Menopause 101: How toInitiate Treatment
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The mean age of natural menopause is 51 years and the majority of women will be postmenopausal for greater than one-third of their lives. 70-80% of postmenopausal women experience symptoms at some point. VMS vary through the duration and VMS vary for individual women. VMS are most prevalent in the late perimenopause and symptoms peak for approximately 1 year after menopause. Longitudinal data from a large U.S. study indicated that hot flashes persist longer than initially thought, with a median duration of 5 years. VMS are associated with decreased sleep, irritability, difficulty concentrating, reduced quality of life, poor health, and bone loss. They are also associated with an increased risk of cardiovascular disease and cognitive changes. Menopausal symptoms that go untreated are also associated with higher healthcare costs and loss of work productivity. Genitourinary syndrome of menopause (GSM), including dyspareunia, vulvar-vaginal atrophy (VVA) and urinary symptoms, affects approximately 30% to 50% of postmenopausal women. Whereas VMS are often transient, VVA symptoms are typically chronic and progressive and usually do not resolve without treatment. Bone loss and fracture risk can also accelerate during this time of estrogen decline but can be maintained if given hormone therapy (HT). Although HT is the most effective treatment for VMS and GSM, and can prevent menopausal bone loss and fracture risk, the use of systemic HT has decreased by at least 50% among U.S. women since the initial findings of the Women’s Health Initiative (WHI) were published in 2002. This is despite the recent WHI 18 year cumulative follow up study which reported that HT was not associated with increased risk of all-cause, cardiovascular, or cancer mortality. In addition, guidelines from NAMS and other professional societies recommend women can continue with contraindications, less than age 68 years, and within 10 years after the onset of menopause. HT is also recommended for women with early menopause or primary ovarian insufficiency, and should be used until at least the average age of menopause, 51 years. Systemic HT is FDA approved as first-line therapy and is the most effective treatment for the relief of menopausal VMS. HT can also reduce bone loss and fracture risk, and when given locally at lower doses, it can relieve symptoms of GSM. The decision to initiate or continue HT involves a careful assessment of the potential benefits and risks, but the majority of symptomatic healthy women will experience a significant quality of life benefit from the use of HT. The benefits of HT usually outweigh the risks for women without contraindications such as breast cancer, endometrial cancer, cardiovascular disease, active liver disease, and undiagnosed vaginal bleeding. Baseline risk of cardiovascular disease and breast cancer, and personalized risk assessment is helpful for an initial therapeutic recommendation. Before initiating therapy, a comprehensive past medical, gynecologic, surgical and family history is advised along with an updated physical exam, pertinent laboratory tests (liver function tests, lipids), and mammogram. Clinical decision support tools, such as the NAMS MenoPro free mobile app provides an algorithm to facilitate the individualized risk assessment required for counseling menopausal women regarding the benefits vs risks of HT. This decision support tool, can help identify appropriate candidates for HT, and includes information for both health care consumers and clinicians. MenoPro, has a separate mode for clinicians and patients, and facilitates shared decision making. For women with contraindications or choose not to use HT, it provides non-hormonal therapies and alternatives for GSM if this is her only symptom. The optimal duration of HT remains a topic of controversy for individuals with the absence of contraindications. If on HT, women and clinicians should share the decision in a preferred dose, formulation, and duration of use, with ongoing yearly reevaluation of the risks and benefits, and education about other alternatives.

Menopause 101: Dose, Route, and Formulation
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The hormone therapy to treat menopausal symptoms is a rich story with many twists and turns. In 1929, estrogen as a hormone was isolated. The first commercial preparation of estrogen was extracted from placental tissue called Emmenin. In 1942, Premarin became commercially available in the US and by 1992 was the number one drug prescribed in the US with sales in excess of $1 Billion by 1997. In July 2002, the release of publications from the Women’s Health Initiative (WHI) abruptly changed the landscape altering women’s attitudes toward hormone replacement therapy (HRT), now referred to as hormone therapy (HT). This fueled the search for safer delivery systems and formulae options for estrogen. Today, all major estrogens are plant or synthesized de-novo and are bioidentical. Most estrogens can be delivered via multiple route; oral, transdermal as a patch, spray or gel, and intravaginal ring, cream, insert, in various forms. Different routes of administration will have different metabolic effects. Oral estrogen produces a systemic effect, whereas transdermal estrogen produces a local effect and vaginal estrogen produces a local effect of the mucosal lining. Nonhormonal Management of Hot Flashes

Hormonal Contraception in Older Reproductive Women and Transition to Menopausal Hormone Therapy
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Although fecundability declines in older reproductive age women, sporadic ovulation continues until menopause. In addition, older reproductive women are more likely to have health issues or adverse consequences to oral contraceptive use. Accordingly, contraception remains important in older reproductive age women. Furthermore, perimenopausal vasomotor symptoms (VMS) and irregular bleeding are prevalent. Fortunately, Centers for Disease Control, ACOG, and NAMS guidance for contraceptive selection or older reproductive age women is congruent. Healthy nonsmoking women can use combination hormonal contraceptives (CHCs: pills, patches, and rings) until menopause. In older reproductive age women smoking, obesity, hypertension, and migrants with aura place women at unacceptable risk and contraindicate oral contraceptive use. In older reproductive age women, progestin-only contraceptives (pills, injection, implant, IUDs) are appropriate. Whether or not combination pills elevate breast cancer risk is controversial: if an increased risk is present, the magnitude of this risk is small and should be weighed against noncontraceptive benefits including reduced risks of ovarian and endometrial cancer and osteoporotic fractures as well as effective treatment of abnormal bleeding and VMS. Checking FSH levels in perimenopausal women is not useful and may be misleading. In healthy nonsmoking women, CHCs can be continued until women are in their mid-50s, at which time they can discontinue contraception and seamlessly transition to menopausal hormone therapy, if they wish. For some perimenopausal women, placing a progestin IUD and adding estrogen when VMS occur represents an appealing strategy.

Maintaining Wellness in Perimenopause and Beyond
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A woman’s perimenopause course is often impacted by significant physiologic changes in transitioning to menopause. Empowering women with education about the perimenopause transition is crucial. Healthcare providers (HCP) should address these ongoing and upcoming changes prior to feelings of confusion or fear among their female patients. Tracking symptoms and both patients and clinicians in individually targeting bothersome symptoms including (but not limited to) vasomotor symptoms (VMS), genitourinary syndrome of menopause (GSM), abnormal uterine bleeding (AUB), mood changes, and sleep disorders which often begin in the perimenopause transition and can occur before a woman’s last menstrual period (LMP). Also, HCP’s should be adequately equipped to address contraception and chronic disease development and management in perimenopause to ensure women reach their long-term health goals. Establishing a foundation and listing common experiences in perimenopause aids women in feeling confident, self-assured, and positive about their health at midlife. This positivity extends into menopause and beyond. Journaling and tracking provides women with a foundation upon which to reflect on bothersome life and body changes, and further allows women to understand the impact each symptom may be having on their personal and professional lives. HCP’s can improve the midlife trajectory by suggesting lifestyle changes centered around individual patient cyclic, chronic, or spontaneous symptoms. These changes are an essential management skill set for HCP’s. Discussing safe vitamins, supplements, and dietary changes may also help with common midlife symptoms such as bloating, constipation, weight management, and mental wellness. HCP’s knowledge of national support groups can also be of benefit to many women seeking further support and validation. With journaling and tracking serving as each woman’s baseline, if needed, treating symptoms can help women regain control and thrive in perimenopause. VMS and AUB can occur during extended periods of low estrogen states in transitioning to menopause and if affecting quality of life (QOL) can be treated with FDA-approved hormone or nonhormone options. AUB is also common and if bothersome can be controlled with medical management such as continuous contraception or long acting reversible contraceptive options (LARCs’s) such as the intrauterine device (IUD), levonorgestrel-releasing IUD, and progesterin-releasing IUD. New onset of mood disorders ranging from anxiety, irritability, and depression are complex at midlife and HCP’s understanding of treatment options for cardiovascular and cerebrovascular events when using CHCs. In older reproductive age women, smoking, or not combination pills elevate breast cancer risk is controversial: if an increased risk is present, the magnitude of this risk is small and should be weighed against noncontraceptive benefits including reduced risks of ovarian and endometrial cancer and osteoporotic fractures as well as effective treatment of abnormal bleeding and VMS. Checking FSH levels in perimenopausal women is not useful and may be misleading. In healthy nonsmoking women, CHCs can be continued until women are in their mid-50s, at which time they can discontinue contraception and seamlessly transition to menopausal hormone therapy, if they wish. For some perimenopausal women, placing a progestin IUD and adding estrogen when VMS occur represents an appealing strategy.

Nonhormone Management of Hot Flashes

Catherine Hansen, MD, FRCCS, FACOG, MPH, NCMP. Empowered Women’s Circle, TX

On average, US women will spend up to one third of their lives postmenopausal and vasomotor symptoms (VMS), the cardinal symptoms experienced around menopause, will impact over 70% of women. These symptoms, which can be incapacitating, occur at the prime of women’s lives with multiple roles and responsibilities both inside and outside her home. VMS usually last 5-7 years but can continue much longer and may be accompanied by a constellation of additional concerns impacting quality of life considerably. It has become standard practice in many women to manage VMS with hormones. However, many women are not candidates for hormones and others wish to avoid hormones for relief of...
their symptoms. Ten percent describe VMS as intolerable and 50-80% of women will experience menopause as a disease state. More than 6 million women experience menopausal symptoms. It should be viewed as a window of opportunity to identify and prevent chronic diseases. We need to provide an integrated approach to preventive care and shift away from viewing menopause as a disease. Appropriation interventions may result in improved health outcomes.

Vasomotor Symptoms (VMS) and Genitourinary Syndrome of Menopause (GSM) are well recognized symptoms of menopause, and affect many aspects of a woman’s postmenopausal life. Hormone Therapy (HT) is the most effective treatment for vasomotor symptoms (VMS). Although HT has other beneficial effects, the principal indication for systemic HT is bothersome VMS that adversely affect quality of life. Estrogen combined with a progestogen is provided for endometrial protection to women with a uterus. For women without a uterus, estrogen alone is preferred. HT use include breast cancer, endometrial cancer, and cardiovascular disease, including heart disease, venous thromboembolic events, and stroke. The Women’s Health Initiative (WHI) randomized, placebo-controlled clinical trials provide information on HT risks and benefits in approximately 27,000 menopausal women aged 50-79 years with a mean age of 63 years. Women with a uterus received conjugated estrogens (CE) with medroxyprogesterone acetate, while women without a uterus received CE alone. The balance of risks and benefits was quite favorable for women receiving estrogen alone and for those under age 60 years or within 10 years of menopause, the years during which most women experience bothersome VMS. There was no significant increased risk of heart disease, and a slight increased risk of stroke, a rare event in this age group. Venous thrombotic events increased. Although estrogen-progestogen therapy increased breast cancer risk slightly after 4-5 years of use, there was no increased risk with short-term use of estrogen-progestogen or with use of estrogen-alone. HT initiated more than 10 years beyond menopause or in women over age 60 years was associated with greater risk. Many HT formulations are available and WHI studied only one HT formulation. Different lower dose oral estrogens, transdermal estradiol, and different progestogens may be associated with reduced risks. Combination estrogen-progestogen products and transdermal formulations are available in a wide variety of doses allowing women to identify a convenient, preferred regimen. Non-oral estradiol administration is advised for women at risk higher cardiovascular disease due to the absence of first pass metabolism benefit on coagulation factors. Transdermal estradiol does not increase venous thromboembolic events in observational studies. Early menopause is associated with increased risk of fracture, dementia, and cardiovascular disease in observational studies. Therefore, women who are experiencing early menopause should be encouraged to use HT until the typical age of natural menopause, approximately age 51 years. For healthy women with bothersome VMS under 60 years of age or within 10 years of the onset of menopause, the benefits of HT typically outweigh risks. The decision to use HT, including dose, formulation, and duration of use, should be made between a woman and her health care provider following discussion of symptoms, benefits, and risks with ongoing assessment.

Nonpharmacologic Therapies for Vasomotor Symptoms

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Treating menopausal vasomotor symptoms can improve women’s health and quality of life. There are evidence-based non-pharmacological therapies clinicians can recommend for women who cannot, or prefer not to, take hormone therapy or other medications to alleviate vasomotor symptoms. Based on evidence, the NAMS position statement on non-hormonal management of menopausal vasomotor symptoms (VMS) is to recommend, recommend with caution, and do not recommend at this time. Recommend: Cognitive-behavioral therapy and clinical hypnosis are effective in reducing vasomotor symptoms. Recommend with caution: Therapies that may be beneficial for alleviating vasomotor symptoms include weight loss, mindfulness-based stress reduction, and stellate ganglion block, but additional studies are needed. Do not recommend at this time: There were negative, insufficient, or inconclusive data suggesting these should not be recommended for managing vasomotor symptoms: acupuncture and medical techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, acupuncture, calibration of neural oscillations, and chiropractic interventions. The purpose of this presentation is to review the evidence base for these treatment options and guide shared decision making in clinical practice. Evidence published following the release of the NAMS position statement on non-hormonal management of vasomotor symptoms will be highlighted. By increasing awareness of and incorporating the most up-to-date and available evidence into clinical practice, healthcare providers can help with shared decision making around women’s use of non-pharmacological therapies for vasomotor symptoms.

Recent Advances in the Treatment of Vasomotor Symptoms—Nonhormonal Therapies

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Though many women manage menopausal symptoms with hormone therapy, increasing numbers of women are considering non-hormonal options. In choosing a non-hormonal medication, women want to understand the effectiveness and side-effects of the non-hormone medication and how it will compare with traditional hormone therapy. New to the nonhormonal armamentarium for treatment of menopause symptoms are drugs targeting the KNDy neuron complex. Clinical use of other nonhormonal therapies effective for menopausal symptoms, including SSRIs, SNRIs, gabapentin, oxycodone, and more recently, fezolinetant have shown variable evidence of efficacy. Nonmedicinal options with varying evidence include lifestyle changes, weight loss, complementary and alternative approaches, mind-body techniques, wearable technologies, stellate ganglion block, dietary management and a vast array of supplements including S-equivalent dosages of soy isoflavones. Understanding which therapies to strongly recommend, which to suggest with caution and which to avoid is based on the personal needs and desires of the woman, level of evidence, proven efficacy, availability, cost, possible adverse effects and potential interactions with medications or other therapies. Expanding awareness, knowledge and familiarity with available nonhormone options combined with healthcare provider comfort to have these essential conversations will alleviate the noteworthy undertreatment of VMS for mid-life women.
development targeting the KNDy neuron complex, side effects of these new novel drugs and their long-term potential as nonhormonal therapies for menopause symptoms. New data on the effectiveness of oxybutynin will be presented and existing data on SSRIs/SNRIs, gabapentin and clonidine will be reviewed. A network of estrogen-sensitive neurons in the hypothalamus, which express Kisspeptin (Kiss1), Neurokinin B (NKB), and Dynorphin (Dy) project to and are immediately adjacent to the thermoregulatory center. NKB neurons express ERα and are the primary targets for estrogen-dependent GnRH regulation. These neurons drive and control the pulsatile secretion of GnRH and LH as evidenced by the fact that blockade of kisspeptin signaling in the brain inhibits GnRH pulses. At menopause, diminished estrogen causes the Kiss1 neurons to go to “hyperdrive”, activating the adjacent thermoregulatory center, resulting in hot flashes. To date, there are no Food and Drug Administration (FDA) approved products for menopause directed toward the Kiss1 neuron complex, but drugs first developed for pain control and sleep disorders acting via KNDy are under investigation for treatment of vasomotor symptoms in the US and Europe and hold great promise, particularly an NKR antagonist ENS 364 (fazeloxifene) and a dual NKR and NKB antagonist, NT-814. VMS efficacy is as good if not better than standard dose estrogen with rapid symptom amelioration and mean decrease of over 5 hot flashes per day over placebo. GI side effects, particularly in pure NKR antagonists, including liver function test abnormalities could ultimately limit widespread use but definitive answers to this question will follow with the completion of ongoing phase 3 trials. Oxybutynin, an anticholinergic medication that binds primarily to M3 muscarinic receptor, is used commonly for over-active bladder. Oxybutynin effectively reduced VMS by approximately 2.5-3.5 hot flashes per day beyond placebo in 2 RCTs. Side effects occur in up to 50% of women and include dry mouth, difficulty urinating, and abdominal pain. To date, RCTs have shown efficacy with the SSRIs paroxetine, citalopram and escitalopram, and the SNRIs venlafaxine and desvenlafaxine, reducing hot flashes by approximately 1.5 per day over placebo. Effectiveness of these nonhormonal agents appears similar to low dose estradiol (0.5 mg oral) with a relatively low side effect profile. RCTs show benefit of gabapentin and venlafaxine even in women with no prior history of vasomotor symptoms. In 2 RCTs, oxybutynin decreases the number of hot flashes by 1.5-3.5 hot flashes per day beyond placebo with side effects greater than SSRIs/SNRIs and gabergines. References: Pinkerton JV and RJ Santeen. Managing vasomotor symptoms in women after cancer. Climacteric, 2019;22:544-52. McCormick CA, Brennan A, Higham R, O'Mahony symptoms effectiveness without hormones. Climacteric. July 2020. Genazzani AR, Gaspard U, Foidart JM. Oral investigational drugs currently in phase I or phase II for the amelioration of menopausal symptoms. Expert Opinion Investigational Drugs. 2019;28(3):235-47. New Hormone Therapies for Vasomotor Symptoms

Hugh S. Taylor, MD. Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, CT

Estrogens have many beneficial properties, yet treatment also has risks. Attempts to identify novel estrogens or selective estrogen receptor modulators (SERMs) with substantial benefit and minimal risk have not produced superior products. The past decade has brought improvements included new SERMs and use of estrogens together with SERMs to replace progestins. Recently we have seen the development of fetal estrogens which have unique properties that distinguish them from estradiol and that have some SERM-like properties. Estriol and estetrol have entered clinical use with new data revealing promising characteristics that distinguishes them from estradiol. Estetrol decreases hot flashes and results in favorable cardiovascular changes while counteracting estradiol stimulation of the breast. Estriol similarly acts as a weak estrogen but can counteract some negative effects of estradiol. While most estrogens activate estrogen receptors alpha and beta, leading to coactivator or corepressor recruitment, fetal estrogens also interact with coactivator complexes in programming antioxidant, immune, and neuroprotective pathways. We have found that, in fetal life, estriol interaction with ER recruits epigenetic modifiers allowing long lasting changes in DNA methylation. Fetal estrogens may be weakest estrogen when function is assessed using the classic definition of estrogen action, however they are powerful tissue specific agents. These estrogens may have added benefits that are yet to be fully explored.

Compounded Bioidentical Hormone Therapy

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Pharmacy compounding fills an important role when an individual patient requires a unique formulation of a medication due to an allergy to an ingredient or excipient of an FDA-approved product or a dose or mode of administration (eg elixir versus tablet) that is unavailable. Because of the low anticipated need for compounding, state pharmacy boards were initially charged with regulation rather than FDA. During the past two decades the mounting of “bioidentical” or “natural hormone therapy; these formulations contain similar contraceptive dose of progestin, but have similar risks of unintended pregnancy as compared to other age groups, though chance of live birth is decreased. A guiding treatment philosophy to remember is that the risks of an unintended pregnancy are always higher than the risks of any contraceptive, including for arterial and venous thromboembolism risks. Various options to treat women during this time include progesterin only contraceptives, progesterin only contraceptives in combination with postmenopausal dose estrogen, menopausal dose estrogen progesteron therapy, or combined (estrogen containing) hormonal contraceptives. Progesterin only implants and IUDs have the highest contraceptive effectiveness, which are important considerations in younger women. However, in perimenopausal women, contraceptive efficacy may not be the highest concern; impact on ovulation, controlling symptoms of hypoeostrogenism, and bone health are often equally important. Typically, women in this age group are not ready to stop contraception just because of the change in hormone delivery, especially as not only prevent pregnancy, but also to optimize cycle control. If postmenopausal dose estrogen with a contraceptive progesteron is to be used separately, long-acting options such as IUDs and implants will ensure long-term endometrial protection. Several of these options (LARC) may be removed with FDA-approved indications, which is an important benefit when women are in the late menopause transition, at times minimizing the need for repeat procedures. When using combined (estrogen containing) hormonal contraceptives during perimenopause, it is important to follow guideline recommendations to ensure that women are safely offered their full range of options. Many estrogen containing contraceptives are often appropriate even in the presence of a family history of breast cancer, migraines without aura, and other cardiovascular risk factors such as diabetes. It is the medical history that determines whether estrogen containing contraceptives are appropriate for women, not simply age. During perimenopause, estrogen formulations containing 20 mcg or less of ethinyl estradiol are often sufficient for symptom control, and provide a more favorable safety profile as compared to higher doses. The difference between the various progestins used in combined hormonal contraceptives are usually of minimal clinical significance. However, patients may have read about safety considerations of different progestins, and thus may need specific counseling to address these concerns. Putting risks in the context of other absolute risk is often preferred to ease communication. Continued use of continuous combined hormonal contraceptives (without a placebo break) will often provide symptom control, but may be associated with more breakthrough bleeding. A new contraceptive vaginal ring (13 mcg ethinyl estradiol with a novel progesteron) as well as a new injection site depot (50 mcg) have recently become available in the United States, expanding the treatment options for women during this important phase of life. In addition, decreasing doses of estrogen is available to seamlessly transition to hormone therapy; these formulations contain similar contraceptive dose of progesteron, but with decreasing doses of estrogen from contraceptive to postmenopausal formulations. With the non-counter access to ethinyl estradiol available in the US for the first time, clinicians should feel comfortable offering low-dose estrogen-based contraceptive
therapies during the menopause transition, when appropriate. Multiple progesterin only contraceptive options are available for those with high risk comorbidities who may not be appropriate candidates for contraceptive doses of estrogen.

**Genitourinary Syndrome of Menopause Management**
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The genitourinary syndrome of menopause (GSM) describes a collection of symptoms affecting the lower urogenital tract attributed to estrogen deficiency after menopause. Vulvovaginal dryness, dyspareunia, pain with urination, urinary frequency, urgency, and incontinence are prominent symptoms reported by more than half of postmenopausal women. Similar symptoms may result from many vulvovaginal and urinary conditions unrelated to estrogen deficiency, and accurate diagnosis requires thorough consideration of other potential causes. First line treatment for vulvovaginal dryness is lubricants and moisturizers. Introtidal dyspareunia may be treated with topical lidocaine. When additional treatment is needed or preferred for vulvovaginal symptoms, low-dose vaginal estrogen therapy (ET) is a well-established therapy with demonstrated efficacy and safety. However, non-estrogen products include the oral estrogen agonist/antagonist (EAA, formerly SERM), ospemifene, and vaginal prasterone (dehydroepiandrosterone, DHEA) (Table). These products have not been compared in head-to-head trials, but individual studies show comparable effectiveness. Prospective trials have shown no evidence of endometrial hyperplasia or cancer after 1 year. Large observational trials have shown no increase in rates of endometrial and breast cancer after several years of use. Lower urinary tract disorders are also responsive to low-dose vaginal estrogen. Several small trials have shown an approximately 50% reduction in recurrent urinary tract infections (UTIs) and associated comorbidities from antibiotic use can be reduced. There is limited evidence that lower urinary tract symptoms (LUTS) such as dysuria, urinary frequency and urgency, nocturia, and stress and urge incontinence are improved with low-dose vaginal ET, but not systemic ET. When women present with both vulvovaginal and urinary symptoms as a trial of vaginal ET is prudent. If LUTS are not improved or resolved after 3 months of vaginal ET, then addition of other evidence-based therapies for LUTS is warranted. Women with a history of breast cancer require special consideration due to the concern that estrogen-sensitive tumors could be stimulated by low-dose vaginal ET. Several large observational and prospective case-control studies have shown no increase in breast cancer with use of low-dose vaginal ET. Systemic absorption does occur with vaginal preparations, but with the lower dose preparations of vaginal estrogen (Table), highly-sensitive estradiol assays demonstrate that serum estradiol levels remain within the range of reported baseline levels in normal, untreated postmenopausal women, 3.1 pg/mL to 4.9 pg/mL. Based on observational data and low systemic absorption, expert consensus in several society guidelines endorses low-dose vaginal ET for symptoms that are not alleviated by nonhormone therapy, in consultation with the patient and their oncologist. Caution is advised for women being treated with aromatase inhibitors, which aim to reduce circulating estrogen levels to zero, an aim that may be offset by low-dose vaginal ET. Overall, clinicians have an attractive menu of options to help women affected by GSM.

**Government-Approved Therapies for Genitourinary Syndrome of Menopause in the United States**

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Novel Phenotypes of Cardiovascular Disease in Women

C. Noel Bairey Merz, MD, FACC, FAHA, FESC. Barbra Streisand Women’s Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA

It is well established that there are sex and gender differences in the clinical manifestation of cardiovascular disease (CVD), the incidence of cardiovascular event, and the use of evidenced-based CVD therapies that contribute to the unexplained of novel phenotypes of CVD in women. There are also gender and sex differences physiologic factors unique to women or to men that may affect cardiovascular risk, diagnosis and therapies. The recognition that sex and gender affect the pathophysiology and the expression of human disease, including CVD, led to the NIH mandate to include both men and women in clinical studies and trials, and to analyze data by sex. However, the number of identified variables contributing differentially to CV outcomes in men and women is large and growing. Many of these variables are not considered during the design of clinical trials or longitudinal cohort studies, which reduces the ability to determine the strength of these variables as sex-specific contributors to health and disease. The purpose of this presentation is to review understanding of etiology, and approaches to diagnosis and therapeutic strategies of novel phenotypes of CVD in women. Research will be reviewed in order to improve clinical CVD investigation to optimize the health of women and men. Recognition of female-pattern IHD offers the opportunity to improve the CVD outcomes in women. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation. 2017 Mar 14;135(11):1075-1092.

**Women’s Cardiovascular Health at Midlife: The Role of Hot Flashes, Sleep Problems, and Trauma**

Rebecca C. Thurston, PhD. Women’s Biobehavioral Health Laboratory, University of Pittsburgh, Pittsburgh, PA

Cardiovascular disease (CVD) is the leading cause of death in women. CVD in women has key features. For example, reproductive factors, including the menopause transition, are increasingly understood to be important to the development of CVD in women. For many women, the menopause transition can be a time of accelerated accumulation of atherosclerosis beyond the effects of aging alone. However, what menopausal factors beyond sex hormones are important to the development of CVD are not fully understood. Vasomotor symptoms (VMS) are the classic menopause symptom, experienced by the majority of women at some point during the menopause transition. Sleep disturbance is also common and reported by up to half of women during the menopause transition. A growing body of research from large epidemiologic studies as well as from clinical physiology studies using physiologic measures of VMS indicates that frequent or persistent VMS may be associated with CVD risk including subclinical and clinical CVD. Further, short or disrupted sleep during the menopause transition is also linked to increased CVD risk beyond the effects of VMS. Our newest findings bridge the peripheral and cerebral vasculature, showing that VMS and poor sleep may also be associated with neuroimaging indicators of cerebrovascular risk among midlife women. These menopause symptom-CVD risk associations are not explained by sex hormones nor by standard CVD risk factors. Finally, psychosexual adversity, such as a history of trauma, can further exacerbate women’s CVD risk at midlife. Novel mechanisms under investigation include alterations in autonomic nervous system function and inflammatory and epigenetic pathways. As women typically develop clinical CVD and stroke during the postmenopause, identification of novel risk factors at midlife may ultimately be leveraged to reduce the burden of CVD in women.

**PLENARY SYMPOSIUM #2**

**Is FSH An Active Driver of Menopause?**

T R. Kumar, PhD. Division of Reproductive Endocrinology and Infertility, University of Colorado Anschutz Medical Campus, Aurora, CO

Follicle-stimulating hormone (FSH) is essential for female fertility. FSH action is required for ovulation induction, and estrogen production by granulosa cells. Although estrogen levels steadily decrease with age, FSH levels continue to significantly rise. Ovarian senescence or menopause results in suppression of estrogen when FSH levels maximally increase and thereafter FSH levels remain steadily high. This altered hormonal milieu, particularly, the loss of estrogen is correlated with osteoporosis and often accompanied by visceral adiposity in women. It is still debated whether loss of FSH action on the ovary causes a decline in estrogen, or whether loss of estrogen triggers production of a different form of FSH that is biologically ineffective at producing estrogen from the ovary. To address this critical question in female reproductive aging, we identified distinct FSH glycoforms in human pituitaries whose abundance changes as a function of age. More recently, a growing body of research from large epidemiologic studies as well as from clinical physiology studies using physiologic measures of VMS indicates that frequent or persistent VMS may be associated with CVD risk including subclinical and clinical CVD. Further, short or disrupted sleep during the menopause transition is also linked to increased CVD risk beyond the effects of VMS. Our newest findings bridge the peripheral and cerebral vasculature, showing that VMS and poor sleep may also be associated with neuroimaging indicators of cerebrovascular risk among midlife women. These menopause symptom-CVD risk associations are not explained by sex hormones nor by standard CVD risk factors. Finally, psychosexual adversity, such as a history of trauma, can further exacerbate women’s CVD risk at midlife. Novel mechanisms under investigation include alterations in autonomic nervous system function and inflammatory and epigenetic pathways. As women typically develop clinical CVD and stroke during the postmenopause, identification of novel risk factors at midlife may ultimately be leveraged to reduce the burden of CVD in women.

**PLENARY SYMPOSIUM #1**

**Human Social Genomics: Implications for Cardiovascular Disease in Women**

Steve Cole, PhD. School of Medicine, University of California, Los Angeles, Los Angeles, CA

Research in human social genomics has begun to map the molecular pathways by which social, psychological, and cultural processes regulate the function of the human genome and thereby influence physiology, development, and health. As research in this area enters its second decade, the existing data is yielding new insights into the molecular underpinnings of resilience and thriving, and in addition to its historical focus on psychosocial determinants of disease. This talk summarizes the burgeoning field of human social genomics and its role in understanding the social patterning of cancer and cardiovascular disease in women’s health.
Estradiol and Estrone: Changing Ratios After Menopause

Richard J. Auchus, MD, PhD. Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI.

With ovarian follicle depletion as menopause approaches, the capacity for a woman to efficiently synthesize estradiol (E2) wanes. The adenals and ovaries, however, continue to produce androstenedione (A4), and extraglandular conversion to estrone (E1) continues to a variable extent and might contribute to the variation in menopausal symptoms. Commercially available direct immunoassays (IA) accurately measure circulating E2 in women throughout the reproductive years, but the performance of these assays for menopausal E2 concentrations has not been established. In order to assess estrogen effects across the menopausal transition, we established a liquid chromatography-tandem mass spectrometry (LC-MS/MS) E1 and E2 assay without derivatization and a lower limit of detection about 4 pg/mL using 0.2 mL serum. We found excellent correlation of E2 by IA and LC-MS/MS to about 15 pg/mL, but the correlation deterioration lower E2 concentrations. The presentation will discuss pitfalls and realities to LC-MS/MS assays, including variability depending on sample characteristics and instrumental performance. Finally, LC-MS/MS also allows simultaneous measurement of other steroids, such as 11-oxygenated androgens derived from A4. In particular, 11-ketotestosterone is a biologically active human androgen and the major androgen in most women and children, which does not decline with age or across the menopausal transition.

PLENARY SYMPOSIUM #3

Body Composition and Fat Patternning: Roles of Age and Estrogens

Wendy M. Kohrt, PhD. Division of Geriatric Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO.

Biophysical testing has shown that the different rates and the consequences of aging in one system can influence other systems. For example, reproductive aging, which results in decreased systemic sex hormone levels, is known to increase osteoporosis risk. This is of particular concern in women, because the loss of ovarian function occurs in mid-life. The understanding of the mechanisms of the loss of estrogen has been well studied, but changes in body composition and fat distribution paralleled those in the previous study, but there were no significant changes. The latter reflects both the suppression of resting metabolic rate and a dramatic reduction in spontaneous physical activity, both of which are prevented by estradiol treatment or by programmed exercise. Preclinical research has demonstrated that the disruption of energy balance involves both increased energy intake and decreased energy expenditure. The latter reflects both the suppression of resting metabolic rate and a dramatic reduction in spontaneous physical activity, both of which are prevented by estradiol treatment. To advance the translation of such findings to humans, we utilize a pharmacologic model of gonadal suppression to experimentally isolate the effects of sex hormones. Using this approach, we demonstrated that suppressing ovarian function in premenopausal women (aged 20-49 y) resulted in a decrease in resting metabolic rate (~50 kcal/d), which was prevented by estradiol therapy. Total energy expenditure was reduced even more dramatically (~130 kcal/d). Ovarian suppression resulted in increased abdominal adiposity and decreased muscle mass, both of which were prevented by estradiol. A similar follow-up study focused on premenopausal women nearing the menopause transition (aged 40+ y). Changes in body composition and fat distribution paralleled those in the previous study, but there were no significant changes in any component of energy expenditure. Our studies demonstrate that estrogens play an important role in body weight regulation in women, but (or proximity to menopause) may have an independent role.

Medical and Surgical Management of Weight Loss

Daniel H. Bessesen, MD. University of Colorado Anschutz Medical Campus, Aurora, CO.

Obesity, growing in incidence and is associated with some of the most common health problems seen in adults including type 2 diabetes, coronary artery disease, osteopathic sleep apnea, infertility, a variety of cancers (including breast, ovarian and endometrial), degenerative joint disease, depression and disability to name just a few. Changes in diet/physical activity, weight loss medications and bariatric surgery are the treatment options currently available to patients with obesity. It is important for health care providers to be comfortable discussing weight and weight loss treatments with their patients. Remembering that ultimately, responsibility for decisions about obesity treatment rests with the patient with support and information from the care provider can help the provider engage in a non-judgmental, supportive conversation about weight. Treatments that are more aggressive are appropriate for those individuals more severely affected by obesity. Lifestyle changes produce on average 5-10% weight loss. There is no one dietary strategy that has been shown to be best for weight loss. The best dietary approach is the one that the person can adhere to. Recent studies of intermittent fasting and weight loss treatments show promise as effective alternatives to macronutrient based approach. Commercial programs are another option that busy clinicians can feel comfortable recommending. Exercise appears to be important for weight loss maintenance but produces only about 2% weight loss when used as a primary weight loss strategy. Orlistat, phentermine, the combinations of phentermine/topiramate or bupropion/biotechnology, give 5-10% more weight loss than lifestyle treatments alone. Sleeve gastrectomy and gastric bypass surgery give 23-30% weight loss and have dramatic benefits on weight related comorbidities, especially type 2 diabetes. While the numbers given above reflect the average weight loss seen with each category of treatment, dramatic inter-individual differences in actual weight loss are characteristic of each approach. Weight loss has beneficial effects on women’s reproductive function and fertility although there are some specific concerns to pregnancy following bariatric surgery. An appreciation of the basic principles of common counseling theories including the transcultural model, the health belief model, motivational interviewing, values based counseling and cognitive behavioral therapy, can help even busy clinicians have more productive and rewarding conversations with their patients about weight.

PLENARY SYMPOSIUM #4

Sleep, Appetite Regulation, and Weight Gain

Kelly G. Baron, PhD, MPH. DBSM. Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT.

As the prevalence of obesity continues to increase, there have also been parallel changes to sleep habits, such as decreases in sleep duration and an increase in circadian disruption through work and leisure activities. The availability of 24h access to energy dense and palatable foods has also coincided with increases in opportunities to trade sleep for other activities, such as electronics. The objectives of this presentation are to discuss the literature on what is known about the role of sleep and circadian rhythms in appetite and weight regulation. This presentation will cover 1) Background on sleep and circadian rhythms, 2) Epidemiology of sleep and obesity, 3) Laboratory studies of sleep and circadian rhythm manipulations and effects on metabolism and eating behaviors and finally 4) Emerging literature examining whether sleep and circadian interventions show promise. Sleep and weight loss interventions will demonstrate the multiple biological and behavioral pathways that link sleep and circadian rhythms to appetite and weight regulation and will discuss potential avenues for sleep and circadian interventions to promote cardiometabolic health.

Women, Anxiety, and Menopause: Novel Treatments for Anxiety Disorders

Andrew M. Novick, MD. Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO.

Anxiety is the most prevalent type of psychiatric disorder yet commonly receives less attention compared to depression. This has held true in the context of menopause where considerably less is known about anxiety during the menopausal transition. Conflicting evidence regarding the vulnerability of menopausal women to anxiety is likely due to the multiple biological and behavioral pathways that link sleep and circadian rhythms to anxiety. This presentation will cover 1) Background on sleep and circadian rhythms, 2) Epidemiology of sleep and obesity, 3) Laboratory studies of sleep and circadian rhythm manipulations and effects on metabolism and eating behaviors and finally 4) Emerging evidence examining whether sleep and circadian interventions show promise. Sleep and weight loss interventions will demonstrate the multiple biological and behavioral pathways that link sleep and circadian rhythms to appetite and weight regulation and will discuss potential avenues for sleep and circadian interventions to promote cardiometabolic health.
factors that influence cerebral blood flow and vascular activation were associated with the development of white matter hyperintensities (WMH). In normotensive women, increases in aortic blood pressure, which may increase prior to changes in brachial pressures, associated with development of WMH as did the quantity of monocye- and endothelium-derived microvesicles. These effects of aortic pressure and activated microvesicles on WMH were independent of menopausal hormone therapies. Although systolic blood pressure was associated with deficits in auditory attention and working memory in women prior to randomization, the long-term consequences of these other peripheral, hormonal and structural changes on cognition are being evaluated in the KEEPS continuation study, which will be completed in 2023.

PLENARY SYMPOSIUM #6
Caution to Menopause Practitioners Addressing Sexual Concerns: Look Both Ways!
Stanley E. Althof, PhD 1,2, Sheryl A. Kingsberg, PhD 1,3. 1Case Western Reserve University, Cleveland, OH; 2Center for Marital and Sexual Health of South Florida, Greenacres, FL; 3University Hospitals Medical Center, Cleveland, OH. In 1970, Masters & Johnson established that “There is no such thing as an uninvolved partner in a marriage or relationship where sexual dysfunction exists.” In this presentation, we review the dynamic and reciprocal relationship of one partner’s sexual function, sexual satisfaction, physical and mental health to the other partner’s sexual health and satisfaction. Drs. Althof and Kingsberg will then invite attendees to “join them” for a series of recorded office visits with standardized patients as they uncover how partners in a long-term relationship often play a role in precipitating and maintaining dysfunction. Through a series of virtual office visits, Drs. Althof and Kingsberg demonstrate how and why menopause practitioners, particularly with patients who present with genitourinary syndrome of menopause or hypoactive sexual desire, need to consider the impact of one partner’s sexual dysfunction on the other partner and how modern treatment planning can consider and successfully engage both partners.

PLENARY SYMPOSIUM #7
Surgical Menopause and Primary Ovarian Insufficiency
Wendy Wolfman, MD, FRCS, FACOG. Department of Obstetrics and Gynecology, University of Toronto, Toronto, ON, Canada. Primary ovarian insufficiency is a serious life altering disorder with multisystemic ramifications. It occurs with a global prevalence of 3.7% of women under the age of 40. Etiologies that can be determined in only 10-20% of patients are genetic, autoimmune, infectious, metabolic, idiopathic and iatrogenic due to surgery and radiation. Surgery is the most common known cause. Removal of both ovaries results in the acute reduction of estrogen, progesterone and testosterone as well as alteration of the hypothalamic pituitary axis. Ovaries are removed at surgery due to a variety of gynecologic reasons such as treatment for endometriosis, risk reducing surgery for genetic high risk carriers and treatment of some gynecologic malignancies. The risk of ovarian cancer after hysterectomy has been found to range from 0.1-0.75%. The potential number of inappropriate oophorectomies at the time of hysterectomy in premenopausal women was 38% of hysterectomies from 2005 to 2011 in California although that number does appear to be decreasing perhaps due to increasing prophylactic salpingectomies to prevent ovarian cancer. There are multiple detrimental health effects of early surgical menopause. These include earlier mortality, cardiovascular disease, cognitive deterioration and mood disorders such as depression, Parkinson’s disease, osteoporosis, and osteopenia. Ovarian insufficiency often results in more severe estrogen deficiency symptoms producing hot flashes, night sweats, mood changes, sleep disruption, sexual and genitourinary symptoms. A cohort study following 144,260 women from the British Medical Health Database confirmed that an increased composite of cardiovascular and genitourinary symptoms. 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Effects of discontinuing osteoporosis drugs • bisphosphonate “holidays” • choosing among osteoporosis treatments • combining osteoporosis agents or using them in specific sequences • treatment goals and goal-directed therapy

PLENARY SYMPOSIUM #9

Heart Fat and Menopause
Samar R. El Khoudary, PhD, MPH, BPharm, FAHA. Department of Epidemiology, Epidemiology Data Center, University of Pittsburgh, Pittsburgh, PA

Visceral adipose tissue is a metabolically active fat depot that produces several inflammatory markers with significant atherogenic properties. Heart fat, which directly surrounds the myocardium and the coronary arteries, has similar inflammatory features to that of visceral fat. The proximity of heart fat to the myocardium and vasculature may result in a higher pro-atherogenic contribution as compared to abdominal visceral fat. Heart fat has been associated with coronary arterial disease risk factors, cardiovascular events, and all-cause mortality. The menopausal transition has been related to an increase in abdominal visceral fat and thus, may also be related to an increase in heart fat in older women. Heart fat may provide a readily detectable, noninvasive, novel risk marker for coronary arterial disease in postmenopausal women. This talk will present accumulating evidence on heart fat as a potential menopause-related risk factor for cardiovascular disease. Recent findings of effects of menopause hormone therapy on heart fat accumulation and its association with subclinical atherosclerosis in early menopausal women will be summarized. Available data on how lifestyle modifications, including diet and exercise, might impact heart fat accumulation and its related risk of developing cardiovascular diseases will be reviewed. With advanced technology, it is now possible to measure heart fat automatically from non-contrast cardiac CT scans using deep learning algorithms in less than 30 seconds! Quantification of heart fat has been shown to provide clinical data beyond the widely used coronary artery calcium score for risk stratification. This makes heart fat a potentially innovative prognostic metric that women’s health care providers can obtain when also measuring coronary artery calcification score.

Heart Disease: Distinctions in Women
Judith Regensteiner, PhD. Department of Medicine, Divisions of Internal Medicine and Cardiology, University of Colorado Anschutz Medical Campus, Aurora, CO

It is still often not well known that cardiovascular disease is the number one cause of death for women. Although heart disease is sometimes erroneously thought of as a man’s disease, almost as many as women as men die each year of heart disease in the United States. The risk of heart disease in women is often underestimated due to the perception that females are “protected” against cardiovascular disease. While this is the case in premenopausal women, after the menopause, women gradually catch up to men (within 7-10 years) with regards to prevalence of heart disease. In addition, in women with type 2 diabetes, the protection against heart disease is not present even in premenopausal women. Women may experience very different symptoms of heart disease in men too, which decreases the ability to recognize and treat it quickly. Women also have a lower referral rate for diagnostic and revascularization procedures, less referral to cardiologists, poorer treatment of cardiovascular risk factors and are more likely to have symptoms ascribed to psychiatric causes. In addition, overall there is reduction in death from cardiovascular disease, this is not true in women with diabetes. The under-recognition of heart disease and differences in clinical presentation in women has led to less aggressive treatment strategies and a lower representation of women in clinical trials. Women who are part of racial/ethnic minority groups suffers the consequences even more than non-Hispanic white women. For instance, African American women are 60 percent more likely to have high blood pressure, compared to non-Hispanic white women. Access to care is another concern for all women and especially those in racial/ethnic minority groups. Thus there are high sex and gender differences in the consequences of heart disease in women. These concerning findings suggest that much more work is needed to promote awareness, provide education and enhance treatment strategies. In terms of awareness, information about heart disease in women needs to be made accessible to women of all ages and all races/ethnicities. Education needs to be provided more widely as well since many women still believe that they cannot get heart disease. Treatment strategies need to be developed focusing on prevention, diagnosis and treatment. These efforts will require that much more research be done on the sex and gender differences in cardiovascular disease in women.

KEYNOTE ADDRESS

What is Wellness?
James Q. Hill, PhD, Nutrition Obesity Research Center, The University of Alabama at Birmingham, Birmingham, AL

The US population is experiencing high rates of lifestyle-related (diet, exercise, sleep, stress) chronic diseases. Efforts focusing on modifying single behaviors (i.e. diet, exercise) have not had significant success. This is illustrated by rising rates of obesity, a marker for lifestyle-related chronic diseases, despite massive efforts directed toward weight management. The concept of wellness might be a way to create a holistic approach to achieving a lifestyle that maximizes health and happiness. It involves physical and mental health. However, wellness is still a rather vague concept with no clear definition and no definitive method of measurement. This presentation will consider advantages and disadvantage of a focus on wellness as well as issues of definition, measurement, and method of change. It may be easier to create a culture of health in our population by focusing on wellness rather than disease prevention.

NAMS/PFIZER WULF H UUTIAN ENDOWED LECTURE

Ghosts from the Past: Impact of Childhood Adversity on Mood and Cognition at Menopause
C N. Epperson, MD. Department of Psychiatry, University of Colorado School of Medicine, Aurora, CO

A vast scientific literature links childhood maltreatment and family adversity to poor health outcomes from adolescence to old age. The biological and psychosocial mechanisms by which these adverse childhood experiences (ACEs) lead to medical conditions such as heart disease, obesity, migraines, autoimmune conditions, as well as depression, anxiety and substance use disorders, are multifactorial and complex. Preclinical and human research have revealed that ACEs have an enduring impact on stress physiology, epigenetics and reproductive and immune function. Gender differences in the timing and type of ACE exposure as well as sex differences in gonadal steroids and their effect on stress and immune physiology suggest that women, particularly during periods of ovarian hormonal change, are more vulnerable to the negative impact of ACEs on their health and wellbeing. The menopause transition, with its unpredictable fluctuating levels of gonadal steroids followed by hypergonadism represents a collision between numerous psychosocial adjustments and biological upheaval that may unmask the impact of ACEs in even formally resilient women. ACEs are associated with first episode major depression and onset of subjective and objective executive function difficulties during the peri and early post menopause. While it is impossible to keep “ghosts from the past” from haunting someone’s memory, it is incumbent upon clinicians to identify menopausal women who are at greater risk of adverse health outcomes due to ACEs. Finally, research is needed to develop prevention and treatment strategies to diminish the adverse effects of childhood adversity on mood, cognition and overall health during the menopause transition.

NAMS/KENNETH W KLEINMAN ENDOWED LECTURE

Social Media and Menopause: Separating Health from Hype and Why It Matters
Jen Gunter, MD, FRCSC(FC), FACOG, DABPM, ABPMR. Obstetrician/Gynecologist, Pain Medicine Physician, San Francisco, CA

The benefits of social media for medical communication about the menopause continuum are significant. Social media increases the speed of access and the volume of health information, removes barriers to knowledge, and disrupts harmful hierarchies. In many cases social media also combines a personal connection — hence the social part — increasing trust in the perceived accuracy of the content and the receptivity of the information. Women in the menopause transition and those who are postmenopausal have long been marginalized by both the medical community and society in general, so not only does social media offer access to needed information it provides community. A major concern regarding social media is the quality of the medical content and the challenge in sorting fact from fiction. Misinformation and disinformation about the menopause continuum on social media are especially common. False safety claims about compounded menopausal hormone therapy (MHT), promotion of salivary hormone testing, misleading information about so-called plant-based therapies, diets that purport to reset hormones, and untested supplements are common examples of the incorrect and potentially harmful messaging found on social media. Medical conspiracy theories are often featured, directly or indirectly, increasing the harm beyond the original content. The influence aspect of social media also inserts significant and often undisclosed bias, bots are an increasing vector of medical disinformation, and information silos that amplify misinformation and disinformation are common. Repetition across multiple platforms, a unique aspect of social media, preferentially increases exposure to incorrect information and may increase belief in unsubstantiated or false claims via the illusory truth effect. Social media offers a wide variety of ways to engage in dissemination of quality information about menopause — from providing links to sites with quality information, studying the impact of social media on medical decision making, to engaging in content creation. Social media is a tool for patient-centered communication and understanding how these platforms are being used to navigate information about the menopause continuum as well as their advantages and their pitfalls is vital as social media has an important role in health literacy.