whom contraceptive estrogen doses are contraindicated, progestin only contraception including the long-acting reversible contraceptive (LARC) methods, implant and hormonal intrauterine contraception, as well as progestin injection or progestin only pill can be used along with menopausal estrogen. Estrogen is usually administered transdermally via patch, gel or ring. Additional topical vaginal estrogen may be needed for GSM. Of note, the combined estrogen and progestin patch does not provide contraceptive dose progestin and is not a good option for women seeking contraception along with menopausal hormone therapy. The levonorgestrel intrauterine contraceptive is being used more widely in perimenopausal women for heavy menses and as progestin component of hormone therapy. Its benefits include safe and efficacious contraception with the added convenience of little if any bleeding and no need to take progestin orally for 10 to 12 days per month for endometrial protection with consequent withdrawal bleeding. Pregnancy should be excluded by history or pregnancy test especially if no reliable method of contraception is used prior to intrauterine contraceptive insertion. History of barrier method use alone is generally not considered adequate prior to intrauterine contraceptive insertion. The World Health Organization has formulated guidelines on the reasonable exclusion of pregnancy. Of note, copper intrauterine contraception should not be used along with menopausal estrogen therapy as it does not provide adequate endometrial protection. However, should non-hormonal treatment of vasomotor symptoms be desired, the copper intrauterine device is ideal for contraception along with non-hormonal treatment of vasomotor symptoms such as venlafaxine or gabapentin. Further, the copper intrauterine device is also effective for emergency contraception for up to 5 days post unprotected coitus. As compared to levonorgestrel and ulipristal emergency contraception, the copper intrauterine device is more effective especially in women with an elevated BMI. In one study, 80% of women receiving the copper intrauterine device for emergency contraception kept it for ongoing protection. With progestin only LARC methods gaining popularity in women throughout the reproductive lifetime, more options exist for using these for endometrial protection in women on menopausal hormone therapy, thus providing a seamless transition with excellent contraceptive efficacy until it is truly no longer needed.

Plenary Symposium 3

The Bimanual Examination: Pro and Con

Supported in part by grant funding from Pfizer Inc.

The Bimanual Pelvic Examination—Pro

Barbara Levy, MD, FACOG, FACS. The American Congress of Obstetricians and Gynecologists, Washington, DC

As evidence based practice guidelines have recommended over the counter availability of hormonal contraception without the need for prescription and cervical cytology only every 3-5 years, there is growing conversation about the value of the screening pelvic examination. In July 2014 the American College of Physicians published a practice guideline recommending against performing screening pelvic examination in asymptomatic, nonpregnant adult women citing moderate quality evidence. BUT….what exactly is asymptomatic? And what are we screening for? The evidence produced by the College was limited to the value of screening for ovarian cancer and other cancers as well as screening for pelvic inflammatory disease (hardly an asymptomatic condition) and STIs. There were NO studies to assess the benefits of pelvic examination for other benign conditions such as sexual dysfunction, vulvar disease, urinary incontinence or prolapse. In addition, the opportunity to identify patients' concerns over sensitive issues (not readily disclosed to office personnel or during initial history-taking) was not evaluated. Lack of evidence regarding the value of pelvic examination should not be construed as evidence for a lack of value.

Plenary Symposium 3

The Bimanual Examination: Pro and Con

Supported in part by grant funding from Pfizer Inc.

Routine Screening Bimanual Examination in Asymptomatic Women—The Case Against

Molly Cooke, MD, MACP. School of Medicine, University of California, San Francisco, San Francisco, CA

Preventive gynecological care in the US is estimated to cost $2.6 billion dollars annually. In 2008, 63.4 million pelvic examinations were performed. For context, the 2010 census found 93.4 million women between the ages of 20 and 64; adding young women between 15 and 19 increases the total to 104.1 million. In the face of these numbers, it is critical to determine which services add significant value and to abstain from performing services whose value cannot be demonstrated. For the purposes of this discussion, the components of the pelvic examination are considered to be 1) the inspection of the external genitalia; 2) speculum examination of the vagina and cervix; and 3) the bimanual palpation of the uterus and adnexae, often including a rectovaginal examination. The rationale for performing any screening examination is that the outcome in a screened population is better than that in a similar, unscreened population. Furthermore, in aggregate the benefits of the screening which accrue only to a minority of the population should justify the harms of the screening intervention, which harms are borne by the entire screened population, most of whom do not have the conditions being screened for and consequently cannot benefit. The questions at hand are whether a screening bimanual examination is useful for the detection of such conditions as non-cervical cancer, pelvic inflammatory disease, and fibroids and whether detection of benign conditions, including atrophic vaginitis, uterine polyps, and fibroids benefits asymptomatic women. There is no evidence that the bimanual examination contributes usefully to the detection of ovarian cancer in asymptomatic women. Pooling data from three studies published in the 1980's and 1990's, the PPV of an abnormal bimanual examination for ovarian cancer was less than 2%. A subsequent study, the PLCO Cancer Screening Randomized Trial (N=78,216) randomized women to screening (annual bimanual examination, CA-125 and TVUS) versus usual care but dropped the bimanual examination five years into the trial as it diagnosed no cases of ovarian cancer. A second study, the UK Collaborative Trial of Ovarian Cancer Screening (N=202,368), did not include bimanual examination as an element of the screening program. Likewise, there is no evidence that the early detection of such benign conditions as fibroids in asymptomatic women produces benefit. Even in a population of symptomatic women, the performance characteristics of the bimanual examination are remarkably poor. In a study of women with pelvic pain, using the presence of abnormal laparoscopic findings possibly accounting for pain (e.g., endometriosis, fibroids, adhesions) the PPV of an abnormal bimanual examination was 53% and the NPV of a normal bimanual examination was 43%. Despite the lack of evidence of benefit, it is tempting to think of an element of the physical examination as benign; however, the performance of routine bimanual examinations in asymptomatic women is associated with harms. A non-negligible proportion of women report embarrassment and physical discomfort associated with the procedure. More materially, given the poor accuracy of the examination, women who undergo bimanual examination are exposed the risks of over-diagnosis, unnecessary additional diagnostic procedures and false reassurance. One ovarian cancer screening study suggested that the findings on bimanual examination led to unnecessary surgery in 1.5% of women screened, a concerning finding given a complication rate of 5.7 – 15%. Finally, given the strong evidence that the bimanual examination does not provide quality information about the presence or absence of gynecologic disease in asymptomatic (and some symptomatic women), our time with our patients can be better used.

Plenary Symposium 4

Diabetes Management in Postmenopausal Women

Supported in part by grant funding from Pfizer Inc.

What is the Effect of Menopause on Diabetes Risk?

Franck Mauvais-Jarvis, MD, PhD. Section of Endocrinology, Department of Medicine, Tulane University Health Sciences Center, New Orleans, LA

Estrogen favors energy balance and glucose homeostasis via estrogen receptors by promoting energy expenditure and adipose tissue health as well as maintaining insulin sensitivity and secretion. As a consequence, after the loss of estrogen production at menopause, women exhibit decreased energy expenditure, develop visceral fat and insulin resistance, impaired insulin secretion and the incidence of type 2 diabetes increases. Menopausal hormone therapy containing estrogens significantly decreases the incidence of diabetes in placebo-controlled randomized trials. We will discuss the mechanisms of menopause-induced diabetes and the effect and mechanism of menopausal estrogen therapies on diabetes prevention.

Supported in part by grant funding from Pfizer Inc.

Some Newer Treatment Options for Type 2 Diabetes

Robert G. Josse, MD, BS. [1]Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, ON, Canada; [2]University of Toronto, Professor of Medicine, Toronto, ON, Canada

Diabetes treatment guidelines from different societies and organizations around the world are updated regularly to accommodate the evidence based data from clinical trials of new agents. Diabetes associations have recommended Metformin as first line therapy together with an appropriate diet and exercise regimen. There is still some controversy about which agents to add and in what order when additional therapy is necessary. The ADA/EASD have developed an algorithm to follow updated in 2015. Other guidelines eg Canadian Diabetes Association [CDA] also have developed algorithms to follow which allow free choice for physician, together with the patient, to decide which additional drugs to use and in what order. The process gets more complex when new agents become available and are added to the armamentarium of established drugs. The newest of the agents are the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin. These drugs work in a novel fashion by acting on receptors in the kidney to enhance glucose excretion. They have been shown to decrease HbA1c, lower blood pressure and decrease weight. Their mechanism of action, clinical trial data and side effect profile will be discussed in detail. Recently, the FDA and EMA have issued warnings about the rare occurrence of unrecognized DKA in patients taking the SGLT2 inhibitors. Other agents to be mentioned are so-called "repurposed drugs," Bromocriptine QR, Cycloset and Colesevelam. Bromocriptine is a dopamine agonist originally developed to inhibit prolactin and to treat prolactinomas of the pituitary. The quick release formulation working on nuclei in the hypothalamus increases dopamine activity, decreases serotonin and noradrenaline and results in decreased lipolytic activity and hepatic gluconeogenesis. The bile acid sequestrant Colesevelam was developed to lower LDL cholesterol by decreasing the enterohepatic circulation of bile acids. During clinical trials it was found to lower blood sugar and modestly decrease HbA1c. The mechanism of action for glucose lowering is unclear. Increased understanding of biochemical and cellular mechanisms has resulted in the development of many other newer agents. These include drugs acting on the pancreas to increase β cell mass and decrease glucagon effect. Other agents will specifically target hepatic glucose production and drugs to enhance insulin sensitivity are again being tested. Finally drugs to decrease aspects of inflammation and to decrease some adrenal glucocorticoid effects are being explored. The field is ripe with new discoveries and we will have more agents to choose from. The difficult task will be to decide whether these new drugs alone or in combination are more efficacious and cost effective. **References:** Diabetes Care 2015;38:140-149. Hasan et al. Diabetes research on clinical practice. 204;104:297-322. Tahrani et al. Lancet Diabetes Endocrinol 2013;1:140-51. Holt RIG et al. Diabetes, Obesity and Metab 2010;12:1048-57. Graziano et al. Diabetes Care 2010;33:1503-1508. Fonseca V, et al. Diabetes, Obesity and Metab 2010;12(5):384-392. Kahn SE and Buse JB. Diabetologia 2015 in press.

Plenary Symposium 4

Diabetes Management in Postmenopausal Women

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Hypoglycemic Agents and Insulin: How to Choose Among the Options

Jane E.B. Reusch, MD. Professor of Medicine and Biochemistry, Division of Endocrinology, Metabolism, and Diabetes, Associate Director, Center for Women's Health Research, University of Colorado, Denver, CO

Diabetes, in particular type 2 diabetes mellitus, is caused by a combination of insulin resistance and impaired beta cell insulin secretion. Over the past few decades the armamentarium of therapies for glucose control has expanded including agents that target beta cell insulin secretion, insulin replacement (many new analogs), agents that targets glucose production by the liver, agents that regulate glucose clearance in the periphery (now including the kidney) and agents acting in the central nervous system. This expansion of therapeutic options leaves the patient and clinician asking which medication, when and in whom? This presentation will build on the prior discussion of diabetes risk in the menopause and oral agents to a discussion of current data on glucagon like protein 1 receptor agonists (GLP1) and insulin and insulin analogs. We will close with an overview of current ADA/EASD and AACE guidelines and a practical clinical decision making model for deciding which drug makes sense in an individual patient based upon duration of disease, adherence, age, co-morbidities, life expectancy and cost.

Plenary Symposium 5

Osteoporosis: What's New and On the Horizon

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

What's New and On the Horizon in Screening, Drug Holidays, Supplements, and Conservative Therapy?

Nelson B. Watts, MD. Mercy Health Osteoporosis and Bone Health Servies, Cincinnati, OH

Despite clear guidelines, excellent diagnostic tests and treatments that are safe and effective, osteoporosis remains underdiagnosed and under treated. Medicare reimbursement for bone density testing has been drastically reduced, news stories are frightening patients about safety concerns that may be real but are extremely rare, the US Preventive Services Task Force recommends against the use of calcium and vitamin D supplements to reduce the risk of fracture, practitioners are unclear about the duration of treatment and the role of "drug holidays" – the list goes on and on. This discussion will review the questions and controversies on these topics and try to provide practical guidance for use in clinical practice.

Plenary Symposium 5

Osteoporosis: What's New and On the Horizon

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

What's New and On the Horizon for Prescription Therapies?

Michael McClung, MD. Oregon Osteoporosis Cener, Portland, OR

Several effective therapies with very different mechanisms of action are available for the treatment of osteoporosis in postmenopausal women and older men. Most of these drugs have been shown to be very effective to prevent bone loss and to reduce the risk of vertebral fracture by 50-70% in patients with osteoporosis. Some of the drugs have also been shown to reduce the risk of hip and non-vertebral fracture although those risks are reduced by only 40-50% and 20-40%, respectively. Additionally, current drugs must be given by inconvenient dosing regimens and have both real and perceived side effects, resulting in poor compliance and long-term persistence with therapy. There is a need for the development of even more effective and acceptable drugs. New drugs currently in clinical development will be discussed. 1. Recombinant PTHrP: PTHrP binds to the same receptor as does parathyroid hormone and teriparatide. Abaloparatide is a synthetic analog of PTHrP. In Phase 2 clinical trials, abalparatide 80 ugm daily by subcutaneous injection increased bone mineral density (BMD) in the hip region more than did teriparatide and was associated with a lower incidence of hypercalcemia. In the Phase 3 fracture prevention triaI, compared to teriparatide, similar and substantial reduction in both vertebral and non-vertebral fracture risk was observed after 18 months of therapy. However, the rapidity of non-vertebral fracture risk reduction appeared to be significantly faster with abaloparaide. 2. Cathepsin K inhibitors: Cathepsin K (CatK) is the major osteoclast-derived protease, responsible for cleavage and clearance of type 1 collagen and other matrix proteins during bone resorption. Genetic deficiency of CatK results in an osteoclast-rich form of high bone mass. In pre-clinical studies, inhibition of CatK reduces bone turnover on trabecular bone surfaces while increasing bone formation on the periosteal surface, resulting in increased cortical thickness and strength of long bones. In Phase 2 clinical studies, dose-dependent, rapidly reversible decreases in bone resorption markers are observed. Markers of bone formation decrease upon starting therapy but return to baseline while therapy continues, resulting in a positive bone balance and progressive increases in BMD over 5 years of treatment. In the Phase 3 fracture trial, odanacatib 50 mg given orally once weekly substantially reduced the risk of vertebral, hip and non-vertebral fracture. 3. Sclerostin inhibitors: Sclerostin is an osteocyte-derived inhibitor of osteoblast function. Sclerostin deficiency results in a phenotype of high bone mass and excellent bone quality. Inhibiting sclerostin in rats and monkey results in marked stimulation of bone formation, reconstruction of trabecular and cortical architecture and normalization of bone strength. Phase 2 clinical trials with romosozumab and blosozumab demonstrate rapid and substantial but transient increases in markers of bone formation while bone resorption markers decrease. Increases in BMD over 12-24 months are substantial. Phase 3 fracture prevention trials are underway. New therapies with novel and unique mechanisms of action may provide more effective treatment options for our patients. Perhaps they can be combined with current drugs to induce rapid and substantial increases in bone strength and protection from fractures. Learning how to integrate these new therapies into our current menu of treatment options will be an interesting and important clinical challenge.

The Placebo Response in Clinical Trials and Treatment

The Placebo Response in Clinical Trials and Treatment

Cindy M. Meston, PhD. University of Texas at Austin, Austin, TX

The placebo response refers to the elicited and measurable response after the placebo administration, and should not be confused with nonspecific factors such as: spontaneous recovery, the natural time course of the disease, statistical artifacts such as regression to the mean, or methodological artifacts such as researcher or participant biases. Traditionally we think of placebo as an inert sugar pill, but a placebo can also be psychological (e.g., a conversation with a health care professional) or, at the extreme end of invasiveness, a sham operation where an individual is cut open for surgery and then closed back up without any surgical alteration. Meta analyses on placebo effects indicate that the majority of conditions significantly impacted by placebo meet the following criteria: symptoms are subjective versus highly identifiable, conditions are chronic, symptoms fluctuate and are often influenced by mood. These criteria describe most sexual disorders, in particular sexual desire, subjective sexual arousal, sexual satisfaction, and distress. Indeed, most studies examining the efficacy of drug treatments for sexual dysfunction in women show a substantial placebo response. In this presentation, I will attempt to define the magnitude of the placebo effect in female sexual dysfunction (FSD) studies, describe factors that impact the placebo effect, and speculate on putative mechanisms for how placebo impacts women's sexual function. In one study (Bradford & Meston, 2009) placebo response effect sizes were calculated on previously published placebo-controlled studies for FSD. In two additional studies (Bradford & Meston, 2007; Bradford & Meston, 2011), a number of patient demographic and study variables were examined as potential predictors of the placebo response. Placebo effect sizes for FSD treatment outcome studies range from ~ .26 - ~ .73 depending on the population studied and the methodology used. Factors influencing the placebo effect in FSD studies include: age, marital status, relationship length, type of sexual dysfunction, level of sexual satisfaction at the beginning of treatment, and changes in distress and number of sexually satisfying events during the course of treatment. The substantial placebo response noted in FSD research may be best explained by changes in expectancies that occur with treatment interventions. Increasing expectations for treatment success could impact a woman's actual sexual experience by decreasing anxiety during sex, improving partner-patient communication, and positively influencing partner's behavior toward the woman. Endogenous opiod release and increased dopaminergic activation could also result from increasing expectations and, subsequently influence sexual responding. Understanding the role of placebo in FSD research can help researchers reduce "bias" in clinical treatment outcome studies, and help inform clinical practice in terms of enhancing therapeutic gains. **References:**

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Plenary Symposium 6

Cardiovascular Disease in Women

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Primary Prevention of Heart Disease—What Works, What Doesn't?

Samia Mora, MD, MHS. Brigham and Women's Hospital, Harvard University, Boston, MA

Atherosclerotic cardiovascular disease (ASCVD) claims the life of approximately one in every three U.S. women, exceeding deaths from all forms of cancer combined. Despite the recent decline in ASCVD mortality rates, it remains the number one cause of death in women and men, with an even slightly higher number of deaths in women. Hence, prevention guidelines recommend assessing ASCVD risk, and targeting the intensity of preventive cardiovascular interventions to the individual level of risk. This risk assessment is usually obtained from a number of traditional risk factors and a global risk score. In 2013, the ACC and AHA published several new guidelines that relate to lifestyle, ASCVD risk assessment, and cholesterol management. A healthy lifestyle is the cornerstone for all ASCVD prevention efforts for all patients, and should include complete smoking cessation and avoidance of second hand smoke, a healthy diet (Mediterranean or DASH diet), regular physical activity, and maintaining a normal body weight (BMI of 18.5 to 24.9 kg/m^2, waist circumference <35 inches in women). The risk assessment guidelines developed new risk prediction (Pooled Cohort) equations that estimate 10-year risk of "hard" ASCVD outcomes, defined as nonfatal myocardial infarction, coronary heart disease (CHD) death, or fatal or nonfatal stroke. The 2013 ACC/AHA Pooled Cohort risk equations are provided separately for women and men, and for blacks and whites. The 2013 ACC/AHA cholesterol guidelines also recommend use of the Pooled Cohort risk equations to inform discussions about initiating statin treatment for adults ages 45 to 75 years old who are without clinical ASCVD or diabetes if their risk level is greater than or equal to 7.5%, and recommend considering statin treatment for those with a risk level between 5.0 and 7.5%. For all primary prevention patients without clinical evidence of ASCVD, the guidelines recommended engaging in a discussion between patient and clinician to address global ASCVD risk management, benefit vs. harms, and patient preferences. The guidelines identified four statin benefit groups: 1) patients with known ASCVD, 2) patients with diabetes aged 40-75 with LDL-cholesterol ≥70 mg/dL, 3) patients with LDL-C ≥190 mg/dL, and 4) individuals with estimated 10-year ASCVD risk ≥7.5%. For the primary prevention of ASCVD with aspirin therapy, decisions regarding aspirin use should be individualized, balancing the benefit:risk ratio and patient preferences for each woman. The 2013 ACC/AHA guidelines did not address aspirin use. The 2011 AHA guidelines for women recommended aspirin (75 to 325 mg/d) in high-risk women (e.g. those with clinical ASCVD), and low-dose aspirin (81 mg/d or 100 mg every other day) in at risk women ≥65 years if blood pressure is well-controlled and the overall benefit of aspirin use outweighs the risk. Aspirin in at risk women <65 years for preventing ischemic stroke may be reasonable if benefit outweighs risk. However, aspirin should not be used for preventing myocardial infarction in optimal risk women <65 years old. Our greatest challenge remains the wider implementation of these principles for ASCVD treatment and prevention in both women and men.

Plenary Symposium 6

Cardiovascular Disease in Women

Supported in part by grant funding from Pfizer Inc.

Cardiovascular Disease and Postmenopausal Hormone Therapy

Tomi S. Mikkola, MD. Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland

In women cardiovascular disease (CVD) accounts more than half of all deaths in Western countries. It is generally accepted that endogenous estrogen protects premenopausal women from CVD. However, whether postmenopausal hormone therapy (HT) confers cardiovascular benefit or harm remains controversial. The current guidelines recommend that HT should be used only in recently menopausal women for moderate-to-severe vasomotor symptoms for the shortest possible time. Increasing evidence, however, indicate that one of the most pronounced factors modifying the cardiovascular effects of HT is age or time since menopause at the initiation of HT. The HT used in Finland contains almost exclusively estradiol alone or in combination with different progestogens. Finland has reliable nationwide registers, which cover all HT use since 1994. Based on data from this register, we have evaluated the risk of cardiovascular mortality among Finnish women who used HT, as compared to the background population (standardized mortality ratio). Furthermore, in this population we have assessed the impact of HT discontinuation on cardiovascular mortality. A total of 489,105 women initiated HT use at the mean age of 52.2 years between 1994 and 2009. They had used any HT for a mean of 6.7 years, estrogen-only (ET) for a mean of 3.9 years, and estrogen-plus-progestin (EPT) for a mean of 4.5 years; follow-up comprised 3.3 million HT exposure years altogether. Of these HT users, 3,843 women died of CVD. Risk of CVD death was reduced among HT users. In absolute terms, among 1,000 women using any HT for at least 10 years, the risk reductions would mean 19 fewer CVD deaths. When evaluated separately ET and different EPT regimen users, women <60 years of age at the initiation of HT tended to associate with greater falls in the CVD death risk than the women age ≥60 yrs. Furthermore, in women who discontinued HT at <60, but not in women aged ≥60 years, within the first post-HT year cardiac mortality risk was elevated. In conclusion, in a nationwide register estradiol based HT was associated with reduce cardiovascular mortality, particularly in women initiating HT close to the menopause. Furthermore, in the first post-treatment year the discontinuation of HT use was accompanied with elevations in the risk for cardiac death. Thus, our findings question the safety of annual HT discontinuation practice to evaluate whether a woman could manage without HT.

Plenary Symposium 6

Cardiovascular Disease in Women

Supported in part by grant funding from Pfizer Inc.

Primary Prevention of Coronary Heart Disease in Women: New Updates

Howard N. Hodis, MD. Atherosclerosis Research Unit, Keck School of Medicine, University of Southern California, Los Angeles, CA

There has been no more controversy than that generated by the role of postmenopausal HT in the primary prevention of coronary heart disease (CHD). Beyond this distraction however, are the public health implications of 2 major findings: 1) The effects of HT appear to be determined by timing of initiation in relation to menopause; and, 2) The effects of standard CHD primary prevention therapies are sex-specific and significantly differ between women and men. The hormone therapy (HT) "timing hypothesis" has been proposed to explain the divergent results of a significant reduction of CHD and total mortality with HT shown in observational studies and a null effect shown in randomized controlled trials in which different populations of women were studied. In the former studies, women who initiated HT were on average 30-55 years of age and <6 years-since-menopause and in the latter studies women were on average age 64 years and >12 years-since-menopause when randomized. The timing hypothesis posits that HT benefits and risks depend on the temporal initiation of HT relative to time-since-menopause and/or age, which in turn is related to the health of the underlying vasculature. Over the past decade, data supporting the timing hypothesis has been predominantly consistent. Two recent trials have provided further information in regards to early initiation of HT. KEEPS, conducted in a low-risk cohort of postmenopausal women on average 3 years-since-menopause and randomized to low-dose oral and patch estrogen regimens with oral progesterone versus placebo showed no treatment effect on the progression of subclinical atherosclerosis. On the other hand, ELITE, showed a significant reduction in the progression of subclinical atherosclerosis in women who were randomized to oral 17β-estradiol and vaginal progesterone versus placebo when <6 years-since-menopause but not in women ≥10 years-since-menopause. Concomitantly, cumulating data continue to support the sex-specific effects of currently recommended primary prevention therapies. Three meta-analyses that solely included randomized controlled trial data of primary prevention in women have shown that the effect of statins on CHD and total morality in women is null. A recent study of women showed that statin therapy alone had no effect on total mortality, whereas women using HT and statins concomitantly had an approximate 50% reduction in total mortality. On the other hand, randomized controlled trials have shown that statins significantly reduce CHD in men in primary prevention although total mortality is not reduced. Aspirin therapy has a null effect on myocardial infarction in women in primary prevention although it appears to reduce ischemic stroke. On the other hand, aspirin therapy significantly reduces myocardial infarction in men and has a null effect on ischemic stroke. Aspirin therapy has no effect on total mortality in women and men and randomized controlled trials do not support the use of aspirin therapy for the primary prevention of CHD in women and men with diabetes. Angiotensin converting enzyme inhibitor (ACE-I) therapy has a null effect on cardiovascular disease and total mortality in women with or without congestive heart failure, whereas in men, ACE-I therapy significantly reduces these outcomes. In summary, the cumulated data indicate that over all ages, HT, lipid-lowering therapy and aspirin have a null effect on the incidence of CHD and total mortality in women. Data supporting the effectiveness of primary prevention of CHD with lipid-lowering therapy and aspirin is limited to men. However, HT appears to consistently reduce CHD and total mortality when initiated in women <10 years-since-menopause and/or <60 years old. In conclusion, the therapeutic effects of interventions on outcomes in women cannot be adjudged through extrapolation from studies conducted in men. HT is a sex-specific therapy that provides opportunity for reducing CHD and total mortality in women. If we are going to extend life and improve primary prevention of CHD in women, we need to think beyond the current paradigm that primary prevention therapy is a "one-size fits all" proposition.

Plenary Symposium 7

Gynecologic Update for the Menopausal Woman

Supported in part by grant funding from Pfizer Inc.

Cervical Cancer Screening—Is It Ever Safe to Stop in the Postmenopausal Woman? What's the Risk of Atypical Glandular Cells?

Lisa C. Flowers, MD. Obstetrics and Gynecology, Emory University School of Medicine, Atlanta, GA

The current cervical cancer screening guidelines recommended by the American Society for Colposcopy and Cervical Pathology, the American Cancer Society, the US Preventive Services Task Force, and the American Congress of Obstetricians and Gynecologists are to stop cervical cancer screening at age 65 as long as the woman has evidence of two negative co-tests or three negative Pap tests within the last 10 years. However, in US women aged 65 years and older, 20% of cervical cancer cases and 36% of cervical cancer deaths occur in this population. The natural history of human papillomavirus (HPV) infection in older women is not well understood, and susceptibility and failure to clear genital HPV infection in this population may be attributed to immune function, sex hormone status, or vaginal epithelial function. Many older women are still sexually active and engage in behaviors such as smoking that are risk factors for HPV infection. Some of these mature women are initiating new sexual relationships in their later lives and may be exposed to different HPV strains for the first time. Population-based studies have shown that the estimate prevalence of high-risk HPV is 6% in women aged 57 to 85 years and that current marital and smoking status, history of cancer, frequency of sexual activity, and hysterectomy were associated with high-risk HPV positivity. Also in women with high-risk HPV infection, 63% had multiple-type infections. These women may test positive for high-risk HPV infection during their screenings and despite being aged 65 years or older will need continual surveillance until they achieve the requirements for cessation of cervical cancer screening. How do we account for recent studies reporting 31% of patients with invasive cervical cancer had negative baseline high-risk HPV testing within 5 years before their cancer diagnosis or rates of negative HPV tests of 9%, 23%, and 25% in less than 1 year, 1 to 3 years, and 3 to 5 years, respectively, before the diagnosis of cancer? This brings up the questions of whether it is safe to ever stop screening the postmenopausal woman and whether primary HPV testing should be the main tool for screening US women. In this symposium, we will address rates of cervical cancer in this population and who really is at risk, what does high-risk HPV mean in women aged at or older than 65 years, and the concern for atypical glandular cells in this population.

Plenary Symposium 7

Gynecologic Update for the Menopausal Woman

Supported in part by grant funding from Pfizer Inc.

Individualizing Management of Fibroids in the Perimenopause

Ally Murji, MD, MPH, FRCS(C). Assistant Professor, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

The prevalence of symptomatic fibroids increases dramatically in the fifth decade of life. This is likely due to anovulatory cycles with unopposed circulating estrogen. Among women in their late forties, approximately 50% of black women and 35% of white women had symptomatic fibroids. In perimenopause, the approach to fibroids must be individualized and clinicians must consider the following: Symptoms (bulk versus bleeding), risk of malignancy, proximity to menopause, location of fibroids and patient's desire for uterine preservation. Abnormal uterine bleeding in perimenopause should be investigated according to guidelines and classified using PALM-COEIN terminology. Endometrial biopsy/cavitary assessment is essential in ruling out malignancy (AUB-M), even in the presence of submucosal fibroids. Recently, the risk of sarcomatous change in fibroids has garnered significant public attention. Best estimates of the prevalence of sarcoma in a presumed fibroid is 0.14% (1:700) with a range from 0.49% (1:204) to 0.014% (1:7,400), depending on age and study type. Fibroid mapping with hysteroscopy or saline infused sonohysterography is another essential component of individualizing treatment. The amount of cavitary distortion can guide management (Levonorgestrel intra-uterine device or global endometrial ablation for normal cavities, hysteroscopic management or medical treatment for distorted cavity). Effective medical management for AUB-L (leiomyoma) from randomized controlled data includes the Levonogestrel intra-uterine device, gonadotropin-releasing hormone analogues (GnRH-a) and selective progesterone receptor modulators (SPRM). Only GnRH-a and SPRM are effective for the treatment of fibroid-associated bulk symptoms. Good results for long-term management of fibroid symptoms to transition patients into menopause have been demonstrated with both GnRH-a and SPRM.

Plenary Symposium 7

Gynecologic Update for the Menopausal Woman

Supported in part by grant funding from Pfizer Inc.

Adnexal Masses in Menopausal Women—Surgery or Surveillance?

Frederick R. Ueland, MD. Markey Cancer Center, University of Kentucky, Lexington, KY

Ovarian cancer is the leading cause of gynecologic cancer death in the United States, and with a mean age at diagnosis of 63 years, it is largely a menopausal concern. Ovarian cancer has been named the "silent killer" because it lacks recognizable symptoms in its early stages. Over two-thirds of women present with advanced stage disease where the 5 year survival is 30% compared to 90% for women with stage I disease. Thankfully, most ovarian tumors are not malignant. Clinicians need a consistent strategy when evaluating ovarian abnormalities to help answer two important questions: 1) Does the adnexal mass require surgical removal or can surveillance be recommended? 2) If surgery is necessary, who should perform the operation? Physical examination is not a reliable way to identify an ovarian tumor or determine its malignant potential. Pelvic exam is consistently less accurate than transvaginal ultrasound in identifying ovarian abnormalities and accurately determining dimensions and irregularities, particularly in menopausal women, larger women, or women with an enlarged uterus. Once detected, a comprehensive ovarian ultrasound should include an objective evaluation of tumor volume and structure, like the University of Kentucky tumor Morphology Index (MI). Unilocular and simple septate tumors are rarely malignant and can be monitored without surgery or biomarker testing. If the patient desires removal of a symptomatic low risk tumor, a gynecologic surgeon can perform the operation. For women scheduled for surgery, biomarker testing may also be helpful. High risk ovarian tumors require increased scrutiny and secondary testing, including: serial sonography, serum biomarker testing, or both. They should be referred to a gynecologic oncologist for evaluation and possible surgery. In 1994, the National Institutes of Health published a consensus statement suggesting that "women with ovarian masses who have been identified preoperatively as having a significant risk of ovarian cancer should be given the option of having their surgery performed by a gynecologic oncologist." Unfortunately, in the United States as few as 1 in 3 women with ovarian cancer are referred to a gynecologic oncologist for their primary surgery. Although many factors contribute to the low patient referral, certainly one of the most significant is the lack of an accepted preoperative strategy to evaluate ovarian tumors. Although any ovarian tumor in a menopausal woman has the potential to be malignant, surgical removal is not always necessary. An ultrasound-based strategy can help quantify the risk of malignancy. A menopausal woman with a high risk ovarian tumor should be referred to a gynecologic oncologist. Since it is not possible to know with certainty which ovarian tumors are malignant at the time of surgery, intraoperative rupture should be avoided to prevent the upstaging of an early ovarian cancer or potential cancer dissemination leading to worse outcomes.

Plenary Symposium 8

BRCA Mutation Carriers—Screening, Risk-Reducing Surgery, and Managing Menopausal Symptoms

Supported in part by grant funding from Myriad Genetics, Inc. and Pfizer Inc.

Screening for Genetic Mutations in BRCA1 and BRCA2

Steven Narod, MD, FRCPC, FRSC. Department of Medicine, University of Toronto, Toronto, ON, Canada

Genetic screening for BRCA1 and BRCA2 mutations is offered to women at a high risk of breast or ovarian cancer and is often recommended for women with early onset breast cancer (<40y ears of age at diagnosis; triple negative breast cancer or invasive ovarian cancer). Screening is also offered to women without cancer but who have a mutation in a family member or a strong family history of breast and ovarian cancer. The majority of breast cancers in BRCA1 and BRCA2 carriers occur in premenopausal women. The mainstay of prevention and of treatment is preventive salpingo-oophorectomy (BSO). In our follow up studies we have reported an 80% reduction in the risk of ovarian/fallopian/peritoneal cancer and a 70% reduction in all cause mortality in unaffected BRCA1 and BRCA2 carriers after an oophorectomy. In women with breast cancer and a mutation, BSO was found to reduce the risk of dying of breast cancer by 60% or more. Women with surgical menopause are offered hormone replacement therapy if they have no history of breast or ovarian cancer. Hormone replacement therapy is not offered to women who have been affected with breast cancer.

Plenary Symposium 8

BRCA Mutation Carriers—Screening, Risk-Reducing Surgery, and Managing Menopausal Symptoms

Supported in part by grant funding from Myriad Genetics, Inc. and Pfizer Inc.

Risk-Reducing Surgery and Managing Menopausal Symptoms

Susan M. Domchek, MD. Basser Center for BRCA, University of Pennsylvania, Philadelphia, PA

BRCA1 and BRCA2 mutation carriers have an elevated risk of breast cancer of approximately 50-70% and a risk of contralateral breast cancer which is age and gene dependent but may be as high as 50%. In addition the lifetime risk of ovarian cancer is 40-60% in BRCA1 mutation carriers and 10-20% in BRCA2 mutation carriers. Prophylactic mastectomy decreases the risk of breast cancer by more than 90%. Data from multiple studies have shown a significant reduction in breast cancer and ovarian cancer following risk reducing salpingo-oophorectomy (RRSO). In addition, RRSO is associated with an improvement in breast cancer specific, ovarian cancer specific and overall survival. Unfortunately, early oophorectomy is associated with significant quality of life effects in BRCA1/2 carriers including menopausal symptoms, sleep disturbances, and cognitive issues. There are also concerns regarding long term cardiac, bone and neurologic health. In women who have not had breast cancer, studies have suggested that the administration of hormone replacement therapy may be safe. There is a breast cancer risk reduction with RRSO which is not mitigated by hormone replacement therapy, at least in the short term. The "tubal hypothesis" of ovarian cancer has led to the consideration of salpingectomy alone as an option for managing the increased risk of ovarian cancer. However, data are insufficient to recommend this at this time outside the context of a clinical study. Menopausal symptoms are more challenging to manage in women with a history of breast cancer and a BRCA1/2 mutation. Data from SOFT and TEXT trials have added additional challenges as women diagnosed with premenopausal breast cancer requiring chemotherapy are now advised to consider ovarian suppression (if they have not already had an oophorectomy) and an aromatase inhibitor instead of tamoxifen. This approach adds significantly to menopausal symptoms which are difficult to manage. Ongoing work is attempting to provide more individualized risks to patients, particularly age specific risks, in order to help in decisions regarding the timing of oophorectomy. Modifiers of risk appear to include modest effects based on the specific region of an individual's gene mutation, as well as other genetic modifiers, as well as reproductive modifiers. In summary, oophorectomy by age 40 in BRCA1 and BRCA2 mutation carriers leads to a reduction in breast and ovarian cancer risk with an improvement in breast cancer specific, ovarian cancer specific and overall survival. However, menopausal symptoms and impact of early menopause on cardiac and bone health much be recognized and aggressively managed.

NAMS/Kenneth W. Kleinman Endowed Lecture

ACOs, the ACA, and ADIDAS: Reinventing Healthcare Is Not Impossible!

ACOs, the ACA, and ADIDAS: Reinventing Healthcare Is Not Impossible!

Stephen K. Klasko, MD, MBA. Thomas Jefferson University and Jefferson Health, Philadelphia, PA

Going around the country, I hear physicians and hospital administrators screaming that the end is near. As a practicing physician and president of a health sciences university and hospital system with a 190 year old history and tradition, I have found my solace not in Maimonides, Sir William Osler or even Dr Oz. An Adidas campaign from a few years ago is what I am banking on. It went something like this "Impossible is just a small word thrown around by small men and women who don't want to do the hard work that needs to be done to transform their world. Impossible is nothing. Impossible is potential." So, academic healthcare is impossible. It would have been impossible to imagine Apple as the world's largest capitalized corporation when they were losing to Microsoft and Dell. Instead of competing on their terms, Steve Jobs changed the dynamic with a square box that held 200 mp3s and inaugurated the digital lifestyle. The ability to look at what will be obvious ten years from now and to start doing it today is the way out of this "impossible" situation. In other words, whether you are a physician, administrator or board member of a small or large hospital or academic entity, here is my advice…forget healthcare reform, think transformation.' Or as Buckminster Fuller, put it. "If you really want to transform something, don't change the existing reality, create a new model that makes the old model obsolete." A few years ago, it became obvious to me as a medical college dean that we were selecting medical student applicants based on their science GPA, MCATs and organic chemistry grades…yet somehow we are amazed that doctors were not more empathetic, communicative and creative. We created a new model, one in which students were selected based on emotional intelligence, self awareness and empathy. Then we changed the curriculum, emphasizing leadership, followership, cultural, patient centered and health system competencies. It is obvious that we will not be selecting and educating physicians in 2025 the way we do now…so why not start today. Two years ago, my clinical leadership felt we needed to start an ACO. So while, hospitals in our area were forming ACO boards, we decided to actually create a *care model* that was *accountable* to the community. We partnered with the country's largest retirement community and created a primary care driven, patient centered, innovative, integrated partnership with the community. Yes a partnership, starting with a public health survey to see how much work we had to do. We then went about building real patient centered medical homes with family physicians recruited from around the country (its not hard to recruit primary care providers when you really allow them to quarterback the system) Add an innovative insurance partner and there you have it…an organization led by the patients and the family health providers. At Jefferson Health, we are similarly creating a new entrepreneurial academic model. We are creating new degrees around emerging health professions. Recognizing the importance of population health and value assessment, our college of population health will create the next generation of leaders. And while many of our neighbors are acquiring, competing and consolidating, we are moving "from Blockbuster to Netflix" offering partnerships with community hospitals and physicians, whereby Jefferson can be a catalyst for their growth and development, and their community's health, while recognizing that the patient would rather stay close to home. Transformation will require us to: 1) Redesign, re-engineer and simplify care processes 2) Make effective use of decision support, telehealth and information technologies (not just buying an EMR) 3) Provide population health and personalized medicine at the same time 4) Develop effective teams between healthcare providers (moving from captains of the ship to leaders of high powered teams) 5) Coordinate care across patient condition, services and settings over time 6) Incorporate performance and outcome measurements for true accountability, including technical and teamwork competence 7) Accelerate physicians' ability to adapt…in other words, change the DNA of your healthcare system, one physician at a time

Plenary Symposium 9

Hormone Therapy After Hysterectomy or BSO: Considerations for Management

Supported in part by grant funding from Pfizer Inc. and Vertical Pharmaceuticals, LLC

Estrogen Therapy After Postmenopausal Hysterectomy—Issues, Challenges, Risks, and Benefits

James H. Liu, MD. Case Western Reserve University School of Medicine, Cleveland, OH

Hysterectomy is one of the most commonly performed gynecological operations with over 600,000 procedures per year in the US. Between 1998 and 2010, over 442,000 women over the age of 50y underwent hysterectomy. Should estrogen therapy be an important option for these women? Fortunately, the Women's Health Initiative randomized trial's estrogen-only arm and its long term follow up is able to provide some important guidelines. During the 6 to 8 year follow up of the estrogen-only (E) treated group, the risk for cardiovascular disease was *decreased* (HR 0.59, 0.38-0.9) in the E group compared to placebo. The E group also had reductions in MI (HR 0.54, 0.34-0.86) and overall *mortality* (HR 0.73, .53-1.0). From a risk benefit analysis perspective, these benefits of estrogen use tend to be highest between the ages of 50-59y; become neutral between 60-69 y, with the risks outweighing the benefits by 70 y. E-alone use was not associated with an increase in breast cancer risk and in fact the risk was reduced compared to placebo, however this decrease was not statistically significant. Other benefits of estrogen include a reduction in fractures and vasomotor symptoms. Other studies in E-treated women suggest a reduction in pelvic prolapse and urinary tract infections. The use of estrogen is not without risk as stroke risk is about 2/10,000 for women < 60 y and the risk for DVT remains. For women who had a history of endometriosis, reactivation of quiescent lesions is unlikely and transformation of these lesions into endometrioid cancer is extremely rare. Based on limited evidence primarily in younger women, the risk for reactivation of endometriosis is <3.5%. For women who do not desire systemic estrogen therapy, the use of local vaginal estrogen is effective in preventing or treating the onset of vaginal atrophy. The types of estrogen and the routes of its administration/advantages will be briefly reviewed. In summary, the discussion of estrogen-alone therapy has evolved with stronger evidence for benefits from randomized trials. This increases our confidence for making clear recommendations during counseling for E therapy.

Plenary Symposium 9

Hormone Therapy After Hysterectomy or BSO: Considerations for Management

Supported in part by grant funding from Pfizer Inc. and Vertical Pharmaceuticals, LLC

Estrogen Therapy After Bilateral Oophorectomy in Premenopausal Women

Walter A. Rocca, MD, MPH. Division of Epidemiology, Department of Health Sciences Research, and Department of Neurology, Mayo Clinic, Rochester, MN

In this invited lecture, I will provide an update on the evidence in support of estrogen and other hormonal therapy after bilateral oophorectomy in premenopausal women. Medical practices should follow the principle of "primun non nocere" (first do no harm), and bilateral oophorectomy performed electively at the time of hysterectomy for a benign indication is now under scrutiny and critical reappraisal because the long-term risks may outweigh the benefits in the majority of women. The ovaries are both reproductive and endocrine organs. They secrete hormones both before menopause (primarily estrogen, progesterone, and testosterone) and after (primarily testosterone, androstenedione, and dehydroepiandrosterone). Ovarian hormones have important reproductive actions; however, they also have important endocrine actions mediated by receptors spread throughout most tissues and organs of the body (Rocca and Ulrich, 2012). Removal of the ovaries reduces the risk of ovarian (by 80-90%) and breast cancer (by 50-60%); however, it increases the risk of all-cause mortality (28%), lung cancer (45%), coronary heart disease (33%), stroke (62%), cognitive impairment (60%), parkinsonism (80%), psychiatric symptoms (50-130%), osteoporosis and bone fractures (50%), and impaired sexual function (40-110%). The magnitude of the risk may vary depending on the study referenced, the age at the time of oophorectomy, and the use of postoperative estrogen therapy. The scientific debate about the risks and benefits of prophylactic bilateral oophorectomy continues, and many women continue to undergo prophylactic oophorectomy in 2015 (Llaneza and Perez-Lopez, 2013; Harmanli et al., 2013; Harmanli, 2014). I suggest that the evidence is sufficient to change this practice. At the time of hysterectomy for a benign condition, if the ovaries are normal and the woman does not carry a high-risk genetic variant (e.g., *BRCA1* or *BRCA2*) or does not have a strong family history of ovarian cancer, the ovaries should be conserved. This conservative practice is particularly important in younger women (Rocca and Ulrich, 2012; Harmanli, 2014). If there is a clear indication for bilateral oophorectomy in premenopausal women, the following key concepts should be considered: 1) The results of the Women's Health Initiative trials do not apply directly to women who have experienced premature or early menopause caused by bilateral oophorectomy. 2) Most women who undergo bilateral oophorectomy prior to age 45 and who do not have a history of hormonally-sensitive cancer or another specific counter-indication will benefit from hormone therapy not only for vasomotor symptom management, but also for prevention of adverse cardiovascular, bone, and neuro-cognitive effects related to premature estrogen deficiency. The concept of hormone replacement therapy should be reintroduced in clinical practice. 3) Several medical societies recommend that hormone therapy should be considered at least until the natural age of menopause for women experiencing premature or early menopause. 4) Higher doses of estrogen (at least the equivalent of 100 μg of transdermal estradiol) may be needed to approximate blood estradiol concentrations similar to those of menstruating women. 5) Although testosterone has been shown to improve sexual function in women, it is not currently routinely recommended in women with bilateral oophorectomy. In summary, women who undergo bilateral oophorectomy before menopause should receive adequate hormonal treatment (Faubion et al., 2015).

Plenary Symposium 10

Addictions and Compulsive Behaviors in Menopausal Women

Supported in part by grant funding from Pfizer Inc.

Alcohol—Use and Abuse

Timothy Lineberry, MD. Chief Medical Officer, Aurora Health Care, Green Bay, WI

Alcohol consumption is one of the top actual causes of death – defined as preventable behavioral conditions – in the United States and the world. Alcohol-use disorders (DSM 5 terminology) includes diagnoses formerly of alcohol abuse and alcohol dependence. In this brief session, key clinical factors differentiating hazardous use of alcohol and alcohol-use disorders will be described along with differences in both epidemiology and clinical course between men and women with alcohol-use disorders. Beyond alcohol-use disorders as a sole diagnosis, a focus of the presentation will be on the co-morbidity between depressive disorders, anxiety disorders and PTSD with alcohol-use disorders. Finally, options for treatment of alcohol use disorders including both behavioral treatments and antidipsotropic medication treatment will be described along with interactions and monitoring requirements.

Plenary Symposium 10

Addictions and Compulsive Behaviors in Menopausal Women

Supported in part by grant funding from Pfizer Inc.

Mental Health Consequences of Prescription Drug Addictions—Opioids, Hypnotics, Benzodiazepines

Ayal Schaffer, MD, FRCPC. [1]Head, Mood and Anxiety Disorders Program, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Substance use disorders (SUD) such as various prescription drug addictions are among the fastest growing source of medical disability in the United States (JAMA 2013;310(6):591-608). These addictions can lead directly to substantial mental health consequences, and often co-exist with other mental health conditions such as mood and anxiety disorders. For instance, the odds ratio compared to the general population for developing a SUD is 1.8 in patients with major depressive disorder and 6.9 in patients with bipolar disorder. Similarly, SUDs are considered a major risk factor for the development of mood disorders. Elevated suicide risk has also been associated with SUDs and intentional overdose of prescribed medications is among the more common methods of suicide attempts and suicide deaths. Within the overall concern regarding the mental health consequences of various types of SUDs, prescription medications have received particular attention of late. Health care providers are rightfully concerned about putting patients at risk of addiction, yet understand that medications like opioids, hypnotics and benzodiazepines can play an important role in many patients' treatment plans. The presentation will examine this complex issue in a number of ways: i) an examination of epidemiological data on the extent of the issue; ii) a clinical discussion on the mental health consequences that are mostly likely to arise in care; iii) a discussion of the factors that place patients at risk for developing prescription drug addictions; iv) an exploration of the issue of suicide risk and suicide prevention in patients receiving prescription medications who may be at higher risk; and v) a brief review of treatment guidelines for management of prescription drug addictions and discussion of management approaches.

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Eating Disorders

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Eating disorders are psychiatric syndromes characterized by a persistent disturbance of eating or eating-related behavior that significantly impairs physical health or psychosocial functioning. In the Diagnostic and Statistical Manual of Psychiatric Disorders, 5th Edition (DSM-5), eating disorders include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and other specified or unspecified eating disorders (cases where there is a clinically significant eating disorder that does not meet criteria for one of the specified disorders). AN is characterized by the failure to sustain a minimally adequate body weight along with psychological characteristics such as overvaluation of shape and weight. BN and BED both are characterized by persistent, frequent binge eating episodes (eating large amounts of food paired with a sense of loss of control over eating), but in the case of BN, binge eating is associated with regular compensatory behaviors such as self-induced vomiting, misuse of laxatives, or periods of fasting. Population-based studies indicate that the lifetime prevalence rates of AN, BN and BED are .6%, 1.0%, and 2.8%, respectively. Although the onset of AN is rare after young adulthood, the onset of BN and BED in mid-life is not uncommon. Moreover, eating disorders with onset in late adolescence or early adulthood may persist or recur in mid-life. For example, in a twenty-year follow-up of women with BN or a related eating disorder, 4.5% had a clinically significant disorder at mid-life (M= 40 $\pm$ 2 years). In addition to frank disorder, the prevalence of eating disorders symptoms such as binge eating and self-induced vomiting, as well as the psychological symptoms of eating disorders including preoccupation with eating, shape and weight and body dissatisfaction are common in older women, and also can be associated with distress and impaired quality of life. One study of a group of women aged 50 years or older found that 13.3% endorsed current symptoms of eating disorders, and another study found high rates (89%) of dissatisfaction with body size in women aged 45-54 years. Indeed, emerging evidence indicates that the menopausal transition is associated with increases in the prevalence of disordered eating and body image concerns (e.g., feeling fat, body dissatisfaction). Although the reasons for increases in mid-life eating problems and eating concerns in women are not known, clinical observers have implicated the interplay among hormonal shifts, mood, and aging-related body concerns. Given the aging of the US population and a cultural milieu that values youth and appearance, it is unsurprising that that mid-life woman appear to be seeking treatment for disordered eating in increasing numbers. Consequently, it is important for clinicians caring for older women to screen for disordered eating, and to evaluate the potential presence of psychiatric (e.g., mood and anxiety disorders) and medical (primarily those associated with overweight and obesity) co-morbidity. Several forms of psychotherapy, in particular cognitive behavior therapy (CBT), have demonstrated utility in the treatment of BN and BED. There is little specific information about the treatment of older women, but at least one study has shown that CBT adapted to address age-related changes in appearance, the importance of self-care, and body acceptance is effective for women in mid-life. Antidepressants have been studied widely in the treatment of BN and BED, and have been shown to be moderately effective in reducing the frequency of binge eating episodes. In particular, fluoxetine is approved for the treatment of BN, and lisdexamfetamine, a drug used to treat attention-deficit hyperactivity disorder, recently has been approved to treat adults with moderate to severe BED. In summary, eating problems and body image concerns are common among mid-life and older women. Routine screening and referral for evidence supported interventions are recommended.

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Compounded Hormone Therapy

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Presentation of Results of NAMS Survey on Compounded Hormone Therapy

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In response to a growing concern about the regulation of compounded medications and the lack of information about the extent of use of compounded hormone therapy (C-HT), The North American Menopause Society (NAMS) conducted a national survey to gather more data on the subject. The survey was developed by a panel of NAMS experts and adapted for internet use by Lake Research Partners. The survey sample was drawn from an online opt-in panel. Of the 156,240 women invited to participate, 22,105 accepted and 3,725 women were eligible. The sample was weighted slightly by age, region, education and race to reflect the population attributes based on United States Census data. Eligible women were those aged 40 to 84 years who were postmenopausal (defined as one year without bleeding or history of bilateral oophorectomy) or currently going through the menopause transition (defined as experiencing irregular menses or menopausal symptoms such as hot flashes). The age range selected was intentionally wide to capture the duration of hormone therapy (HT) use as well as the use of HT for anti-aging purposes. Key objectives of the survey were to estimate the percentages of women using either C-HT or HT approved by the Food and Drug Administration (FDA-HT) and to identify differences between the two groups. In this survey, 9% of women were current users of HT, with the highest rate of use observed in the women aged 40-49 years (12%), followed by age group 50-59 years (9%). Approximately 28% of all respondents were ever-users of HT. Identifying C-HT users by several methods indicated that approximately 31% of ever-users of HT were C-HT users. The rate was slightly higher among current users and younger users. The most cited reasons for using HT were similar in both groups and included vasomotor symptoms (70%) followed by vaginal dryness, osteoporosis, and moodiness/irritability (20%-28%). Other non-approved indications for using HT, such as improving energy, depression, muscle mass, memory/concentration, sexual desire, overall appearance, and preventing aging, were selected more often by the C-HT users. The majority of women in both groups indicated that a physician recommended HT. C-HT users were more likely to have had C-HT recommended by non-medical sources. More FDA-HT users than C-HT users reported alleviation of hot flashes (40% and 31%, respectively) and benefit for vaginal dryness (9% and 5%, respectively). More C-HT users than FDA-HT users reported “Better mood/more energy” (18% and 12%, respectively). Approximately 16% of both groups reported “None, few benefits.” The most common side effect reported was breast tenderness, and almost three-quarters of both user groups indicated no side effects. There were higher rates of vaginal bleeding among C-HT users compared to FDA-HT users, and four reports of endometrial cancer among the 325 C-HT users compared to no cases reported among the 739 FDA-HT users. Among all HT ever-users, approximately 13% indicated current or past use of testosterone. Only 9% of testosterone users indicated use of other hormones. Benefits reported by testosterone users were similar to those reported by other hormone users. More testosterone users than other HT users discontinued their treatment by 3 years (60% versus 40%, respectively). There is a need for better data collection on the extent of use of compounded hormones, their benefits and risks.

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The Compounded Hormone Therapy Fantasy—Concerns Regarding Purity, Dose, Poor FDA Oversight, and Media Irresponsibility

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The 2002 termination of the estrogen-progestogen therapy (EPT) arm of the WHI was a major speed bump on the road of menopause history. The subsequent massive backlash against the use of FDA-approved hormonal therapies has had an unanticipated and unfortunate outcome: a shot in the arm for a new school of "natural" hormone therapies. This fad has been enabled by a generally uninformed media giving credibility to celebrity marketers at the expense of providing scientifically valid information to its audience. The practice of medicine has historically involved the compounding of medications based on a physician's determination that an FDA-approved product either did not exist, or could not be used for medical reasons. Today, prescriptions for non-FDA approved compounded drugs may be driven by fanciful pharmacy advertisements to physicians and patients, which is largely unregulated, thus placing prescribers in the backseat for clinical decision-making. This presentation outlines essential differences between FDA-approved drugs and compounded drugs and reasserts the primary medical role of physicians for determining what medical circumstances may necessitate treatment with non-FDA approved products. Compounders, often at industrial scale, have capitalized on the word 'bioidentical,' a non-scientific term not recognized by the FDA, and have marketed a variety of so-called 'bioidentical hormone therapies,' none with supportive product-specific research to justify their use. Specific compounds, dose, and route of administration may have different outcomes. There should be an explanatory patient package insert in all hormone prescriptions, whether commercial or compounded, that clearly explains to women the benefits and risks associated with the product. The responsibility to counsel women about risks and benefits of all pharmacotherapies is the physician who signs the prescription, who thus carries the liability. It is time to tell women, "Buyers beware!" and to remove the word 'bioidentical' from our medical lexicon. Sellers S, Utian W.H. Pharmacy compounding primer for physicians. Prescriber beware. Drugs 2012:72 (16);2043-2050.