

MENOPAUSE 101 COURSE

Management of Vasomotor Symptoms

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Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) of menopause and is first-line therapy for bothersome hot flashes and night sweats. FDA-approved indications for systemic HT include treatment of moderate to severe VMS, genitourinary syndrome of menopause (GSM), premature menopause, and prevention of postmenopausal osteoporosis. Indirect benefits may include improvements in mood, sleep, sexual dysfunction, and joint pain. Contraindications include unexplained vaginal bleeding, prior estrogen-sensitive cancers (breast or endometrial), history of stroke or myocardial infarction, history of or inherited high risk for venous thromboembolism (VTE), and severe active liver disease. The Women's Health Initiative (WHI) trials fundamentally shaped our understanding of HT risks and benefits. Age-stratified analyses demonstrate that for women younger than 60 years or within 10 years of menopause onset, the benefit-risk ratio is favorable, while initiation in older women who are more than 10 years past menopause carries greater absolute risks of coronary heart disease, stroke, VTE, and dementia. This "timing hypothesis" is now central to clinical decision-making. A contemporary approach to HT prescribing incorporates ASCVD risk assessment using the PREVENT calculator: women with less than 3% 10-year ASCVD risk may consider oral or transdermal HT, while those with 3% to 10% risk should optimize modifiable risk factors and treat cardiovascular disease risk factors according to guidelines before initiating therapy and should preferentially use transdermal formulations. HT is not recommended for women with ASCVD risk greater than 10%. Based on observational data, transdermal estradiol may be preferred over oral because it avoids first-pass hepatic metabolism, resulting in less effect on clotting factors, blood pressure, triglycerides, C-reactive protein, and sex hormone-binding globulin. Women with an intact uterus require a concomitant progestogen for endometrial protection; micronized progesterone is preferred given its more favorable safety profile regarding VTE and breast cancer risk. The tissue selective estrogen complex (conjugated estrogens plus bazedoxifene) offers an alternative without increases in breast tenderness, breast density, or endometrial thickness. FDA-approved bioidentical hormone options include oral and transdermal 17-beta estradiol and oral micronized progesterone. Custom compounded hormone preparations are not recommended due to lack of data on purity, potency, safety, and efficacy; batch-to-batch variability; absence of a package insert; and incomplete adverse event reporting. Importantly, women with common chronic conditions may still be candidates for HT. In women with controlled hypertension, transdermal estrogen has a neutral effect on blood pressure, and micronized progesterone is preferred. In women with obesity, transdermal HT is recommended given lower VTE risk, and HT favorably affects body composition by preserving lean mass and reducing visceral adiposity. In women with type 2 diabetes, HT improves glycemic control and insulin resistance, with transdermal formulations preferred. For women with a history of VTE, systemic HT is generally avoided, but transdermal estrogen with micronized progesterone may be considered in appropriately anticoagulated women with significant VMS. In BRCA mutation carriers without cancer, systematic reviews suggest HT does not appear to increase breast cancer risk. For women with contraindications to HT or who prefer nonhormonal options, neurokinin (NK) receptor antagonists represent a major advance. Fezolinetant, an NK3 receptor antagonist (FDA-approved 2023), and elinzanetant, a dual NK1/NK3 receptor antagonist (FDA-approved 2025), have demonstrated significant reductions in VMS frequency and severity in phase 3 trials, with elinzanetant also showing significant improvements in sleep disturbances and menopause-related quality of life. Treatment of menopause symptoms must be individualized using shared decision-making, with periodic reassessment of the benefit-risk balance.

Management of Genitourinary Syndrome of Menopause

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Over 50% of women experience genitourinary syndrome of menopause (GSM), which can have a significant negative impact on quality of life. GSM encompasses vaginal dryness, vulvovaginal irritation, dyspareunia, dysuria and urinary urgency, among other symptoms. In this presentation we will discuss the presentation and evaluation of GSM, as well as how to distinguish this from other conditions that occur after menopause. Treatment for GSM can range from simple changes to personal care habits, to non-hormone, over-the-counter interventions, to prescription therapies. Additional treatments that have been marketed include devices, lasers and injections. This talk will review the range of treatment options for different presentations of GSM and the available evidence supporting their use.

Management of Hypoactive Sexual Desire Disorder

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Sexual problems are common in midlife women, affecting over 40% of this population, and are associated with detriments in quality of life and relationship satisfaction. When sexual problems cause clinically significant distress for a woman, and the symptoms are not due to another cause, the woman can be diagnosed with sexual dysfunction. One in ten midlife women meet diagnostic criteria for sexual dysfunction. The most common type of sexual dysfunction encountered in midlife women is hypoactive sexual desire disorder (HSDD). Women can be screened using a brief validated tool called the Decreased Sexual Desire Screener (DSDS). When assessing women with HSDD, it is important to take a multifaceted, biopsychosocial approach, as many factors can impact

sexual function during midlife. These factors can include relationship quality, changing romantic partners, partner sexual dysfunction, social roles such as caring for children or aging parents, career stressors, financial strain, development of medical problems and the treatment of those problems, mood disorders, and cultural factors. While longitudinal studies show that, on average, sexual desire tends to decline as women move through midlife, not all women will experience desire declines. The relationship between serum sex steroid levels and sexual desire in women is complex and non-linear. No routine bloodwork is required for the assessment of HSDD unless review of systems and physical examinations suggest an underlying cause, such as undiagnosed diabetes or thyroid disorders. Treatment of HSDD requires a multifaceted approach. If genitourinary syndrome of menopause or another sexual pain disorder is present, it should be treated in tandem with HSDD. There is some evidence that psychotherapies, such as tailored cognitive behavioral and mindfulness approaches, are effective for HSDD. The ASSET website has a searchable database of certified sex therapists. There are two FDA-approved medications for the treatment of HSDD, bremelanotide and flibanserin. Bremelanotide is only approved for pre-menopausal women, while flibanserin is approved for women under 65 years of age. Bremelanotide is an on-demand injection and can be associated with nausea or hyperpigmentation of the skin. Flibanserin is a daily pill and can be associated with dizziness, especially if taken simultaneously with alcohol. There is a substantial body of evidence showing that transdermal testosterone is effective for the treatment of HSDD in surgically and naturally post-menopausal women, but it is not approved for this purpose, and FDA-regulated products at dosages appropriate for women are not available in the United States. Bupropion and sildenafil also have some more modest evidence for efficacy in the treatment of HSDD as well as antidepressant-induced sexual dysfunction.

Cognitive Changes in Midlife

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Cognitive complaints, commonly described as "brain fog," are increasingly recognized as an important concern among women during the menopausal transition. Among the cognitive domains studied, verbal memory is the most consistently demonstrated area of change, with prospective studies showing declines in the ability to learn and recall verbal information as women transition from premenopause into perimenopause. These changes are generally modest and remain within the normal range of cognitive function for most women, but they may be subjectively noticeable and bothersome. Evidence that memory changes also occur following surgical removal of the ovaries or pharmacologic suppression of ovarian hormone production with gonadotropin-releasing hormone agonists (GnRHa) provides additional support for a potential role of changing ovarian hormone exposure in midlife cognitive changes. Brain fog encompasses a broader range of subjective experiences, including difficulties with attention, word retrieval, maintaining a train of thought, and switching between tasks, and can meaningfully affect daily functioning. Although brain fog is subjective and lacks a validated measure of severity, women's cognitive complaints can correspond with objective measures of memory performance. Importantly, cognitive changes associated with the menopausal transition should be distinguished from cognitive disorders such as Alzheimer's disease. Clinical evaluation should consider the broader menopausal context and assess potentially modifiable contributors to cognitive symptoms. Sleep disturbance, vasomotor symptoms (VMS), and mood symptoms have each been associated with cognitive performance, with sleep emerging as an important contributor to memory difficulties in some studies. VMS may also be independently associated with changes in verbal memory, suggesting that management of bothersome menopausal symptoms may have relevance for cognitive well-being. Although menopausal hormone therapy (MHT) is an established treatment for VMS, evidence regarding its effects specifically on cognition during perimenopause remains limited, and current data do not support its use solely to treat cognitive symptoms. Addressing sleep, VMS, and mood symptoms, together with attention to cardiovascular and lifestyle factors, may provide a comprehensive approach to cognitive health during midlife. Midlife hypertension is associated with increased risk of subsequent cognitive decline and dementia, highlighting the importance of blood pressure control and broader cardiovascular risk reduction. Regular physical activity, healthy weight management, a heart-healthy diet, social engagement, and cognitively stimulating activities may further support long-term brain health. Recognizing verbal memory decline as a characteristic cognitive change during the menopausal transition, while appropriately evaluating symptoms and conditions that may contribute to cognitive difficulties, can help clinicians validate women's experiences, identify modifiable contributors, and provide individualized strategies to support cognitive and overall health during midlife.

Cardiovascular Health

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The menopause transition represents an important opportunity to assess cardiovascular health and focus on prevention. Although menopause itself does not directly cause cardiovascular disease, the transition is accompanied by hormonal, metabolic, and physiologic changes that can influence cardiovascular risk. Changes in lipids, body composition, visceral adiposity, metabolic health, vasomotor symptoms, and sleep apnea may emerge or become more clinically relevant during this stage of life. Understanding which changes are associated with ovarian aging, and which are primarily related to chronologic aging can help clinicians provide more individualized cardiovascular risk assessment and counseling. This presentation will review cardiovascular changes associated with the menopause transition, including menopause characteristics that may identify women at greater risk. Current approaches to lipid assessment and cardiovascular prevention will be discussed, including the 2026 ACC/AHA multi-society dyslipidemia guidelines, Life's Essential 8, and use of the PREVENT calculator to personalize cardiovascular risk.

Mood Changes in Midlife

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Women are more susceptible to depression and anxiety than men, with research highlighting a higher risk of both new and recurrent depression at certain stages of their reproductive cycle. This has led to the conceptual framework of 'reproductive-related windows of vulnerability' for depression. Hormone fluctuations are believed to influence the development of mood symptoms, their clinical characteristics, and severity. For instance, women may experience mood disturbances and dysphoria during the luteal phase, develop depressive symptoms postpartum (puerperium), or experience depression around menopause, where hormone shifts and other factors can impact the emergence, severity, and presentation of mood issues. During midlife, women face psychological stressors and physical changes, the latter including metabolic issues, cardiovascular disease, diabetes, osteoporosis, osteoarthritis, chronic pain, and menopause-related problems such as vasomotor symptoms (VMS) and sleep disruptions, which can affect their quality of life and functioning. Depressive symptoms may include poor motivation, low engagement in usual activities, reduced enjoyment, and disrupted sleep. These symptoms tend to increase during the menopause transition and are associated with poorer quality of life. Major depressive episodes (MDDs) are less common but often recur among those with a prior history of depression. Depression during midlife can be examined through two factor clusters: 1) continuum-related factors, which include socioeconomic conditions, psychosocial stressors, and overall health; these factors tend to follow a woman throughout her life, making prior depression a strong predictor of recurrence; 2) window-related factors, which are time- or context-specific; they include hormone fluctuations, sleep disturbances, vasomotor symptoms, stressful life events near menopause, and the worsening of chronic medical conditions during midlife. Healthcare professionals should recognize these factors to better prevent, detect, and treat depression in midlife and beyond. Antidepressants and behavioural interventions remain the first-line treatment of depression across the life span, including the menopause transition and beyond. The use of antidepressants should be prioritized for women who experienced multiple depressive episodes in the past and/or for those reporting severe depressive symptoms, functional impairment, or suicidal ideation. For recurrent episodes, a previous response to a specific antidepressant (agent, class) should influence the decision on what to try first—ie, if a particular medication was helpful in the past, this should be considered. For those who are experiencing depression for the first time or are treatment-naïve, there is evidence of the efficacy and safety of various agents including fluoxetine, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, desvenlafaxine, and vortioxetine. Overall, there is no evidence to support a superior efficacy of a particular antidepressant agent or class over the others for the management of midlife depression. Safety information should be considered when choosing antidepressants for midlife women, especially when they are on other treatments. Drug interactions are important to consider, as perimenopausal and postmenopausal women often take multiple medications for other conditions. Tolerability is also key, as sexual dysfunction and weight changes are common concerns. Existing data on the additional benefits of antidepressants for managing other menopause-related symptoms (VMS, pain, disrupted sleep) could also help guide clinicians and patients during their decision-making process. Behaviour-based interventions such as cognitive behavioural therapy (CBT) have been shown to be effective not only for depression but also for managing other menopause-related problems, including anxiety, sleep problems, and VMS. Ultimately, treatment strategies need to be tailored to individual needs and priorities, considering shifts in symptom presentation and severity that may occur over time and therefore require adjustments. Importantly, neither depression nor anxiety during midlife should be managed in isolation. Sleep problems, cognitive complaints, genitourinary symptoms, sexual dysfunction, and context-related life stressors are relevant factors when developing comprehensive, effective treatment plans.

Night Sweats: What If It's Not Menopause?

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Night sweats unrelated to estrogen deprivation have a wide differential diagnosis spanning benign and serious conditions; careful clinical assessment is essential to distinguish menopausal vasomotor symptoms from alternative etiologies and to identify the minority of patients requiring more extensive evaluation and treatment. Vasomotor symptoms, particularly night sweats, can severely disrupt sleep and impair functioning at home and work, yet not all nocturnal sweating in midlife women is attributable to menopause. When menstrual history and associated symptoms do not meet clinical criteria for perimenopause or menopause, clinicians must consider broader causes and avoid overreliance on serum follicle-stimulating hormone or estradiol levels, which are often unreliable in women older than 40 years. The differential diagnosis of night sweats includes obstructive sleep apnea, obesity, gastroesophageal reflux disease, hyperthyroidism, mood and anxiety disorders, endocrine conditions such as diabetes and pheochromocytoma, autoimmune diseases, malignancy, infection, and lifestyle factors including smoking, alcohol use, and substance withdrawal. Medication-related sweating is common, especially with antidepressants (notably tricyclics, bupropion, venlafaxine), benzodiazepine withdrawal, cardiovascular agents, thyroid replacement, hypoglycemic therapies, and drugs that stimulate sweat glands; symptoms may persist for 1–2 weeks after discontinuation. Malignancies—particularly hematologic cancers such as leukemia and lymphoma, and solid tumors including renal cell carcinoma and medullary thyroid carcinoma—are established causes of night sweats and may present with nocturnal symptoms as a dominant feature. Infectious etiologies (HIV, tuberculosis, endocarditis, malaria, mononucleosis, and acute respiratory viruses) are less common in general practice but should be considered based on geography, travel history, and socioeconomic context. There is no single evidence-based algorithm for evaluating

non-menopausal night sweats; however, a detailed history and physical examination after excluding environmental factors (excessive bedding, clothing, room temperature) is the critical first step. In patients without high-risk features (weight loss, fever, lymphadenopathy) or a clear clinical diagnosis, a basic workup may include complete blood count, thyroid-stimulating hormone, inflammatory markers, testing for tuberculosis and HIV, blood cultures when indicated, chest radiography, and consideration of sleep studies given the high prevalence of obstructive sleep apnea in menopausal women with elevated body mass index. Empiric antibiotics are not appropriate during the initial evaluation; management should target identified underlying conditions, with escalation to advanced imaging or nocturnal temperature diaries when symptoms persist and no diagnosis is apparent. For idiopathic or mild night sweats, options directed at hyperhidrosis (aluminum chloride hexahydrate, anticholinergic or adrenergic agents) offer limited benefit, and emerging therapies such as neurokinin receptor antagonists may hold promise but have uncertain efficacy when symptoms are unrelated to estrogen decline. In primary care cohorts, persistent night sweats without a serious etiology are not associated with increased mortality, and many menopausal women with non-estrogen-related night sweats can be safely managed with reassurance and clinical monitoring when high-risk features and significant distress are absent.

BONE HEALTH 101 COURSE

Screening for Osteopenia or Osteoporosis—Who, When, and How?

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Osteoporosis is a common and chronic disorder characterized by low bone mass and heightened fragility fracture risk. Despite the severe consequences of osteoporotic fractures, including chronic pain, loss of physical independence, and increased excess mortality, a widening treatment gap persists. To address this gap, screening guidelines in the United States recommend dual-energy X-ray absorptiometry (DXA) screening for all postmenopausal women aged 65 and older, as well as younger adults with clinical risk factors. Clinical evaluation should also evaluate fracture risk factors that are independent of bone density, such as prior fractures, parental hip fracture, low body mass index, glucocorticoid use, active smoking. It is important to screen for secondary causes of osteoporosis, including rheumatoid arthritis, diabetes, as well as other bone-modifying endocrine and gastrointestinal disorders. Laboratory evaluation should start with standard tests (eg, calcium, phosphate, creatinine, alkaline phosphatase, and 25-hydroxyvitamin D), with more comprehensive work-up indicated if the bone density is lower than expected for age. Importantly, while osteoporotic bone density (T-score of -2.5 or lower) predicts high fracture risk and warrant treatment, many patients with osteopenia (T-score between -1.0 and -2.5) will also suffer fragility fractures and therefore may also benefit from treatment. The Fracture Risk Assessment Tool (FRAX) is utilized to estimate the 10-year probability of hip and major osteoporotic fractures and can guide clinical decision-making in treatment-naïve patients with osteopenia. However, FRAX has several limitations, including underestimating risk in patients with Type 2 diabetes or high frailty. Furthermore, FRAX incorporates race and ethnicity adjustments which has sparked clinical controversy. Under current United States guidelines, pharmacological intervention is recommended for individuals with a prior hip or spine fracture, a T-score of -2.5 or lower, or osteopenia combined with a 10-year FRAX probability of 3% or higher for hip fracture or 20% or higher for major osteoporotic fracture. For patients who do not meet these intervention thresholds, decisions regarding serial DXA re-screening must be individualized, balancing baseline bone mineral density, age, and patient-specific risk factors for accelerated bone loss.

How Can Patients Prevent Developing Osteopenia, Osteoporosis, or Fractures?

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The menopausal transition is characterized by accelerated bone loss driven by declining estrogen levels. Bone mineral density (BMD) may decrease by up to 2.5% per year during the perimenopause, with the most rapid losses occurring in the late perimenopause and the early postmenopausal (PMP) years. Women can lose an average loss of 10% to 12% (about 1 T-score) in the spine and hip. Thereafter age-related rates of bone loss fall to about 0.5% per year. This accelerated resorption predisposes women to osteoporosis and fragility fractures, which carry substantial morbidity, mortality, and economic burden. Identifying effective preventive strategies during this critical window is essential. Systemic estrogen therapy (ET), oral or transdermal with or without a progestogen, effectively prevents bone loss in PMP women and can maintain BMD and reduce fracture risk at all skeletal sites. In the Women's Health Initiative (WHI), conjugated equine estrogen (CEE) alone reduced clinical fractures by 29% and hip fractures by 35% over 7 years; CEE plus medroxyprogesterone acetate reduced clinical fractures by 24% and hip fractures by 33% over 5 years. This was in low-risk women without osteoporosis. Current guidelines recommend ET for fracture prevention in women younger than 60 years or within 10 years of menopause who are at low risk of venous thromboembolism (VTE), breast cancer, and cardiovascular disease, particularly when vasomotor symptoms (VMS) are present. Lower doses and transdermal formulations may confer a more favorable safety profile, though fracture reduction data are derived primarily from standard-dose oral regimens. An ultra-low-dose transdermal estradiol patch (0.014 mg/day) is FDA-approved for osteoporosis prevention. The effects of both oral and transdermal estrogen preparations on bone density are dose related. There are no randomized trials evaluating the effects of oral or transdermal estradiol on fracture

risk in women with osteoporosis. Therefore, estrogen is not approved or recommended for the treatment of osteoporosis. Although controversial, some experts will consider its use for healthy, younger postmenopausal women with no fracture history and borderline osteoporosis especially if they cannot tolerate other therapy. Among Estrogen Agonist/Antagonists (SERMs), raloxifene reduces vertebral fracture risk by approximately 40% but has not demonstrated efficacy against hip or nonvertebral fractures. It is an appealing option for younger PMP women at vertebral fracture risk who also have elevated breast cancer risk, given its approximately 56% reduction in invasive breast cancer incidence. Adverse effects include VTE, hot flashes, and leg cramps, limiting its use in women with significant VMS. Bazedoxifene shows similar vertebral fracture reduction and safety profile but not approved in the US or Canada. The tissue-selective estrogen complex (TSEC) combining CEE with bazedoxifene is FDA-approved for osteoporosis prevention and VMS treatment; it significantly improves lumbar spine and hip BMD compared with placebo, with favorable endometrial and breast safety profiles, though fracture reduction data are lacking. The beneficial skeletal effects of estrogen and SERMs are quickly lost on stopping therapy therefore consideration for a transition to another bone specific agent is often recommended. Adequate amounts of calcium and vitamin D are foundational to bone metabolism. Studies evaluating the effects of calcium and vitamin D supplementation alone on BMD and fracture risk are inconsistent. Vitamin D supplementation alone consistently shows no fracture reduction. Nearly all pharmacotherapy trials have included calcium and vitamin D in both arms, making adequate intake a prerequisite for pharmacologic efficacy. Most guidelines recommend 1000-1200mg of calcium and 600-800 IU vitamin D3 daily. Dietary sources of calcium are preferred over supplements due to the potential risk of nephrolithiasis and uncertain cardiovascular effects associated with supplements. Overall, treatment decisions should be individualized, balancing fracture risk, menopausal symptom burden, and the risk-benefit profile of each intervention.

Side Effects of Antiosteoporosis Medications

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A menu of treatment options is available to reduce fracture risk in women with postmenopausal osteoporosis. Because the skeletal benefits of all osteoporosis therapies dissipate at variable rates upon discontinuation, long-term if not lifelong management is required. Despite the very positive benefit:risk ratio of these therapies, most women at high fracture risk are not treated. Among those who do receive therapy, the average duration of therapy is only 1-2 years. This treatment gap is due, in large part, to concerns by both patients and providers about rare side effects, especially with bisphosphonate therapies. By understanding the nuances of adverse events (AEs) with different therapies and strategies to minimize those risks allows more effective communication with our patients. High daily doses of oral calcium preparations often cause nausea or constipation. One study showed an increased incidence of myocardial infarction with total daily intakes of calcium of 2000 mg or more. In the absence of malabsorption, daily calcium supplement doses of more than 800 mg are rarely needed, and these doses are not associated with side effects. High doses of vitamin D (>4000 IU daily) have been associated with hypercalciuria and, less commonly, hypercalcemia. Raloxifene is associated with an estrogen-like increased risk of venous thrombosis, and it may increase the frequency or severity of vasomotor symptoms. In a study of older women with risk factors for cardiovascular (CV) disease, the risk of death from stroke was increased with raloxifene compared to placebo. Oral bisphosphonates (BPs) have the reputation for increasing the incidence of upper GI symptoms. However, upper GI AEs are common in older postmenopausal women, and no differences in the rates of these AEs were observed in placebo-controlled trials. Flu-like symptoms (acute phase reaction) lasting 1-3 days occur in one-third of patients after the first but not subsequent doses of Intravenous zoledronate and rarely with the initiation of oral bisphosphonates. The frequency and severity of those symptoms is reduced with antipyretic therapy or can be fully prevented by 3 daily doses of dexamethasone. The background risk of osteonecrosis of the jaw (ONJ) with bisphosphonate is less than 1:10,000 patient-years (0.01%), increasing to 0.21% after 4 years of therapy. In a large Korean database, the incidence of ONJ in patients receiving either a bisphosphate was 0.43%-0.85% after tooth extraction and 0.13% after implant surgery. Similar rates were observed in women with osteoporosis receiving a SERM. Discontinuing osteoporosis therapy before invasive dental procedures does not reduce the risk of ONJ whereas optimizing oral health prior to the procedure reduces the very low risk by up to 70%. The risk of atypical femoral fracture is extremely low during the first 3 years of oral bisphosphonate therapy and is higher in Asian vs White women. Because there is no incremental benefit to continuing bisphosphonate therapy beyond 3-4 years, no patients should receive continuous oral BP therapy for more than 3-4 years at a time. PTH receptor agonists have vasodilatory effects and may cause lightheadedness soon after dosing but are not associated with increased risks of cardiovascular (CV) events. Compared to alendronate, romosozumab was associated with an increased incidence of CV events, but no relationship was observed in comparison to placebo. Several large observational studies have shown no difference in the rates of CV events with romosozumab compared to therapy with bisphosphonates or teriparatide. The side benefits of osteoporosis therapies should also be considered. Raloxifene significantly reduces the risk of invasive estrogen-receptor positive breast cancer. BP therapy has been associated with reduced mortality in both prospective, controlled, and observational studies. Denosumab therapy has been associated with a 21% reduction in fall frequency and a 16% reduction in incident type 2 diabetes. It is important to be able to communicate comfortably and accurately with patients about their concerns about side effects of osteoporosis therapies. This includes an appreciation of the relationships between adverse events and the efficacy of therapies to reduce fracture risk and an understanding strategy to minimize the risk of serious adverse events.

Two Sides of the Coin: Balancing Obesity Treatments with Bone Loss and Fracture Risk

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As metabolic bariatric surgery and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) become highly prevalent therapies for obesity, evaluating and addressing their distinct impacts on skeletal metabolism, bone mineral density (BMD), and fracture risk is clinically vital. Metabolic bariatric surgery offers durable health benefits but leads to skeletal fragility in a procedure-specific manner. Roux-en-Y Gastric Bypass (RYGB) triggers high-turnover bone loss, which ultimately doubles hip fracture risk. Sleeve Gastrectomy (SG) similarly drives high bone turnover, although the magnitude of bone loss is less than after RYGB. There are mixed data regarding the impact of SG on fracture risk. These surgical skeletal declines appear to be driven by a combination of mechanical unloading, nutritional deficiencies, and altered gut-adipocyte hormones. To optimize bone health after bariatric surgery, clinicians should encourage aggressive nutritional supplementation, weight-bearing exercise, regular laboratory monitoring, and consider parenteral antiresorptive therapy when T-scores are low or prior fractures exist. In contrast, the skeletal effects of GLP-1 RAs depend heavily on the clinical population and dosage. In patients with type 2 diabetes, lower-dose GLP-1 RAs demonstrate osteogenic properties that improve bone markers, increase BMD, and exert a neutral or protective effect on overall fracture risk. However, at the higher doses prescribed for obesity, GLP-1 RAs appear to accelerate bone loss and may elevate fracture risks in vulnerable subgroups, including in women and older participants. Ultimately, while both surgical and pharmacological obesity therapies are highly effective, their use necessitates proactive bone preservation strategies, particularly among postmenopausal women.

OPENING SYMPOSIUM

Move the Needle: What the Evidence Actually Says About Exercise in Menopause

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The menopause transition is a healthspan inflection point where women experience acceleration of bone loss, sarcopenia, visceral adiposity, and cardiometabolic risk. Exercise at midlife is a modifiable intervention that can effectively address these changes and help protect long-term function. This presentation reframes the clinical goal from lifespan to healthspan: what midlife women most want is years of independent function, not merely added survival. Data from the Study of Women's Health Across the Nation (SWAN) showed that only 7.2% of midlife women consistently met physical activity guidelines, and only 24% of US women perform resistance training at least twice per week. Thus "prescribing" exercise to women in perimenopause and menopause is essential for disease prevention. There are 5 exercise domains important to healthspan during menopause: aerobic activity, resistance training, impact and weight-bearing loading, balance training, and sedentary behavior. Aerobic activity (150-300 min/week moderate or 75-150 min/week vigorous) is the cardiometabolic foundation and carries the strongest mortality signal; escalating toward 300 min/week yields additional bone-density benefit. Progressive resistance training at least twice weekly has been shown to improve body composition, strength, cardiovascular risk factors, and bone mineral density. Women should aim to add at least 2 muscle-strengthening sessions per week to their aerobic activity, further lowering mortality risk and improving both lumbar spine and femoral neck bone mineral density. Impact and weight-bearing loading, such as jumping, stepping, jogging, and rope skipping, further reduce the risk of bone loss. The LIFTMOR trial showed that high-intensity resistance and impact training improved spine and hip bone mineral density in postmenopausal women with osteopenia without increased fracture risk, dispelling the myth that heavy loading is unsafe in low bone mass. Balance training and tai chi, especially after age 65, target fall and fracture prevention. Finally, increased sedentary time is an independent risk factor for all-cause and cardiovascular mortality. It is important that healthcare providers counsel patients about the benefits of physical activity during menopause. A *JAMA* report noted that women often turn to Google, Instagram, TikTok, and ChatGPT before discussing symptoms or other concerns with their healthcare team. Because people increasingly rely on digital platforms for health information, it is essential that women receive accurate, evidence-based guidance. Myths circulating on these platforms include lifting heavy weights will cause one to "bulk up," weighted vests alone are adequate for strength training, intense exercise spikes cortisol and "causes a menopausal belly," and that body composition changes are not possible during menopause. An important strategy to combat these myths and help patients is to write an exercise prescription. In a randomized controlled trial of 1,089 relatively inactive women aged 40-74, receiving an exercise prescription with coaching increased physical activity and improved physical functioning and mental health scores. Exercise prescriptions are therefore an important strategy to reduce physical inactivity. These prescriptions may be written in the FITT format—frequency, intensity, time, and type—which has been shown to outperform verbal advice. A pragmatic exercise prescription for midlife women would include: 150-300 min/week of aerobic activity; resistance training at least 2-3 days/week, focused on major muscle groups; impact or jumping exercises, unless contraindicated; balance training; and limiting sedentary behavior—keeping total sedentary time under 8 hours/day, breaking up sitting roughly every 30 minutes, and treating standing up frequently as a prescription distinct from sitting less. To move the needle on exercise in menopause, it is clear that no single modality addresses the whole healthspan portfolio; multicomponent programming, including attention to limiting sedentary time, should be part of counseling for every midlife woman. Exercise prescriptions are one concrete way to translate this into behavior change. The goal is not simply more years, but more years of independent, capable function.

Cutting Through the Noise: A Clinical Dietitian's Perspective on Dietary Supplements in Menopause

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A majority of women experience one or more menopausal symptoms. According to CDC NHANES data, 64% of women use dietary supplements, and usage rises with age. Older data show up to 70% of perimenopausal and menopausal women do not disclose their supplement use to their physicians, and approximately 30% report using dietary supplements alone — without other treatment — for hot flashes. Epidemiological studies show differences in menopausal symptom burden across populations, and some of this variation has been linked to food consumption patterns and lifestyle. This dietary epidemiology has fueled interest in specific nutraceuticals targeted to menopausal symptoms. At the same time, symptom severity and duration lead many women toward lifestyle interventions — diet, exercise, stress reduction, and dietary supplements — to address vasomotor symptoms (VMS), weight gain, mood changes, brain fog, bone health, and genitourinary syndrome of menopause (GSM). Many women use dietary supplements alongside menopausal hormone therapy or as their primary approach to symptom management. Patients bring these questions to their physicians, but limitations exist: time is short, and supplement-specific nutrition training is not a standard part of medical education. Drawing on clinical dietetics practice, this talk gives physicians a practical, evidence-based framework for the current menopause supplement landscape — which supplements have supporting evidence for which symptoms, and how to talk to a patient who has already started supplements or is considering them for menopausal symptom relief.

Socially Connected and Clinically Well: What the Evidence Says About Connectedness in Menopause

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Menopause is not experienced in isolation. A full contact list is not the same as support. A woman may have a full calendar, a partner, colleagues, and family nearby yet lack someone who understands or can help when symptoms disrupt daily life. At midlife, sleep disruption, mood and cognitive concerns, caregiving, and work demands may increase the need for support while making connection harder to sustain. Social health includes network structure and objective isolation; loneliness, the gap between desired and experienced connection; emotional, informational, and practical support; and the positive or negative quality of close relationships. The clinically useful question is not simply, “Is she connected?” but “What kind of connection or support is missing, unsafe, or unusable?” Menopause-specific evidence remains limited. In Lin et al.'s 2026 cross-sectional study of 903 perimenopausal women, loneliness and social isolation were independently associated with greater odds of membership in the study-defined severe subjective cognitive decline group; women with social isolation and moderate-to-severe loneliness had the greatest odds. In Bromberger et al.'s 8-year SWAN analysis, each 1-point higher concurrent score on a 0–16 social-support measure was associated with lower odds of high depressive symptoms (OR, 0.81; 95% CI, 0.79–0.83). By contrast, Arot et al.'s longitudinal analysis of nine SWAN interview waves involving 2,718 women found little evidence that greater social support was associated with less frequent vasomotor symptoms. These findings suggest that associations may differ by outcome. Intervention evidence suggests that a generic “connect more” message may be inadequate; the response should match the gap. In Rindner et al.'s four-arm primary-care trial, 370 women were randomized; clinician-delivered person-centered support improved health-related quality of life at 12 months and reduced mental, urogenital, and stress-related symptoms. In Bahri et al.'s trial of 100 married women, three-session spouse education improved menopause-related quality of life at three months. Hansen et al.'s umbrella review of 29 RCT-based systematic reviews found modest, heterogeneous effects: interventions that increased social contact or support showed the clearest signal for isolation, whereas psychological approaches showed the clearest signal for loneliness. Many midlife women are the ones everyone else depends on. That may look like connection while hiding overload. In Saadedine et al.'s cross-sectional sample of 4,295 midlife women, 34.1% of caregivers providing fewer than five hours of care weekly and 50.4% of those providing at least 15 hours reported moderate or worse menopause symptoms in at least one domain. Workplace conditions may compound symptom burden. The Menopause Society's 2024 consensus recommendations support menopause-supportive cultures, review of policies and health benefits, individualized flexibility or accommodations, and informed occupational health support. Depending on the gap, responses may include partner or support-person education when desired and safe, practical help to reduce or redistribute caregiving, or workplace accommodations. An evidence-informed clinical approach is to ask separately about loneliness, isolation, usable support, relationship safety, caregiving, and work strain. Possible prompts include: “Who understands what you are carrying?” “Who can help on a hard day?” “What support would make this plan more feasible?” Identify the gap most likely to affect health or interfere with care. Then choose one fitting next step: evidence-based menopause information, practical help, partner or support-person education, person-centered support or psychological care, community connection, workplace accommodation, resource navigation, or safety assessment and referral. Agree on one outcome and a follow-up date. The goal is not to add another task to a woman's already full life, but to make social health visible and align care with the life she is living.

Beyond Self-Care: Precision Menopause Care Through an Evidence-Based Integration of Lifestyle, Integrative, and Mind-Body Medicine for Stress and Mental Well-Being

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Psychological symptoms—including stress, anxiety, depressed mood, sleep disturbance, cognitive complaints, emotional dysregulation, and diminished resilience—are among the most common and burdensome manifestations of the menopause transition. Growing evidence supports a precision menopause care approach that integrates evidence-based lifestyle, integrative, and mind-body interventions tailored to an individual's symptom profile, biological vulnerabilities, comorbidities, lived experience, and treatment goals. This clinical education session presents a practical, evidence-based framework that moves beyond the traditional concept of “self-care” by positioning lifestyle and behavioral interventions as therapeutic strategies supported by mechanistic science and clinical evidence. Participants will review how hormonal changes during menopause affect the brain, stress response, sleep, nervous system regulation, and inflammation, contributing to changes in mood, cognition, and emotional well-being. Understanding these interconnected pathways provides the scientific foundation for personalized, multimodal interventions that address the underlying drivers of symptoms rather than relying on a one-size-fits-all approach. Drawing upon the principles of Lifestyle, Integrative, and Mind-Body Medicine, the session synthesizes current evidence supporting interventions that influence these underlying mechanisms. Research examining anti-inflammatory dietary patterns, exercise prescription, sleep optimization, stress recovery, social connection, and evidence-based behavior change will be reviewed alongside structured mind-body interventions, including cognitive behavioral therapy, mindfulness-based stress reduction, meditation, yoga, breath regulation, and compassion-based practices. Emerging research will be used to explain the biological pathways through which lifestyle and mind-body interventions may influence stress, mood, sleep, and resilience, while emphasizing where high-quality clinical evidence supports their use and where additional research is needed. A central focus of the presentation is translating evidence into precision clinical practice. Participants will learn a structured framework for recognizing symptom phenotypes—including sleep disturbance, anxiety, chronic stress, cognitive concerns, mood symptoms, metabolic dysfunction, and persistent vasomotor symptoms—and developing individualized care plans based on symptom burden, risk profile, patient preferences, and the strength of available evidence. Practical clinical tools for assessment, interdisciplinary collaboration, lifestyle counseling, and sustainable behavior change will facilitate implementation in routine menopause care. Participants will leave with a clinically applicable framework that integrates menopause medicine, neuroscience, Lifestyle Medicine, Integrative Medicine, and Mind-Body Medicine into personalized care plans that optimize stress management and mental well-being. By reframing lifestyle and behavioral interventions as evidence-based therapeutics within a precision menopause care model, clinicians can deliver comprehensive, whole-person care that enhances resilience, improves patient-reported outcomes, and advances menopause care.

Rest Assured: What We Know and What We Can Do About Sleep at Menopause

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Sleep is a biological necessity, yet sleep disruption is one of the most burdensome symptoms affecting women in midlife, reported by 40% to 60% of women in the menopause transition and postmenopause. The current conceptualization of sleep health views sleep as multidimensional, extending beyond duration to include regularity, satisfaction, timing, and daytime alertness. Sleep is governed by two fundamental processes — a homeostatic drive that builds with wakefulness and a circadian rhythm that controls the timing of both alertness and sleep — and optimal sleep depends on their alignment. Understanding these mechanisms, and the lifestyle behaviors and health habits that influence the brain's sleep controllers, is critical to achieving good sleep health. Because sleep disturbance pervades the general population, advice on achieving healthier sleep is disseminated through countless channels. This information is often limited in scope, based on a paucity of scientific data, and at times delivered by those with monetary or personal interests — creating misinformation and confusion for people in need, many of whom are self-managing their symptoms. This session applies a lifestyle medicine lens — focusing on evidence-based, modifiable health behaviors — to separate myth from fact and equip clinicians with practical strategies for improving sleep in midlife women (and for themselves). The most commonly disseminated advice centers on “sleep hygiene,” yet the evidence supporting its individual components varies widely, with several familiar tips resting on little or no clinical trial data. Among the better-supported practices are consistent sleep-wake timing, strategic light exposure, regular physical activity, and limiting evening alcohol and caffeine — though even these are insufficient for treating insomnia disorder. Recent data highlight sleep regularity as a predictor of health outcomes independent of sleep duration, and morning light exposure as a circadian anchor with downstream effects on sleep timing and mood. Exercise — particularly aerobic exercise — improves sleep quality in midlife women, though optimal timing remains understudied. Evening screen use is widely cautioned against. While healthy sleep behaviors form the foundation, many patients turn to over-the-counter supplements marketed for sleep. Melatonin is widely used but frequently misunderstood — it is a circadian signal, not a sedative, and evidence for its efficacy in midlife sleep disturbance is limited. Magnesium, valerian, and cannabinoids are similarly popular despite a lack of rigorous data supporting their use in this population. Distinguishing evidence-based recommendations from marketing claims is essential to counseling patients effectively

and avoiding delays in appropriate treatment. Finally, this session will address when and how to escalate care. For patients with persistent sleep symptoms despite engaging in healthy sleep behaviors, differentiating the potential causes and contributors is critical for ongoing management. Recognizing when to move from lifestyle strategies to targeted treatments for sleep disorders, including evidence-based cognitive and behavioral therapies, pharmacotherapy, or referral for evaluation of an underlying sleep disorder is a core clinical skill at the menopause transition. The appropriate use of sleep testing and the interpretation of consumer wearable data will also be reviewed.

Is It Helping or Hurting? Clinical Counseling Strategies for Substance Use in Midlife Women

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Alcohol, tobacco, and cannabis are the most commonly used recreational substances in the US, with particular relevance to health in midlife women. Over 60% of U.S. adults report past-year alcohol use. While women often name managing stress and sleep difficulty as motivations for alcohol use, it can contribute to sleep disruption, vasomotor symptoms, and the onset and exacerbation of mental health concerns. Risk increases with level of consumption, but negative health outcomes such as breast cancer risk have been identified with any level of alcohol use. Menopause-related changes in alcohol metabolism increase sensitivity to the effects and negative consequences of alcohol, and some studies suggest increased onset or exacerbation of problematic alcohol use and alcohol use disorder in the menopause transition. An estimated 19% of U.S. adults use tobacco in some form, most commonly smoking and vaping, and 480,000 deaths a year are attributable to tobacco dependence. Women face unique health risks related to tobacco use, including telescoping effects with accelerated progression from initiation to dependence as well as higher addiction risk in women relative to men. Tobacco use is linked to risk for chronic diseases that typically develop in and after the menopause transition (e.g., osteoporosis, cardiovascular disease, cancer), and smoking is strongly and consistently associated with vasomotor symptoms and earlier age at menopause. These health-related risks are mitigated with tobacco cessation and elapsed time since quitting. Finally, an estimated 18% of U.S. adults use cannabis in some form, making it almost as common as tobacco use. Cannabis use has been linked to cardiovascular and respiratory health risks, neuropsychiatric disorders, and dependence, with risks particularly related to smoking (the most common form of use in the U.S.), frequent (e.g., daily or near-daily) use, and high potency (e.g., THC content >15% or 10 mg) use. Women and adults aged 50 and older have been identified as some of the fastest growing groups using cannabis and are more likely to report medical rather than purely recreational cannabis use, with management of anxiety, chronic pain, and sleep difficulty commonly named as motives. In a growing literature, midlife women also identify menopause symptom management as a common motive for use and perceive cannabis as a safe and beneficial alternative to other treatment options. Given widespread use of substances including alcohol, tobacco, and cannabis, limited evidence of efficacy for common medical motives for use, and ample evidence that use can contribute to negative health outcomes, identifying and addressing substance use in the clinical setting is paramount. Clinical considerations may include psychoeducation, evidence-based approaches for behavior change, screening for higher risk patterns use, and substance use disorders, and identification and referral to treatment options as needed. Patients may benefit from monitoring use to identify patterns and triggers; open and nonjudgmental communication with providers about use, menopause, and alternative coping strategies; and active engagement in health promoting behaviors including movement, nutrition, meaningful social connection, and stress management. Providing evidence-based guidance and support for patients to avoid and reduce risky substance use is a pillar of lifestyle medicine, and essential in comprehensive menopause-related care.

From Pillars to Practice: Integrating Lifestyle Medicine into Menopause Care

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Because menopause is a condition that impacts multiple body systems, thereby increasing the risk of chronic illness, lifestyle medicine interventions can be particularly impactful for women navigating the menopausal transition. A predominantly whole-food plant-based diet, regular physical activity, stress management techniques, strong social connections, limitation of risky substances, and optimizing sleep can improve many of the most bothersome symptoms of menopause and decrease risk of chronic conditions like diabetes, cardiovascular disease, and obesity. Lifestyle medicine interventions are commonly offered within a framework of shared medical appointments (SMAs), in which multiple patients are seen in a group setting for the management of a shared medical condition. SMAs have been associated with improved clinical outcomes, increased patient self-efficacy, satisfaction, and trust, as well as increased revenue and less stress and greater satisfaction for the healthcare provider. SMAs can provide effective and comprehensive menopause care to a group of patients by: a) delivering interventions that complement the medical management of symptoms; b) providing efficient patient education regarding concepts surrounding menopause; and c) increasing patient self-efficacy for behavior change in a group setting. Important factors in successful implementation of SMAs include a one-on-one component within each session for each participant, and provision of a detailed after visit summary of class topics with additional resources. Participants must agree to protect the confidentiality of the group members and be willing to discuss their own situation within the group. A 6-session SMA course covering hormonal/nonhormonal treatments, nutrition/weight management, testosterone/vaginal/sexual health, mood/stress/mental health, physical activity for healthy aging, and promoting healthy sleep was piloted in the Stanford Menopause Clinic. All group visits

were led by a single Menopause Society certified practitioner, and the pilot consisted of a total of 14 patients divided into two groups. The pilot was primarily designed to evaluate financial feasibility and acceptability of the group visit structure for both patients and clinicians, but preliminary data regarding behavior change was also collected. The 14 group participants were compared to 14 control patients who received standard one-on-one menopause care from the same provider and were matched for age, menopausal stage, therapy received, and date of initiation of care. Patients in the group visits were successfully billed at a 99214 level based on documentation of at least 2 stable chronic illnesses and medication management at each visit. A questionnaire was sent to all 28 patients approximately 6 months after conclusion of the pilot inquiring about initiation of new healthy behaviors since their last office visit. Ten participants in the group visits responded (71%) and 11 control patients responded (79%). The percentage of patients reporting positive behavior changes in five areas is shown in Table 1. 100% of patients participating in the group visits (14/14) were positive about the experience, citing the benefits of learning from others in the group and feeling less isolated in their menopause experience. Although larger-scale trials are needed, SMAs show promise as an efficient and cost-effective method of care delivery to support positive behavior change in women during the menopausal transition.

Table 1. Participant-reported initiation of healthy behaviors

	Exercise	Nutrition	Sleep	Mental health	Sexual function
SMA participants	80% (8/10)	80% (8/10)	60% (6/10)	70% (7/10)	40% (4/10)
Control	73% (8/11)	82% (9/11)	18% (2/11)	27% (3/11)	18% (2/11)

PRESIDENTIAL SYMPOSIUM #1

The Cardiovascular Consequences of Estrogen Avoidance

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The menopause transition is increasingly recognized as a cardiovascular inflection point during which vascular and cardiometabolic health deteriorate beyond the effects of chronological aging alone. Declining estrogen levels contribute to endothelial dysfunction, reduced nitric oxide bioavailability, oxidative stress, vascular inflammation, arterial stiffness, and dysregulation of the renin–angiotensin–aldosterone system. Simultaneous increases in visceral adiposity, insulin resistance, blood pressure, and atherogenic lipoproteins further accelerate vascular aging and contribute to the rising cardiovascular risk observed after menopause. These biologic changes may be reflected by alterations in established and emerging cardiovascular biomarkers and markers of subclinical vascular disease, including apolipoprotein B, lipoprotein(a), inflammatory markers, coronary artery calcium, and breast arterial calcification. Estrogen deficiency may also influence the development of coronary artery atherosclerosis, coronary microvascular dysfunction, heart failure, and other cardiovascular conditions that disproportionately affect women during midlife and beyond. Understanding these pathways is essential as traditional cardiovascular risk assessment tools may not fully capture the effects of menopause-related vascular and metabolic changes. This presentation will examine the mechanisms through which estrogen deficiency accelerates vascular aging, influences cardiovascular biomarkers, and contributes to cardiovascular morbidity and mortality. It will also explore how the timing and duration of estrogen deprivation may influence cardiovascular risk across the life course.

The Toll of Estrogen Avoidance—Bone Health

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Menopause-related bone loss is a key contributor to postmenopausal osteoporosis, accounting for 40 to 50% of the changes in bone mass and structure that occur between early perimenopause and age 80. Estrogen or prevention-dose bisphosphonates began in early perimenopause effectively prevent those changes, and BMD can be maintained if estrogen is discontinued with intermittent dosing of bisphosphonates. If the menopause-related skeletal changes are not prevented, 15 to 20% of women will have bone density values consistent with osteoporosis by age 65 years. For women who enter perimenopause with a T-score ≤ -1, more than half will have osteoporosis before age 65. The lifetime risk of major osteoporotic fracture for a woman who comes to menopause with a T-score -1.0 can be decreased from 42.1% to 27.5% if her BMD can be maintained at that level. Similarly, the lifetime hip fracture risk would be decreased from 10.7% to 3.1%. These values likely substantially underestimate the benefit since having a fracture increases the risk for subsequent fractures. It is more effective and less expensive to prevent menopause- and age-related bone loss than it is to treat women who have already developed osteoporosis. Because of the WHI-related concerns about estrogen safety, a generation of women have not been given the opportunity to preserve bone mass. Appreciating that the positive benefit:risk of estrogen begun during perimenopause or early menopause, estrogen should be considered as a strategy to prevent menopause-related bone loss, especially in women at increased risk for osteoporosis. The women at highest risk for developing osteoporosis can be identified by BMD testing at the onset of perimenopause. Ideally, screening that should be routine for all women but especially those who are thin, have a family history of osteoporosis or have medical conditions predisposing to low bone mass. Preventing menopause-related bone loss with estrogen, coupled with lifelong management to maintain BMD, is more effective and less expensive than waiting until osteoporosis is evident before initiating treatment.

Early Menopause and the Impact on All-Cause Mortality

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Globally, approximately 10% of women will undergo menopause before the age of 45 years.¹ The early onset of menopause can have a profound impact on reproductive aging, general health, and somatic aging particularly in those under the age of 40 years.² When menopause happens before the age of 40 years, it is referred to as primary ovarian insufficiency or premature, occurring in up to 3% of women worldwide and 1% in the US.^{3,4} While the premature loss of ovarian follicular function may be attributed to a multitude of etiologies, including iatrogenic causes due to chemotherapy or radiation, autoimmune disorders, infections and genetic disorders (eg, Turner's syndrome, Fragile X syndrome), the most common cause is bilateral salpingo-oophorectomy; the surgical removal of both ovaries.² Surgical menopause results in abrupt loss of the reproductive sex hormones (estrogen, progesterone and testosterone) and can have a profound effect on overall quality of life, including sexual health and mood disorders, and is associated with increased morbidity and mortality.^{2,4,5} In contrast, natural menopause occurring early (between the ages of 40-44y) or prematurely has more of an insidious onset, however, still is associated with significant long-term health consequences, such as osteoporosis, cardiometabolic disease, and cognitive decline.^{1,4,5} The premature loss of estrogen seems to play a pivotal role in the increased risk of all-cause mortality. It's hypothesized that the premature loss of ovarian follicular function contributes to prolonged activation of the renin-angiotensin-aldosterone system resulting in a cascade of events marked by endothelial dysfunction, inflammation and immune dysfunction thereby accelerating the progression of chronic diseases and mortality.⁴ All of which may be exacerbated by underlying genetic, epigenetic, socioeconomic, and lifestyle factors. Management hinges on restoring estrogen concentration to the premenopausal range. Hormone replacement therapy (HRT) should be initiated at the time of diagnosis and continued until the average age of natural menopause (45-55 years), withstanding contraindications. If the uterus is present, endometrial protection with a progestogen is required, however, for those without a uterus, evidence does not support concurrent progesterone replacement. Nor has testosterone been shown to improve health outcomes.³ Observational studies have shown a reduced risk of osteoporosis, cardiovascular disease, and all-cause mortality among those receiving HRT. In addition, restoring estrogen concentrations to premenopausal levels may reduce neurocognitive effects related to hypoestrogenism.^{2,3,5,6} Still much is unknown about optimal management, and despite benefits of HRT, it can be associated with some risk and maybe contraindicated in some women. Stressing the importance of preventative strategies and addressing modifiable risk factors will have the greatest impact on long-term health outcomes. HRT should be viewed as one component of the management paradigm. 1. Muka, T, et al, *Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis*. JAMA Cardiol, 2016. 1(7): p. 767-776. 2. Faubion, SS, et al, *Long-term health consequences of premature or early menopause and considerations for management*. Climacteric, 2015. 18(4): p. 483-91. 3. Stuenkel, CA and Gompel, A, *Primary Ovarian Insufficiency*. N Engl J Med, 2023. 388(2): p. 154-163. 4. Huan, L, et al, *Meta-analysis: Early Age at Natural Menopause and Risk for All-Cause and Cardiovascular Mortality*. Biomed Res Int, 2021. 2021: p. 6636856. 5. Dobson, AJ, et al, *Menopause age and type and dementia risk: a pooled analysis of 233 802 women*. Age Ageing, 2024. 53(11). 6. Briceno Silva, G, et al, *Influence of the Onset of Menopause on the Risk of Developing Alzheimer's Disease*. Cureus, 2024. 16(9): p. e69124.

Contextualizing Risk of Stroke and Breast Cancer: Estrogen Compared to Other Therapies

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On November 10, 2025, the US Federal Drug Administration (FDA) removed the black box warning on all menopausal hormone therapy (MHT) products due to lack of evidence to support such a warning for breast cancer, cardiovascular disease, stroke, and probable dementia, which was entirely removed from the label. The unsubstantiated statement to use MHT at the lowest effective dose for the shortest duration was also eliminated from the label and guidance to initiate MHT within 10 years of the onset of menopause or younger than 60 years was issued by the FDA. When MHT is initiated within 10 years of menopause and/or before age 60, potential risks are rare. Further, the effects of MHT on breast cancer and other potential risks are in general no greater than other commonly used medications. Medications across various classes have shown similar or greater risk of breast cancer than that reported for conjugated equine estrogen + medroxyprogesterone acetate reported from the Women's Health Initiative (HR=1.26; 95% CI, 0.83-1.92). For example, current use of calcium channel blockers for 10 or more years has been associated with higher risks of ductal breast cancer (OR=2.4; 95% CI, 1.2-4.9) and lobular breast cancer (OR=2.6; 95% CI, 1.3-5.3), antibiotic use of more than 500 cumulative days associated with incident breast cancer (OR=2.14; 95% CI, 1.60-2.88) and fatal breast cancer (OR=4.37; 95% CI, 1.82-10.51), and randomized controlled trials of statin therapy suggest an association with breast cancer (RR=1.45-1.65). Likewise, aspirin, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors (SSRIs), calcium supplementation, and statin medications are associated with risk of ischemic and/or hemorrhagic stroke equal to or greater than that of MHT. Medications developed specifically for the treatment of osteoporosis carry risks including atrial fibrillation, atypical femur shaft fractures, and jaw osteonecrosis, none of which are associated with MHT while commonly used medications such as proton pump inhibitors and SSRIs are associated with bone adverse effects including osteoporosis and bone fractures, including hip fractures. Other commonly used medications have adverse effects that are diametrically opposed to the beneficial effects of MHT. For example, statins increase new onset diabetes mellitus and subjective cognitive symptoms such as

brain fog while MHT reduces both. Whereas MHT reduces all-cause mortality, other medications and therapies (eg, intensive diabetes control) are associated with increased all-cause mortality. In general, MHT risks are rare in magnitude, not significantly different from placebo, and no greater than other commonly used therapies especially when initiated within 10 years of menopause and/or before age 60, consistent with FDA guidance reflecting the safety and optimal benefit-risk balance of MHT. Placing MHT alongside other common medications clarifies its low risk and contextualizes its safety. "It is past time to stop overstating risks and promoting fear and confusion about MHT, which has been shown to safely offer life-enhancing and life-saving benefits for countless menopausal women."

Breast Cancer Survivors: The Consequences of Estrogen Avoidance and Reconsidering the Estrogen Option

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Menopausal symptoms affect a substantial proportion of breast cancer survivors and often arise secondary to chemotherapy, ovarian suppression, endocrine therapies, surgically induced menopause, or discontinuation of previously used hormone therapy. Vasomotor symptoms, sleep disruption, cognitive complaints, sexual dysfunction, genitourinary syndrome of menopause, and musculoskeletal symptoms can significantly impair quality of life and contribute to poor adherence to endocrine therapies. Despite these clinical burdens, systemic menopausal hormone therapy (MHT) has traditionally been considered contraindicated following breast cancer because of concerns regarding recurrence risk. This presentation reviews historical, biological, and clinical evidence relevant to the use of MHT among breast cancer survivors. Historically, high-dose estrogens were used successfully for the treatment of advanced breast cancer beginning in the 1940s. Subsequent laboratory and translational research led to the concept of the "estrogen paradox," whereby prolonged estrogen deprivation can render estrogen receptor-positive breast cancer cells susceptible to estrogen-induced apoptosis. Long-term estrogen-deprived cellular models demonstrate adaptive changes in receptor sensitivity, signaling pathways, and transcriptional regulation such that estradiol reintroduction may activate stress responses and programmed cell death rather than breast cell or breast cancer cell proliferation. These findings provide a biologic framework for understanding seemingly contradictory clinical observations regarding estrogen exposure and breast cancer outcomes. Clinical studies evaluating MHT after breast cancer have produced mixed findings. Numerous observational studies reported no increase in recurrence and, in some cases, reduced recurrence rates. Randomized clinical trial evidence remains limited, principally involving the HABITS and Stockholm trials. HABITS reported increased breast cancer events among women assigned to hormone therapy, whereas the Stockholm trial demonstrated no significant increase in recurrence risk, but a non-significant risk reduction. Differences in study design, duration, hormone regimens, progestin exposure, baseline imaging requirements, concurrent endocrine therapy use, and statistical power complicate the interpretation of the results of both studies. Collectively, these studies highlight the difficulty of making broad recommendations based on heterogeneous populations and treatment approaches. A central theme is that breast cancer should not be viewed as a uniform disease when considering MHT. Individual recurrence risk varies considerably according to stage, grade, receptor status, genomic profiling, treatment response, and time from diagnosis. Contemporary clinical tools such as PREDICT, CTS5, Oncotype DX, Breast Cancer Index, and other genomic assays offer opportunities to personalize risk assessment/estimate and facilitate informed discussions for shared decision-making. Current expert consensus increasingly favors individualized decision-making rather than universal prohibition. Shared decision-making should incorporate symptom burden, estimated recurrence risk, treatment goals, quality-of-life considerations, and patient preferences. Nonhormonal therapies remain first-line treatment; however, selected women with severe symptoms and low recurrence risk may reasonably consider MHT after careful counseling and oncologic consultation. Future research, including prospective trials using contemporary body-identical hormone formulations (estradiol, progesterone, testosterone), is needed to better quantify risks and benefits and guide evidence-based survivorship care.

PLENARY SYMPOSIUM #2

Cancer Treatment and the Hormonal Milieu: An Oncologist's Perspective

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Approximately 2 in 3 patients with breast cancer will harbor a subtype that is dependent on estrogen to sustain its growth as evidenced by the presence of the estrogen receptor (ER). Management of these cancers often centers on long-term therapy with anti-estrogen receptor or estrogen-depleting therapies by themselves or in combination with other newly available precision drugs. For patients with early-stage disease, these drugs have been transformative leading to durable remissions and cures for a very large proportion of patients. For patients with advanced or metastatic disease where cure is less likely, there may be long-term 'indefinite' use of these agents with strong evidence of durable efficacy. The downside of these strategies is the loss of estrogen to normal tissues resulting in nearly every organ system being potentially at risk for toxicity. Moreover, in young women with ER+ breast cancer, treatment is often a combined strategy of systemic anti-estrogen treatments with either intentional chemotherapy use to destroy ovary function, ovary removal, or ovarian function suppression. These young pre-menopausal patients are both highly symptomatic and are more vulnerable to long-term toxicities from estrogen minimization. One simple treatment for symptoms would be to consider systemic estrogen replacement but would be counterproductive because of a higher risk

of recurrence or progression and would generally be considered unacceptable. In some instances, targeted tissue specific replacement could be considered, for example, direct topical vaginal estrogen to mitigate gynecologic symptoms. Instead, other non-hormonal interventions with high-level support from well-done clinical trials for focused symptom management could be considered. Some examples include NK1/NK3 inhibitors (sleep and vasomotor symptoms), acupuncture (arthralgia/myalgia), or yin yoga (arthralgia, myalgia, sleep disturbance). Of note, patients whose cancers are not driven by estrogen pathways could be counseled on use of hormone replacement therapy.

Gynecologic Care of Breast Cancer Survivors

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Breast cancer is the most diagnosed cancer nationwide among people assigned female at birth. Despite the high prevalence, prognosis is usually favorable, with most breast cancers being identified at stage I and carrying a 91% 5-year survival. Healthcare providers often feel ill-equipped to care for breast cancer survivors longitudinally, for which there can be a mix of routine care versus special considerations for those with a history of breast cancer. In this talk, we will explore 3 objectives: to learn the basic gynecologic care of breast cancer survivors, to understand treatment side effects and considerations, and to address common questions from breast cancer survivors. Generally, patients who have undergone breast conservation surgery will continue with annual breast screening imaging, whereas those who have undergone bilateral mastectomies do not undergo routine screening imaging but could undergo diagnostic imaging if there is a clinical finding. Since some chemotherapy agents are gonadotoxic, patients may experience a temporary or permanent chemotherapy-induced menopause. Patients may also experience menopausal symptoms from medically induced menopause from GnRH agonists or surgical oophorectomy for ovarian ablation to facilitate use to aromatase inhibitors from endocrine therapy. Non-hormonal therapies could be used for those undergoing treatment who are experiencing hot flashes. Tamoxifen is another option for endocrine therapy that has gynecologic side effects such as abnormal uterine bleeding, polyp formation, and increased uterine cancer risk in postmenopausal patients. Any abnormal bleeding on tamoxifen should be assessed via hysteroscopy and possible biopsy, given that tamoxifen causes subepithelial stromal hypertrophy which can lead to false positives on ultrasound. Genetic risk assessment should be performed routinely, as patients often have concerns about other cancer risks after a breast cancer diagnosis. Menopausal hormone therapy has historically been avoided in breast cancer survivors. However, it is important to weigh risks and benefits in this patient population and evaluate the patient holistically.

Shared Decision-Making for Menopause Management in Cancer Survivorship

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There are 4.3 million breast cancer survivors in the US, and 8.2 million worldwide. Around 1 in 400 individuals in the general population carry a pathogenic variant, such as BRCA that significantly increases the risk of breast, ovarian, and other cancers. Estrogen-modifying treatments play a significant role in the treatment of breast cancer, at times long term. Women who have not been diagnosed with breast cancer but are at increased risk (previvors) may pursue risk-reduction strategies such as estrogen-depleting medications or preventive surgery (e.g., bilateral salpingo-oophorectomy). Studies find 60-100% of breast cancer survivors report at least one general menopausal symptom: vasomotor symptoms (hot flashes, night sweats), genitourinary issues, arthralgias/myalgias, sleep disturbances, fatigue, etc. These symptoms can significantly impact quality of life. Survivors may also face increased risks of cardiovascular disease, dementia, and bone density loss. Systemic estrogen can relieve these symptoms but has traditionally been contraindicated in breast cancer survivors because of risk of recurrence. Recent research shows the risks of MHT may vary depending on cancer stage, grade, hormone receptor status, and age. There is growing evidence to tailor MHT use carefully in some survivors through shared decision-making. 42-55% of breast cancer survivors expressed a lack of involvement in shared decision-making, dissatisfaction with information provided by their providers, and a lack of satisfactory access to ongoing support and symptom management. This can result in survivors prematurely discontinuing endocrine therapy thus negatively impacting survival and recurrence risk. This information underscores the importance of personalized care and ongoing support for breast cancer survivors, balancing symptom relief, and risk reduction. Patient-centered discussion of treatment symptoms and addressing them are key components of cancer survivorship. Many effective symptom control strategies exist including the use of SSRIs, adjustment of endocrine therapy, exercise, therapeutic massage, yoga, acupuncture, and topical estrogen. In carefully selected cases, systemic MHT may be considered based on individualized, evidence-based decisions.

PLENARY SYMPOSIUM #3

Hormone Therapy and Cognition: Current Evidence and Clinical Implications

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Menopausal hormone therapy (MHT) remains an important and evolving topic in women's health, particularly regarding cognitive symptoms during menopause and potential effects on dementia risk. MHT is FDA approved for treatment of vasomotor symptoms (VMS), vulvovaginal symptoms, and prevention of osteoporosis. Recent FDA

labeling changes have removed statements regarding probable dementia from the boxed warnings of some MHT products, including both estrogen-alone and estrogen-plus-progestogen formulations. These changes have raised questions about how regulatory language should be interpreted in the context of the underlying scientific evidence. MHT may indirectly support cognitive functioning by improving menopause-related sleep disturbance and mood symptoms, which can adversely affect a range of cognitive functions. Consistent with this potential pathway, The Menopause Society recognizes that MHT can improve sleep in women with VMS and that estrogen therapy may benefit mood in perimenopausal women with depressive symptoms; however, MHT is not recommended specifically to treat cognitive difficulties or prevent dementia. Longitudinal studies demonstrate that verbal memory is the cognitive domain most consistently affected during the menopausal transition, with modest declines occurring from premenopause to perimenopause. Evidence from surgical menopause or treatment with gonadotropin-releasing hormone agonists (GnRHa), in which suppression or abrupt loss of ovarian hormone production is associated with verbal memory decline that may improve with MHT, further supports a potential relationship between ovarian hormone exposure and cognitive function. In contrast, randomized clinical trials in naturally postmenopausal women have not demonstrated meaningful cognitive benefits from MHT. Important evidence gaps include the absence of large, randomized trials evaluating cognition in perimenopausal women and limited evidence regarding cognitive outcomes among women with bothersome VMS. Treating VMS may yield secondary cognitive benefits by improving sleep and daily functioning, although similar benefits may be achievable with effective nonhormonal VMS therapies. The relationship between MHT and dementia risk is complex. The Women's Health Initiative Memory Study reported increased probable dementia risk with estrogen-plus-progestogen therapy, whereas the estrogen-alone trial did not demonstrate a statistically significant increase, although point estimates were in the direction of increased risk. More recent epidemiologic evidence has also reported modest associations between MHT use and Alzheimer's disease risk. Conversely, women with premature menopause may benefit from MHT through the usual age of natural menopause, with evidence suggesting preservation of cognitive function and potential reduction in dementia risk. Overall, current evidence supports an individualized approach in which MHT is prescribed for established menopausal indications, particularly VMS, rather than for cognitive enhancement or primary prevention of dementia. Further research is needed to determine whether menopausal stage, timing of treatment, symptom burden, formulation, and underlying ovarian hormone exposure modify cognitive and dementia outcomes.

Hormone Therapy and Cardiovascular Disease Risk: Current Evidence and Clinical Implications

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Menopausal hormone therapy (HT) is the most effective treatment for vasomotor symptoms and reduces postmenopausal bone loss. Its cardiovascular risk-benefit profile is influenced by age, time since menopause, baseline cardiovascular risk, and the route, dose, and formulation of therapy. This presentation will review randomized clinical trial and contemporary observational evidence to define what is known, identify remaining areas of uncertainty, and clarify what clinicians should discuss when counseling women about the cardiovascular effects of HT. Two pivotal randomized trials helped shape both our initial and current understanding of the cardiovascular effects of HT. The Heart and Estrogen/progestin Replacement Study (HERS), conducted in women with established coronary heart disease, found an early increase in coronary events and no overall benefit for secondary prevention, while the Women's Health Initiative did not support hormone therapy for the primary prevention of cardiovascular disease. Subsequent analyses stratified by age and time since menopause have provided greater reassurance that, among appropriately selected women who initiate HT within 10 years of menopause, treatment is not associated with an increased risk of coronary heart disease or all-cause mortality overall. A 2024 meta-analysis of randomized trials found no significant overall reduction in all-cause mortality or cardiovascular death and nonfatal myocardial infarction with HT. Outcomes were more favorable in trials categorized as initiating HT closer to menopause; however, initiation timing was not randomized, and some trials were categorized using mean age rather than actual time since menopause. The findings are therefore reassuring regarding cardiovascular safety in appropriately selected younger women but do not establish that earlier initiation prevents cardiovascular disease. Whether initiating HT near menopause reduces clinical cardiovascular events therefore remains uncertain. To further examine whether the vascular effects of HT differ according to the timing of initiation, the Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE) randomized placebo-controlled trials enrolled younger postmenopausal women and assessed vascular imaging measures rather than clinical cardiovascular events. KEEPS found no significant difference in carotid artery wall thickness or coronary artery calcium between hormone therapy and placebo. ELITE found slower thickening of the carotid artery wall when estradiol was started within 6 years of menopause, but not when it was started 10 or more years later. Participants in both trials were healthy women whose baseline carotid intima-media thickness values were well below levels used to define subclinical atherosclerosis; therefore, the findings do not demonstrate that HT prevents subclinical atherosclerosis or atherosclerotic plaque. Neither trial was designed or powered to assess myocardial infarction, stroke, cardiovascular death, or all-cause mortality. The reassuring message from the evidence to date is that, in appropriately selected women using HT for menopausal symptoms, cardiovascular risk does not appear to be increased overall. This supports confident, symptom-directed treatment while recognizing that a neutral risk profile is not evidence of cardioprotection. HT should therefore not be initiated to prevent cardiovascular disease or with the expectation or promise that it will reduce cardiovascular events.

PLENARY SYMPOSIUM #4

Mood Disorders and the Menopause Transition: What Every Clinician Needs to Know

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The menopause transition constitutes one of the reproductive-related 'windows of vulnerability' for depression across a woman's lifecycle. Hormonal fluctuations are believed to influence the emergence of mood symptoms, their clinical characteristics, and their severity. Depressive symptoms – not a major depressive episode – are more common and may include poor motivation, low engagement in usual activities, reduced enjoyment, and disrupted sleep. These symptoms can significantly affect quality of life. Major depressive episodes (MDEs), on the other hand, are less common and often represent a recurrence of illness in those with a prior history of depression. Midlife depression can be understood through two main clusters of factors: 1) continuum-related factors, such as socioeconomic status, psychosocial stress, and general health, which tend to persist throughout a woman's life and make previous depression a strong predictor of future episodes; and 2) window-related factors, which are specific to certain times or contexts, including hormonal changes, sleep issues, vasomotor symptoms, stressful events near menopause, and the exacerbation of chronic illnesses during midlife. Healthcare providers should be aware of these factors to improve the prevention, detection, and treatment of depression during and after midlife. Importantly, depression or anxiety during midlife rarely occur in isolation. Sleep problems, cognitive complaints, genitourinary symptoms, sexual dysfunction, and context-related life stressors are relevant factors that need to be considered when developing comprehensive, effective treatment plans. Antidepressants and behavioural interventions remain the first-line treatment of depression across the life span, including the menopause transition and beyond. Overall, there is no evidence to support a superior efficacy of a particular antidepressant agent or class over the others for the management of midlife depression. Safety information should be considered when choosing antidepressants; the potential for drug-drug interactions are important, as perimenopausal and postmenopausal women often take multiple medications for other conditions. Tolerability is also key, as sexual dysfunction and weight changes are common concerns. Existing data on the additional benefits of antidepressants for managing other menopause-related symptoms (VMS, pain, disrupted sleep) could also help guide clinicians and patients during their decision-making process. Behaviour-based interventions such as cognitive behavioural therapy (CBT) have been shown to be effective not only for depression but also for managing other menopause-related problems, including anxiety, sleep problems, and VMS. Menopause hormone therapies (MHT) may have a positive impact on mood and improve quality of life (QoL) by addressing other problems (VMS, sleep, sexual function). Nonhormonal interventions (eg, neurokinin-targeted therapies) are also promising due to their effects on VMS, sleep, and QoL. Ultimately, treatment strategies must be tailored to individual needs, taking into account changes in symptom presentation and severity over time; menopause care therefore requires reassessments and possible treatment adjustments.

Suicide Risk in Midlife Women: Recognizing the Warning Signs During the Menopause Transition

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Rates of suicide are rising faster for women than men with an increase of 40% from 2002 to 2022 according to the CDC. Women are more likely to report suicidal thoughts and three times more likely than men to make a suicide attempt. The highest rates of lethal suicide are for women age 45-64. These higher rates are multifactorial, and more research is needed to better understand suicide risk in midlife women. Changing hormonal levels—both lower baseline levels along with greater shifts up and down—associate with higher risk in individuals whose moods are more sensitive to changes in hormone levels. Within person and between person studies are needed to assess suicidal ideation across perimenopause and to identify related biomarkers. Studies that can more accurately assess first onset of suicidal ideation will identify individuals with first onset in perimenopause in comparison to individuals with prior episodes before midlife and worsening in perimenopause. Early onset menopause is associated with higher risk of suicidal ideation and may have biological, social, and psychological contributors. Symptoms including irritability and anxiety can be more prominent in perimenopause and are associated with greater suicide risk. Hormonal shifts have also been associated with psychosis that then increases risk of suicide. Alcohol use increases risk; with increases in alcohol use in midlife by women as women are holding a lot for others, less time for self-care and relaxation, and more symptoms such as sleep disruption and anxiety. Social supports are also an important consideration in assessing risk. More is needed to understand factors related to changes in partner and family dynamics, work environments that may occur in midlife. Other health changes such as development of chronic pain or immune changes are important considerations. These risk factors require improved ways to systematically assess and discuss in non-judgmental ways. The systematic use of screening tools given to all individuals such as the last question of the PHQ-9 and screeners specific to suicidal ideation such as the Columbia Suicide Severity Rating Scale (C-SSRS) provide a way to ensure everyone has space to disclose. These are more effective as beginnings of conversations. For example, a person may not disclose initially if they think it will lead to an involuntary hospitalization and had a traumatic prior experience with the mental health care system or are trying to weigh feelings of hopelessness along with large sense of responsibility for family, friends, work colleagues and community. It is important to recognize that suicidal ideation can be dynamic, and thoughts may be intrusive at times while at other times thoughts may have intent and a sense of relief when individuals don't see another way to alleviate suffering. Identifying and treating mental health conditions such as major depression with anxiety, PTSD, and

bipolar disorder are critical; however, patients also desire new and more personalized treatments. It is important to investigate sex and gender differences in treatment response; for example, sustainability of ketamine effects versus other treatments may be different for female patients than for male patients. More is needed to understand factors unique to midlife women in answering questions on screening tools, the context of giving the screening tools that may impact feeling comfortable to disclose thoughts and intent, and in creating more precision in treatments and care plans that can then be offered and utilized. Factors such as dismissiveness around perimenopausal mood symptoms may leave the individual feeling ignored and they cannot get help, furthering hopelessness. Research has been limited—particularly research that engages individuals with lived experience and diverse experiences of midlife and perimenopause—and more inclusive research will provide important information to improve assessment and precision in care provided. Discussing suicide and assessing risk factors requires time and empathetic, kind spaces for shared decision-making; advocacy is needed to create time and these spaces in our health care systems and communities.

Beyond the Diagnosis: Resilience, Loneliness, and Psychological Wellbeing

Ellen E. Lee, MD. Geriatric Psychiatry, VA San Diego Healthcare System, San Diego, CA Psychological resilience, or the "positive adaptation, or the ability to maintain or regain mental health, despite experiencing adversity," has been associated with better health outcomes (eg, less depression, less pain, better social functioning, and better physical health) across the lifespan. Greater resilience predicts better future health outcomes. As women age, resilience plays a critical role in responding to biological and psychosocial changes during the menopause transition, including social disconnection. Social disconnection can be conceptualized as including structural (social isolation), functional (loneliness), and quality (relationship strain) components. Loneliness and social isolation are associated with early menopause, worse lifestyle factors, and worse health outcomes in women. Sex differences in the assessment of loneliness, risk factors for loneliness, patterns of loneliness with aging offer insight into women-specific social needs. While findings are mixed about changes in social disconnection relative to the menopause transition, several studies have shown that social disconnection increases with age after mid-life among women. Psychological resilience may buffer the negative health effects of social disconnection, presenting a novel modifiable target for promoting healthy aging for women. Resilience-enhancing interventions tested in this population primarily include mindfulness-based, cognitive behavioral therapy-(CBT)-based, and combined approaches. Similar intervention approaches have been shown to improve loneliness in older adults, though the impact on women has not been specifically examined. Increasing resilience and social connection for women across the menopause transition can impact overall psychological wellbeing.

PLENARY SYMPOSIUM #5

Skin, Hormones, and Menopause: From Research to Clinical Practice

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Skin and mucosal changes are among the most visible, distressing, and widely discussed concerns during and after the menopause transition, yet clinicians often lack a clear, evidence-based approach to their evaluation and management. This presentation translates current research on menopause, menopausal therapies, and their intersection with dermatologic care into practical guidance. Topics encompass changes associated with declining estrogen, relative androgen predominance, or both, including acne, hirsutism, and skin aging. Data on topical and systemic estrogen for aging skin are critically examined, with attention to the strengths and limitations of available studies. Evidence linking menopause and menopausal hormone therapy to common dermatoses, such as rosacea, psoriasis, and hidradenitis suppurativa, is reviewed, with emphasis on established findings, inconsistencies, and key research gaps. The intersecting roles of antiandrogen and testosterone therapy in skin disease and sexual function are addressed, along with the recognition and management of genitourinary syndrome of menopause and its distinction from vulvar disorders such as lichen sclerosus. Prescribing considerations focus on dermatologic medications with thromboembolic warnings or precautions in patients receiving menopausal hormone therapy and how the route of estrogen administration may influence risk. Clinicians will leave with a practical approach to recognizing hormone-related dermatologic changes, evaluating treatment claims, initiating appropriate management, and identifying when coordinated care is needed.

Midlife Hair Loss: What Every Menopause Clinician Needs to Know

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Hair loss is one of the most common dermatologic concerns reported by midlife women, yet it is frequently underrecognized and under-addressed in routine menopause care despite its profound effects on quality of life, self-image, and psychological well-being. Women may report progressive hair thinning, increased shedding, inability to grow hair to its previous length, textural changes, loss of volume, and accelerated hair greying, among other symptoms. Viewing menopause as a biologically vulnerable period for the hair follicle provides a unifying framework for understanding and treating these heterogeneous hair concerns. The hair follicle is both an estrogen and androgen target tissue. Androgens drive follicular miniaturization on the scalp while stimulating terminal hair growth on the face and body. In contrast, estrogen plays a broad protective role in maintaining follicular function by prolonging the anagen phase of the hair cycle, modulating perifollicular inflammation, enhancing microvascular support, and counterbalancing androgen signaling. Menopause is characterized not only by estrogen deficiency but also by hormonal variability and altered androgen-to-estrogen ratios.

In genetically predisposed individuals, these hormonal changes may unmask androgen sensitivity, leading to female pattern hair loss characterized by follicular miniaturization. In others, abrupt hormonal fluctuations and hair cycle instability may precipitate excessive shedding consistent with telogen effluvium. Within susceptible immune environments, estrogen loss may contribute to collapse of hair follicle immune privilege, facilitating inflammatory scarring alopecias such as frontal fibrosing alopecia. Despite the heterogeneous mechanisms contributing to midlife hair loss, clinicians can adopt a practical, mechanism-based management strategy centered on three pillars: (1) support hair growth through evidence-based therapies that promote follicular function, including minoxidil and, when appropriate, anti-androgen therapies (2) reduce inflammation when inflammatory processes are present, and (3) encourage healthy lifestyle practices that optimize metabolic health, nutrition, sleep, stress management, and other modifiable factors influencing follicular resilience. Recognizing menopause as a high-risk, vulnerable period for follicular dysfunction may enable earlier diagnosis, individualized evaluation, and personalized treatment strategies that integrate hormonal, metabolic, inflammatory, and lifestyle considerations. **References:** 1. Gupta AK, Economopoulos V, Mann A, Wang T, Mirmirani P. Menopause and hair loss in women: Exploring the hormonal transition. *Maturitas*. 2025 Jul;198:108378. doi: 10.1016/j.maturitas.2025.108378. Epub 2025 May 2. PMID: 40318238. 2. Mirmirani P. Managing hair loss in midlife women. *Maturitas*. 2013 Feb;74(2):119-22. doi: 10.1016/j.maturitas.2012.10.020. Epub 2012 Nov 24. PMID: 23182767. 3. Mirmirani P. Hormonal changes in menopause: do they contribute to a 'midlife hair crisis' in women? *Br J Dermatol*. 2011 Dec;165 Suppl 3:7-11. doi: 10.1111/j.1365-2133.2011.10629.x. PMID: 22171679.

PLENARY SYMPOSIUM #6

Assessing the Risk: Primary Prevention Guidelines and Their Application in Midlife Women

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Cardiovascular disease remains the leading cause of morbidity and mortality among women, yet risk assessment in midlife women is often challenging because traditional risk calculators may incompletely capture sex-specific and life course risk factors. Midlife represents a critical window for cardiovascular prevention, as women experience dynamic changes in cardiometabolic health during the menopausal transition, including worsening blood pressure, lipids, insulin resistance, adiposity, and vascular function. At the same time, pregnancy-related complications such as hypertensive disorders of pregnancy, gestational diabetes, preterm birth, and adverse pregnancy outcomes, as well as premature menopause, polyendocrine metabolic ovarian syndrome, autoimmune disease, inflammatory conditions, and social determinants of health, may substantially modify long-term cardiovascular risk. Contemporary primary prevention guidelines increasingly emphasize a comprehensive approach to risk assessment that integrates traditional risk estimation with risk-enhancing factors, shared decision-making, and selective use of additional testing such as lipoprotein(a), apolipoprotein B, coronary artery calcium scoring, and assessment of subclinical atherosclerosis when treatment decisions remain uncertain. This session will review current approaches to cardiovascular risk assessment and primary prevention in midlife women, with attention to the practical application of cholesterol, blood pressure, diabetes, and lifestyle guidelines in clinical practice. We will highlight common scenarios in which estimated 10-year risk may appear low despite meaningful lifetime risk, discuss how sex-specific risk enhancers should inform preventive counseling and treatment thresholds, and review strategies to communicate risk in a way that supports patient-centered decision-making. By applying guideline-based prevention through a woman's health and life course lens, clinicians can better identify midlife women who may benefit from earlier or more intensive preventive interventions and help reduce sex-based gaps in cardiovascular prevention.

Lipids and Lipoproteins Across the Menopause Transition: Applying Updated Guidelines to the Assessment of Atherogenic Dyslipidemia

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The 2026 ACC/AHA/Multisociety Guideline on the Management of Dyslipidemia recognizes premature or early menopause as risk enhancers. This lecture will focus on the lipid biology of the menopause transition and on what the guidelines recommend for women moving through it. As ovarian estrogen declines through perimenopause and beyond, lipid patterns become more atherogenic with rise in low density lipoprotein (LDL)-cholesterol, apolipoprotein B (apoB), triglycerides and triglyceride-rich remnant particles, and lipoprotein(a) [Lp(a)]. The updated guidelines broaden how atherogenic risk is measured and when it is treated in women. Total cholesterol, LDL-cholesterol, and triglycerides increase several years before and after the final menstrual period. Evidence from the SWAN study suggests that high-density lipoprotein (HDL) function becomes impaired during perimenopause, reducing its cardioprotective properties. Dysfunctional HDL may lose its anti-inflammatory and reverse cholesterol transport capabilities potentially explaining the paradoxical associations between higher HDL-C levels and increased atherosclerotic burden in postmenopausal women. Furthermore, metabolic changes including shifting fat distribution to increased visceral adiposity and increased insulin resistance worsen dyslipidemia during the menopause transition. Recommendations relevant to women during menopause include: 1) Use apoB and non-HDL-C as more accurate markers of atherogenic burden when triglycerides and insulin resistance climb, as they commonly do after menopause; triglyceride-driven dyslipidemia receives greater attention, 2) Consider sex-specific and reproductive risk enhancers—premature (<40 years) or early (<45 years) menopause, preclampsia and other hypertensive disorders of pregnancy, gestational diabetes, and PCOS—toward

earlier, more individualized treatment, 3) Keep lifestyle the foundation (nutrition, activity, weight management), with statins as first-line therapy and ezetimibe or PCSK9 inhibitors added when LDL-C goals are unmet.

Beyond Statins: Novel Treatment Strategies for Lipid Management and ASCVD Risk Reduction

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Atherosclerotic cardiovascular disease is driven primarily by the cumulative, lifelong exposure to atherogenic lipoproteins. Although statins have historically served as the cornerstone of lipid-lowering pharmacotherapy, a substantial residual cardiovascular (CV) risk persists in high-risk individuals. Women are often less likely than men to receive statins and more likely to report statin associated muscle symptoms. Additionally, women of childbearing age who are at very high risk of CVD (due to familial hypercholesterolemia or prior ASCVD event) require special consideration of treatment strategies to reduce CV risk during pregnancy and lactation. Recognizing the unique CV risk trajectories of women and addressing treatment gaps with combination therapy is important to reduce preventable ASCVD events across the female life course. The 2026 ACC/AHA Multisociety Guideline on the Management of Dyslipidemia provides a more personalized framework that combines PREVENT-ASCVD risk estimation, reproductive risk assessment, Lp(a) and apoB measurement, selective CAC imaging, reinstates LDL-C and non-HDL-C treatment goals, and earlier incorporation of nonstatin therapies. The use of **nonstatin therapies is increasingly central to achieving guideline-directed LDL-C reduction**. Ezetimibe, PCSK9 monoclonal antibodies, small interfering RNA PCSK9 inhibitor, bempedoic acid, and evinacumab provide complementary mechanisms for patients who do not achieve LDL-C goals, have statin intolerance, or require substantial additional LDL-C lowering. Triglyceride rich remnants are an independent risk factor for the development of ASCVD as well as pancreatitis. Statins are the first line therapy for those with hypertriglyceridemia and either ASCVD or at increased ASCVD risk. While fibrates and apo-C III inhibitors are additional nonstatin therapies for the management of hypertriglyceridemia. This session explores these novel treatment paradigms, synthesizing the latest evidence on non-statin mechanisms and highlighting how the 2026 ACC/AHA Multisociety Dyslipidemia guideline redefines modern CV risk reduction through aggressive, individualized, and multi-agent lipid management.

PLENARY SYMPOSIUM #7

Visually Directed, Clinically Confident: Uterine Evaluation in the Peri- and Postmenopausal Woman

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Every patient with abnormal uterine bleeding carries a question clinicians can't afford to get wrong: is this benign, or is something being missed? Cancer is the diagnosis no one can afford to miss, but it is not the most common culprit: population data show endometrial cancer accounts for only about 5% to 10% of postmenopausal bleeding, while the majority of cases trace back to benign structural pathology, chiefly endometrial polyps, and submucosal fibroids. Blind endometrial sampling is not designed to find them, since a Pipelle characterizes tissue histology, not cavity structure, and the numbers reflect that blind spot directly. A blind Pipelle samples only about 4% of the endometrial surface. It misses roughly 1 in 4 to 5 endometrial cancers and nearly two-thirds to three-quarters of endometrial polyps. For submucosal fibroids, reported sensitivity is as low as 1.4–10%. Blind dilation and curettage miss over half of polyps despite direct instrumentation. Transvaginal ultrasound, the default first step in most practices, misses well over a third of intracavitary lesions overall and cannot reliably distinguish focal pathology, polyps, or submucosal fibroids, from diffuse endometrial thickening. Benign does not mean inconsequential. Missed polyps and fibroids drive recurrent bleeding, anemia, unnecessary repeat visits, and sometimes unnecessary hysterectomy, an outcome-relevant cost even when cancer is never in question. Blind sampling also yields an inadequate specimen in up to 40% of postmenopausal women, and among those inadequate samples, roughly 1 in 14 was later found to harbor precancerous change on follow-up hysteroscopy. A test that cannot be read is not a negative test, yet it is often treated as one. Direct visualization tells a different story, for cancer risk and for the benign pathology driving most cases. Saline infusion sonography detects 92 to 100% of intracavitary lesions overall, including 94% of submucosal fibroids, and when endometrial sampling is directed by visualization rather than performed blindly, diagnostic accuracy rises from roughly 52% to 89%. Hysteroscopy-directed biopsy cuts the risk of missing a concurrent endometrial carcinoma in atypical hyperplasia by more than half, and that same direct visualization sharply reduces the risk of missing focal lesions, with office hysteroscopy missing only about 5% of polyps and other intracavitary pathology, compared with the two-thirds to three-quarters missed by blind sampling. Because hysteroscopy visualizes the lesion directly, biopsy or excision can target it precisely, instead of sampling blindly nearby. Performed as the first step, either can function as one-stop evaluation, sparing patients and the health care system the escalating cycle blind sampling so often sets in motion — another round of repeat tests, more unresolved worry, cost that keeps climbing. This presentation translates that evidence into a clear, actionable framework: why structured uterine evaluation, attentive to both malignant and benign structural pathology, is now the clinical imperative for peri- and postmenopausal women being considered for hormone therapy or presenting with abnormal bleeding; when to incorporate hysteroscopy, endometrial biopsy, or saline infusion sonography, before initiating therapy and at key intervals if bleeding recurs; and how to proceed, stepwise, in the scenario every menopause clinician eventually faces: the patient already on hormone therapy who develops unexpected bleeding. Attendees

receive a decision pathway, grounded in current diagnostic accuracy data, which replaces reflexive blind biopsy with the tool that actually answers the clinical question the first time. This presentation is built for practice change. Many gynecologists and radiologists received little to no formal training in office hysteroscopy or in interpreting saline infusion sonography during residency, and this session closes that gap directly. Attendees leave equipped to recognize when a negative blind sample, or a reassuring ultrasound, may not mean what they think it means, whether the concern is cancer or the more common benign pathology behind most bleeding, and ready to make direct visualization the standard that meaningfully raises diagnostic sensitivity, bringing genuine certainty back to their own patients.

Overactive Bladder and Other Updates in Urogynecology

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Urogynecologic conditions like overactive bladder (OAB), recurrent urinary tract infection (RUTI), urinary incontinence (UI), and pelvic organ prolapse (POP) are particularly impactful to midlife health. Rates of OAB and UI increase up to 13-fold after menopause, and antibiotic overuse for presumed UTI is rampant in older women because of symptom overlap with genitourinary syndrome of menopause (GSM). Updated treatment guidelines for OAB and RUTI from the American Urological Association (AUA) have introduced paradigm shifts in management over the last 2 years. Surgical treatments for stress urinary incontinence (SUI) and POP have also evolved. **Overactive bladder (OAB)** is urinary urgency, often with frequency and nocturia, with or without UI. AUA guidelines updated in 2024 eliminated the concept of “step therapy,” emphasizing instead shared decision-making to select therapies, regardless of invasiveness, based on patient needs, desires, and side effect tolerance. The guideline emphasizes the importance of treating comorbid conditions that impact OAB symptoms, including GSM. Treatments include non-invasive (incontinence management strategies, bladder training, behavioral therapies, pelvic floor muscle training), pharmacologic (antimuscarinic and beta-3 adrenergic agonist), minimally invasive (onabotulinum toxin A injection, tibial nerve stimulation, sacral neuromodulation), and invasive options (catheterization, diversion, bladder augmentation). Patients should be advised about the association between antimuscarinic medications and cognitive decline. Advances in tibial nerve stimulation (TNS) treatments include multiple FDA-approved implantable TNS therapies and a better understanding of stimulation settings that enable patients to perform home-based TNS using a transcutaneous electrical nerve stimulation (TENS) unit. **RUTI** (2 UTIs in 6 months or 3 in 12 months) is prevalent in menopausal women because of changes in the urogenital microbiota with menopause. The AUA guideline on uncomplicated RUTI in women was updated substantially in 2025 and aligns with similar updates made by the Infectious Disease Society of America (IDSA) in support of clearer definitions of UTI as localized (confined to the bladder) versus systemic, avoidance of testing in the absence of acute symptoms, and more judicious antibiotic use for the shortest possible duration of treatment in the setting of localized UTI. UTI is one of the top 3 indications for antibiotic outpatient antibiotic use and there is rising concern about the dangers of antibiotic overuse, particularly to treat asymptomatic bacteriuria or localized UTI in the absence of complicating factors that increase risk of pyelonephritis and urosepsis, where repeated antibiotic exposure may actually increase the risk of recurrent UTI, multidrug resistant UTI, and *Clostridioides difficile* infection. The AUA guideline proposes supportive care (oral non-steroidal anti-inflammatory drugs (NSAIDs), urinary analgesics (eg, phenazopyridine), and increased hydration) with consideration of transition to antibiotics if not responding as an appropriate strategy for episodic management in women with RUTI, in line with recommendations from many other countries that avoiding presumptive antibiotic use in low-risk women with UTI is safe and prudent. Vaginal estrogen is a recommended first-line prevention strategy for peri and postmenopausal women with RUTI and may also improve other GSM symptoms. **SUI**, leakage of urine with increased abdominal pressure, such as from coughing or exercising, may be treated with pelvic floor muscle exercises, intravaginal inserts or pessaries, or surgical procedures in the office or operating room. Synthetic (mesh) midurethral slings have the most robust evidence of effectiveness and remain the most common surgery for SUI. Single incision slings and urethral bulking injections have increased in popularity, with polyacrylamide hydrogel being more effective and durable than older urethral bulking agents. Trends in surgery for **POP** (descent of the pelvic organs related to relaxation of pelvic floor tissues) include increased use of robotic-assisted surgery and uterine-sparing procedures and decreased use of vaginal mesh. Urogynecologic research captures both anatomic and patient-reported subjective outcomes but increasingly favors patient-reported outcomes to guide surgical counseling.

When Pain Persists: Chronic Pelvic and Sexual Pain in Midlife Women Through a Biopsychosocial Lens

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Chronic pelvic pain and sexual pain are common yet often underrecognized concerns during the menopause transition and beyond. Although genitourinary syndrome of menopause is a common contributor, many women experience overlapping musculoskeletal, neurologic, visceral, and psychosocial factors that perpetuate pain and negatively affect sexual function, intimate relationships, emotional well-being, and quality of life. As a result, patients frequently undergo delayed diagnosis, fragmented care, and ineffective treatment. While hypoestrogenism contributes to pain for many women, persistent symptoms often arise from overlapping hormonal, musculoskeletal, neurologic, and psychosocial mechanisms that require a broader diagnostic and therapeutic approach. This presentation will provide an evidence-based introduction to the evaluation and management of pelvic and sexual pain in perimenopausal and menopausal women using a biopsychosocial framework. Participants will learn a practical approach to identifying common pain generators, recognizing symptoms that warrant further

evaluation, and distinguishing hormonal, pelvic floor, visceral, and centrally mediated contributors to persistent pain. Current evidence supporting multimodal management will be reviewed, including hormonal and nonhormonal therapies, pelvic floor physical therapy, behavioral interventions, and multidisciplinary care. Through clinical cases and practical diagnostic algorithms, attendees will gain strategies for developing individualized treatment plans that address the complexity of chronic pelvic and sexual pain while improving patient outcomes. This presentation aims to expand clinicians' understanding of persistent pain during the menopause transition and provide practical tools that can be readily incorporated into clinical practice to improve the care and quality of life of midlife women.

PLENARY SYMPOSIUM #8

Realizing the Full Potential Of the Estrogen Receptor As a Therapeutic Target in Different Estrogenopathies

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Originally described as reproductive hormones, it is now well established that estrogens, acting through their cognate estrogen receptors (ERs), exhibit clinically important non-reproductive actions in bone, cardiovascular system, central nervous system and in immunity. The dramatic physiological changes that emerge in women as they transition through perimenopause to menopause highlights the importance of estrogens, primarily 17- β estradiol, in maintaining tissue homeostasis and well-being. However, balancing the positive actions of estrogen containing medicines against the significant liabilities that have been linked to exogenous estrogen supplementation and/or dysregulated estrogen signaling (ie, increased risk of breast and gynecological cancers and stroke), remains a clinical challenge. It was with the goal of separating the positive from the negative effects of estrogens that emerged Selective Estrogen Receptor Modulators (SERMs) and a newer class of drugs, Tissue-Selective Estrogen Complexes (TSECs). Whereas the early development of SERMs occurred in an empirical manner the more modern medicines of this class, like lasofoxifene, bazedoxifene and ospemifene and the TSECs, leveraged a more contemporary understanding of ER pharmacology in target cells yielding drugs that can manifest distinct biological actions in different cells/target organs. Contributing to these discovery efforts was our groups development of the concept of “functional allostery” that encapsulates three important observations (a) subtle alterations in the chemical composition of ligands induces distinct conformational changes in ER (b) differently conformed receptor-ligand complexes present different protein-protein interaction surfaces which enable the recruitment of functionally distinct coregulators and (c) the relative and absolute expression of coregulators are not the same in all target cells. Exploitation of this new pharmacology enabled the development of several new ER-modulators that are either approved or in clinical evaluation for a variety of diseases in which tissue selective activation or repression of estrogen action is a desired outcome. Notwithstanding this already complex pharmacology we have recently determined that target organ response to ER-modulators is also influenced by their actions in the immune system and in the brain which can either increase or decrease their therapeutic efficacy. Notably, in immune cells estrogens facilitate the development of an immune suppressive tumor microenvironment through direct actions on myeloid cells resulting in the attenuation of T cell activation/function, an activity that can be reversed with classical ER antagonists. Surprisingly, inhibition of ER action in specific loci in the brain has the paradoxical effect of increasing bone mineral density, impacting immune cell function and increasing the growth of peripheral solid tumors of different origins. Thus, in addition to defining the specific mechanisms by which ER-modulators directly modulate the function of specific target cells there is a need to understand the actions of these drugs in the immune system and in the brain. Cumulatively this information will inform how best to use existing ER modulators, be instructive as to approaches to develop the next generation of modulators and enable the development of new drug combinations for use in the treatment of a wide variety of estrogenopathies.

Rewiring the Thermostat: From the Thermoneutral Zone to KNDy Neurons and Targeted Menopause Therapies

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Vasomotor symptoms (VMS) affect up to 80% of menopausal women and often persist for 7–10 years. Although estrogen (E2) therapy has long been known to relieve hot flashes, the neural mechanisms linking E2 withdrawal to VMS remained unclear for decades. The foundation for our current understanding began in the 1970s and 1980s with physiologic studies by Robert Freedman and colleagues who demonstrated that menopause is associated with a marked narrowing of the thermoneutral zone; the range of core temperatures between the sweating and shivering thresholds. In reproductively aged women, normal fluctuations in body temperature occur within this zone without triggering autonomic responses. In menopausal women, however, even small increases in core temperature exceed the sweating threshold, resulting in vasodilation, sweating, and the sensation of intense heat. While these studies explained the physiology of hot flashes, they did not define the underlying neural mechanism. Investigators also observed that hot flashes frequently coincided with pulsatile LH secretion, leading to the hypothesis that LH or GnRH might trigger VMS. Subsequent studies demonstrated that hot flashes could occur independently of LH secretion, suggesting that both were parallel outputs of a common hypothalamic pathway. This finding focused attention on the hypothalamus as the likely site of thermoregulatory dysfunction. A breakthrough came in the early 2000s when Naomi Rance and colleagues reported striking hypertrophy of neurokinin B (NKB)-expressing neurons in the hypothalamic arcuate nucleus of postmenopausal women. These neurons were subsequently shown to co-express kisspeptin, neurokinin

B, and dynorphin and became known as KNDy neurons. Initially recognized for their role in metabolism and reproductive hormone regulation, KNDy neurons were found to be highly sensitive to E2 feedback. Under normal conditions, E2 suppresses KNDy neuronal activity. The hypogonadism of menopause disinhibits KNDy neurons, leading to neuronal hypertrophy and hyperactivity. The next advance was the discovery that KNDy neurons influence thermoregulation as well as reproduction. KNDy neurons project to the median preoptic nucleus (MnPO), a key thermoregulatory center containing neurons that express the NK3R. Excessive NKB release activates these neurons, triggering heat-defense responses including vasodilation, sweating, and the subjective sensation of a hot flash. A series of animal and human studies confirmed this pathway. Ablation of KNDy neurons reduced thermoregulatory responses in rodents, while activation of NK3R signaling lowered core body temperature. Most compellingly, intravenous infusion of NKB in healthy premenopausal women induced hot flashes indistinguishable from naturally occurring menopausal hot flashes, providing direct evidence that NKB signaling is sufficient to generate VMS in humans. These discoveries transformed treatment development. Hormone therapy remains highly effective because it restores E2-mediated inhibition of KNDy neurons. However, many women cannot or choose not to use hormones. Identification of the KNDy–NKB–NK3R pathway enabled development of the first mechanism-based nonhormonal therapies. Fezolinetant, approved in 2023, selectively blocks NK3R signaling and significantly reduces VMS frequency and severity. Elinzanetant, approved in 2025, combines NK3R and NK1R antagonism. While NK3 signaling appears central to thermoregulation, NK1 signaling through substance P may contribute to sleep disturbances, potentially offering additional sleep benefits with dual antagonism. The evolution from observations of a narrowed thermoneutral zone to the discovery of KNDy neurons and NK antagonists represents a remarkable example of translational neuroscience. What began as a physiologic observation ultimately led to identification of the neural circuitry responsible for hot flashes and the development of the first nonhormonal therapies designed to directly target their underlying biology.

The Effect of NKB Antagonism Beyond the Hot Flash: Sleep, Bone and Cognition

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 Vasomotor symptoms (VMS), including hot flashes and night sweats, affect up to 80% of menopausal women. Sleep disturbances, including insomnia, poor sleep quality, and sleep apnea, impact approximately 69% of women and are associated with hormone fluctuations and VMS during menopause. Recent research indicates that VMS and sleep disruption may signal increased sensitivity to hormone changes and greater long-term health risks. Observational studies show that women with frequent VMS or menopause-related complaints face higher risks of adverse health outcomes. Frequent VMS and sleep disruption have been linked to increased risk of cardiovascular disease, including higher BMI, cholesterol, blood pressure, arterial damage, and mortality; osteoporosis, with increased bone turnover, lower bone density, and higher fracture risk; and cognitive decline, including impaired memory and greater risk of neurodegenerative disease. Neuroimaging studies show that objectively measured VMS are associated with changes in brain structure (white matter hyperintensities) and function (altered connectivity in memory-related regions), suggesting a potentially modifiable risk factor for cognitive impairment. Nonhormone therapies targeting neurokinin pathways (NKT), such as fezolinetant (NK3 antagonist) and elinzanetant (dual NK1/NK3 antagonist), have shown sustained efficacy in reducing VMS frequency and severity for up to 52 weeks. By acting on KNDy neurons in the hypothalamus that regulate thermoregulation, they reduce vasomotor symptoms without affecting hormone levels. Both agents also improve mood and quality of life. Additionally, both drugs enhance sleep quality, with elinzanetant providing more consistent benefits. A recent mediation study found that elinzanetant offers a direct sleep benefit independent of VMS reduction, suggesting NK1 receptor blockade as a novel mechanism. Clinical data show that neither drug adversely affects bone density nor turnover markers beyond normal age-related changes, nor do they prevent menopausal bone loss or osteoporosis. Fezolinetant has a neutral effect on bone mineral density, while recent analyses indicate elinzanetant does not accelerate skeletal decline compared to placebo over 52 weeks. Safety profiles are generally favorable; however, fezolinetant requires liver monitoring due to rare enzyme elevations, and elinzanetant is associated with increased somnolence. These findings support neurokinin antagonists as promising non-hormonal options for managing VMS and sleep disturbances. Depending on the neurokinin receptor targeted, these therapies may also help reduce long-term risks such as cardiovascular disease, osteoporosis, and cognitive decline in individuals who cannot or choose not to use hormone therapy. Further research is needed to confirm these potential benefits. For breast cancer survivors, elinzanetant has shown reduction in VMS frequency and safety in a 52-week published trial for endocrine associated VMS (tamoxifen and aromatase inhibitors) and fezolinetant has an ongoing phase 3 trial (NCT06440967).

PLENARY SYMPOSIUM #9

Hypoactive Sexual Desire Disorder: Applying the Updated International Society for the Study of Women’s Sexual Health Guidelines in Multidisciplinary Practice

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Hypoactive sexual desire disorder (HSDD) is a common and often underrecognized condition that impacts women across their lifespan, with important ramifications for quality of life, relationships, and even overall well-being. Despite its high prevalence, barriers to diagnosis persist, including limited clinician training, time constraints, and

discomfort with sexual health discussions. Guidelines from the International Society for the Study of Women’s Sexual Health (ISSWSH) provide an evidence-based framework for the identification, assessment, and management of HSDD, emphasizing a biopsychosocial approach and individualized care. The ISSWSH guidelines highlight the importance of distinguishing characteristics of HSDD, contextual factors, and the role of comorbid conditions, including menopause, mood disorders, relationship concerns, and medical therapies. Validated screening tools and structured clinical assessment can facilitate diagnosis in routine practice. Management strategies include education, sex therapy, and targeted interventions addressing contributing factors, along with pharmacologic options when appropriate. Emerging data and evolving therapeutic options add important tools to the HSDD treatment toolkit. A multidisciplinary model which integrates primary care, women’s health, gynecology, psychiatry, and sexual health specialists is essential to optimizing outcomes. Practical strategies for implementation include normalizing sexual health conversations, embedding screening into clinical workflows, and leveraging team-based care to address complex needs. This session will translate the ISSWSH guidelines into real-world clinical practice, providing clinicians with practical tools to identify and manage HSDD. Emphasis will be placed on improving clinician confidence, reducing stigma, and advancing comprehensive, patient-centered sexual health care. **Reference** Parish SJ, Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. International Society for the Study of Women’s Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. *Climacteric*. 2021 Dec;24(6):533-550. doi: 10.1080/13697137.2021.1891773. Epub 2021 Apr 1. PMID: 33792440.

When Arousal and Orgasm Are Elusive: A Clinical Framework for Midlife Women

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 Female sexual arousal disorder (FSAD) and female orgasmic disorder (FOD) are common, distressing, and frequently under-recognized concerns among menopausal women. Population-based data from the PRESIDE study demonstrate that low desire with distress was found to affect roughly 12–15% of women age 45-64. In this cohort of menopausal women reporting low desire, over one-third also report problems with arousal, orgasm, or pain, underscoring the overlapping and interrelationship of these domains. Pain conditions (vulvovaginal atrophy, pelvic floor dysfunction), urinary incontinence conditions, mood, and anxiety disorders, cardiometabolic disease, neurologic injury, vasculopathies, hormone deficiencies and iatrogenic factors (SSRIs, antihypertensives, pelvic surgeries) frequently contribute to both FSAD and FOD. Contemporary ISSWSH guidance distinguishes female genital arousal disorder (FGAD)—persistent and distressing difficulty attaining and/or maintaining lubrication, genital engorgement, or pleasurable genital sensitivity despite adequate stimulation—from female cognitive arousal disorder (FCAD), defined as persistent and distressing difficulty attaining and/or maintaining feelings of excitement and increasing pleasure, attention to and mental engagement with erotic stimuli. FOD is characterized by persistently reduced orgasm frequency, intensity, timing, or pleasure, accompanied by distress. The female orgasm is a complex process involving a sensorimotor, cognitive, and emotional experience of variable intensity and pleasure that occurs at the peak of excitation, triggering a subsequent release of overall muscle tension. A biopsychosocial care approach is essential in the evaluation and treatment of FSAD and FOD. A simplified and organized approach utilizing the 4 A’s: ASK/ASSESS, ADDRESS, ANALYZE, ACTIONS. The first step, “ASK/ASSESS,” is to gather information using open, sex-positive, culturally sensitive, and non-judgmental language to obtain the following: sexual history including temporal relationship to changes in any element of the bio-psycho-social-relationship; evaluation of distress; pelvic and vulvar exam; pelvic floor assessment; targeted neurologic screening; review of hormonal, cardiometabolic, and medication contributors. The first line management for all female sexual concerns including FSAD and FOD is to “ADDRESS” the patients concern with empathic witnessing, reassurance and basic health recommendations including: education and normalization (POSIT model), optimization of stimulation, lubricants, vibrators, sleep and mood management, and partner communication skills. The “ANALYZE” therapies focus on the psychosocial techniques of sensate focus to rebuild comfort and body awareness; mindfulness to enhance attention to erotic cues; cognitive-behavioral therapy to address avoidance, negative self-appraisal, and performance anxiety. Basic core psychosocial tools may be initiated or introduced when comfortable with the material, but in-depth direction is likely best addressed with a referral to a sex therapist/counselor or sexologist (to find one in your area use the ASSECT or SSTAR websites). Lastly, the medical or procedural interventions, “ACTIONS,” are directed at optimizing blood flow, nerve sensation, muscle tension and treatment of pain and contributing medical conditions using: hormonal optimization; medications, self-stimulation, and pelvic floor physical therapy. By integrating desire, arousal, orgasm, and pain within a unified menopause-informed framework, clinicians can more confidently identify and treat sexual dysfunction in midlife women, improving sexual well-being and overall quality of life.

What the Pelvic Floor Has to Do With It: Rehabilitation Science and Sexual Function in Midlife Women

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The menopause transition produces clinically relevant changes in the aging pelvic floor that extend beyond vulvovaginal symptoms alone. Declining ovarian hormone exposure affects estrogen-responsive muscle, fascia, connective tissue, mucosa, and vascular structures throughout the pelvis. These changes may contribute to reduced tissue elasticity, altered muscle bulk and contractile performance, impaired coordination,

diminished pelvic organ support, increased tissue sensitivity, and reduced tolerance for pressure, penetration, and sustained sexual positioning. Pelvic floor function in midlife depends on more than strength. The muscles must lengthen, contract, relax, coordinate with breathing and intra-abdominal pressure, support continence, and pelvic organs, and respond appropriately during arousal and orgasm. With aging and menopause, some women develop weakness and reduced support, while others develop guarding, overactivity, impaired relaxation, or pain in response to tissue irritation, genitourinary syndrome of menopause, prior childbirth injury, surgery, chronic pain, or fear of anticipated discomfort. These differing presentations require individualized assessment rather than routine strengthening alone. Pelvic floor disorders, including urinary incontinence, pelvic organ prolapse, dyspareunia, and pelvic pain, are associated with poorer sexual function and reduced sexual participation in perimenopausal and postmenopausal women. Pelvic floor muscle rehabilitation may improve pain, arousal, orgasm, satisfaction, and overall sexual-function scores; however, current evidence is limited by heterogeneous treatment protocols, variable patient populations, and low-certainty findings. Rehabilitation may include coordination and relaxation training, progressive strengthening when indicated, manual therapy, graded exposure, tissue mobility interventions, breathing and pressure management, and education regarding positioning and load tolerance. The aging pelvic floor also functions within a changing whole-body system. Menopause-related losses in skeletal muscle strength, connective-tissue resilience, bone density, joint mobility, cardiovascular conditioning, and pain tolerance may further affect pelvic floor performance and the physical capacity required for intimacy. Hip and spinal mobility, lower-extremity strength, trunk control, endurance, and comfortable positioning can influence whether sexual activity is physically accessible, sustainable, and pleasurable. A rehabilitation approach centered on the aging pelvic floor therefore addresses both local impairments and the broader physical factors that influence sexual participation. The clinical goal is not simply to increase pelvic floor strength, but to restore adaptable pelvic floor function—support, coordination, relaxation, sensory tolerance, and responsiveness—within the whole person.

PLENARY SYMPOSIUM #10

The Interrupted Night: Silent Health Consequences of Menopausal Sleep Disturbance

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The menopause transition is an inflection point of risk for sleep disruption and adverse cardiometabolic and neurocognitive outcomes. Menopausal sleep disruption is unique and characterized by repeated awakenings throughout the night after initially falling asleep. This repeated fragmentation is typically not associated with shortened sleep duration, unlike in other forms for sleep disruption or insomnia. Women, therefore, often meet the recommended 7-8 hours despite poor quality sleep. Vasomotor symptoms (VMS), affecting ~80% of women for an average of 7.4 years, are strongly linked to this fragmented pattern of sleep, which carries a range of consequences for cardiometabolic and neurocognitive health. To isolate the contributions of estradiol loss, which is universal and a major contributing factor to adverse health outcomes, and those of sleep fragmentation, we used a robust experimental model combining pharmacologic estradiol suppression with experimentally provoked menopause-pattern sleep fragmentation in healthy premenopausal women, removing the confound of aging. Women were studied under inpatient laboratory conditions with controlled diet and environmental conditions, with subjective and objective assessments of exposures and outcomes. Our approach allowed for examining the mechanistic roles of estradiol suppression and menopausal sleep fragmentation individually and together on altering cardiometabolic, neurocognitive and affect-related outcomes. On the cardiometabolic side, sleep fragmentation increased heart rate, fasting glucose, and bedtime cortisol, blunted the cortisol awakening response, and shifted substrate oxidation from fat to carbohydrates. Additionally, estradiol suppression independently reduced the levels of satiety-related hormone leptin, elevated circulating lipid levels, and reduced bedtime cortisol. On the neurocognitive and affective side, sleep fragmentation increased attentional lapses, reaction times, and subjective sleepiness throughout the day. Sleep fragmentation also worsened positive and negative affect, and women who developed VMS during estradiol suppression showed a more persistent reduction in positive affect, suggesting additive effects on mood. Encouragingly, work from us and others show that pharmacologic and behavioral strategies can improve menopausal sleep fragmentation. The therapeutic potential of such approaches on mitigating long term health risks associated with chronic sleep disruption in midlife women with VMS needs further systematic evaluation. Together, our findings establish menopausal sleep fragmentation as an independent, modifiable driver of adverse cardiometabolic, neurocognitive and affect-related health outcomes, distinct from shortened sleep duration, and potentially targetable through both medications and behavioral strategies. These findings underscore VMS-targeted sleep interventions to improve sleep consolidation and quality as a scalable strategy to reduce long-term health risk across the menopausal transition and highlight sleep continuity as a priority for healthy postmenopausal aging.

Are You Sleeping? Recognizing, Managing, and Referring Sleep Disorders at the Menopause Transition

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Sleep disturbance is among the most burdensome symptoms experienced by perimenopausal and postmenopausal women, affecting 40% to 60% of women in midlife. Middle-of-the-night awakenings and difficulty returning to sleep are the most bothersome sleep-related symptoms. While vasomotor symptoms (VMS) and changing

reproductive hormonal profiles are specific drivers of sleep disruption, sleep difficulties are multifactorial. They reflect a complex interplay of aging, primary sleep disorders, medical comorbidities, mood disturbances, and midlife psychosocial and caregiving demands. Causality is also bidirectional: nocturnal awakenings trigger maladaptive compensatory behaviors — extending time in bed, napping — that perpetuate chronic insomnia. A structured clinical evaluation that establishes a differential diagnosis of perimenopause- and menopause-related sleep disturbance is therefore essential to guide targeted, evidence-based treatment. Targeting VMS to improve sleep is a reasonable first-line approach, though data on therapies that directly target sleep in midlife women vary by treatment class, and clinical response varies substantially. Estrogen may confer some sleep benefit independent of VMS, but the evidence remains limited and inconsistent. Progesterone is commonly prescribed for midlife sleep disturbance despite a paucity of supporting data. The sleep impact of hormonal VMS-targeted treatments derives largely from secondary analyses of short-term trials designed to reduce hot flashes, and results suggest modest improvements in insomnia symptoms. Recent data on neurokinin receptor antagonists demonstrate statistically significant but variable improvements in sleep disturbance and sleep-related daytime symptoms, with larger effect estimates reported for elinzanetant than fezolinetant; in the absence of head-to-head trials, whether either reaches a clinically meaningful within-patient threshold remains unresolved. Healthy sleep practices are necessary but insufficient for treating chronic insomnia disorder. Cognitive behavioral therapy for insomnia (CBT-I) is the guideline-recommended first-line intervention, with robust efficacy even in the presence of VMS. Benzodiazepine receptor agonists and dual orexin receptor antagonists are reasonable second-line or adjunctive options when CBT-I is unavailable or incompletely effective, with shared decision-making regarding residual sedation, fall risk, tolerance, and discontinuation. Beyond insomnia, primary sleep disorders increase in midlife and must be evaluated. Postmenopausal status, age, weight redistribution, and declining ovarian hormones influence upper airway and ventilatory control, increasing the incidence of obstructive sleep apnea (OSA). OSA in midlife women is frequently overlooked because women more often present with nonspecific symptoms — insomnia, fatigue, and depression — than with loud or habitual snoring, and because widely used screening instruments have reduced sensitivity in women. Objective sleep testing is indicated when OSA, parasomnias, other sleep disorders, or refractory symptoms are suspected. Restless legs syndrome also increases in prevalence in midlife and requires careful history to distinguish it from its mimics. Clear referral pathways and multidimensional care strategies are needed to match midlife women to the specific diagnosis driving their sleep complaint.

SWAN SYMPOSIUM: TRANSFORMING WHAT WE KNOW ABOUT MENOPAUSE

Daily Hormone Patterns Across the Menopause Transition: New Insights and Discoveries

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The Study of Women's Health Across the Nation (SWAN) began in 1994, with the goal of characterizing as many aspects of a woman's health as possible as she traversed her final reproductive years, and linking these changes to future health in the postmenopausal years. One of the opportunities that SWAN presented was to be able to capture a 'snapshot' of an entire menstrual cycle (or up to 50 days, whichever came first) in a subgroup of 848 of the original 3302 women enrolled in SWAN. Eligible women collected a baseline cycle when they were either pre (no irregularity) or early perimenopausal (>7 days difference in cycles or a skipped cycle) and annually thereafter until they have a final menstrual period (FMP) after which a single, 25-day collection was performed. Analysis of these cycles has been able to highlight the changes in % of ovulatory cycles as women approach their FMP, key associations of body size with hormone levels, and a progressive decline in progesterone metabolite production as the FMP nears. Anovulatory cycles have been examined to better understand how key endocrine mechanisms such as estrogen positive feedback fail in perimenopause. Further analyses have examined the trajectory of cycle lengths (stable, early increase, and late increase) and have associated these cycle length trajectories with health outcomes, with those demonstrating a late increase in cycle length having overall healthier outcomes despite a slightly earlier age at their FMP. More recent analyses have involved examination of entropy—or the degree of 'disorder' that accompanies the breakdown of many energy driven processes. Entropy analysis has shown that of the 4 cardinal hormones of the menstrual cycle, reduced Pdg entropy is most predictive of the approach of the FMP. Elevated environmental pollutant exposure has been associated with reduced cycle hormone entropy and more advanced reproductive aging. Finally vasomotor symptoms have been associated with elevated Pdg and E1c entropy and decreased LH and FSH entropy.

Menopause and Women's Cardiovascular Health: What the SWAN Data Tells Us

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The Study of Women's Health Across the Nation (SWAN) is one of the most comprehensive, longitudinal studies of the menopause transition, ongoing from 1994-1996 and now in its 30th year. SWAN enrolled 3302 premenopausal and early perimenopausal midlife women across five racial and ethnic groups and spanning seven study sites in the United States. Participants have undergone up to 18 visits during this 30-year period. SWAN has provided important insights into the role of menopause

and its symptoms in women's cardiovascular health. Cardiovascular disease (CVD) is the leading cause of death in women, and the menopause transition is a key inflection point for women's cardiovascular health. SWAN has shown that, beyond the effects of aging alone, menopause is accompanied by accelerated accumulation of atherosclerosis, increases in vascular stiffening, adverse changes in lipids, and increased incidence of metabolic syndrome. Further, SWAN has found while midlife represents a time of accelerated weight gain, menopause is accompanied by adverse changes in body composition including decreases in lean mass and increases in fat mass, even for weight stable women. SWAN has also underscored that the menopause-related determinants of women's cardiovascular health transcend sex hormones alone. Specifically, SWAN findings have illuminated that menopausal symptoms such as vasomotor symptoms (VMS), experienced by up to 75% of women, and sleep problems, experienced by up to 50% of women, are more than bothersome midlife symptoms; VMS and sleep problems, particularly when experienced persistently, are associated with a 70-80% increased risk of CVD events such as myocardial infarction and stroke, beyond the effects of endogenous estradiol, hormone therapy, and CVD risk factors. Further, with its multi-ethnic design, SWAN has also demonstrated key racial and ethnic differences in women's cardiovascular health as they age. Thus, SWAN has provided critical insights into women's cardiovascular health during this pivotal period of the lifespan, findings that can be leveraged for preventive efforts to support women's cardiovascular health as they age.

THE MENOPAUSE SOCIETY/PFIZER WULF H UTIAN ENDOWED LECTURE

A New Era in Therapy for Autoimmune Diseases: Chimeric Antigen Receptor T-Cell Therapy Brings the Prospect of 'CURE' within Reach

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There are huge challenges in management of autoimmune diseases. Despite advances, outcomes have plateaued. Current immunosuppressive therapies are ineffective in achieving remission and in preventing relapses in up to 50% of patients with complex and refractory autoimmune illnesses, particularly systemic lupus erythematosus. Hence there remains an unmet need for better treatments. B-cell depleting therapies are a cornerstone of therapy for many autoimmune illnesses. Despite good peripheral B cell depletion, bispecific and antibody-based B cell targeting therapies rarely induce stable drug-free remission in autoimmune disease. Shallow B cell depletion that does not tackle resident autoimmune B cell clones may be the reason for this limitation. Deeper B cell depletion with a 'living drug' to allow targeting resident autoimmune B cell clones, enabling potential immune tolerance is the goal such that long-term drug therapy is not needed. CAR-based cellular therapy is emerging as a time-limited strategy for severe autoimmune disease, but its clinical value depends on more than early response. Autologous CD19 CAR T-cell therapy seems to be the most mature evidence, particularly in systemic lupus erythematosus and other systemic rheumatic diseases. Early studies also support disease-specific development in systemic sclerosis, idiopathic inflammatory myopathy, rheumatoid arthritis, autoimmune cytopenias, and selected neurologic disorders. However, cohorts remain small and heterogeneous, and both short-term and long-term toxicity remains a concern. Immune reset, long-term therapy free disease remission and potentially a cure may be possible in these diseases. However, future development requires disease-specific comparative trials, biomarker-guided platform selection, standardized clinical and immune-reconstitution endpoints as well as close monitoring for long-term side-effects and disease outcomes.

THE MENOPAUSE SOCIETY/KLEINMAN ENDOWED LECTURE

The US Food and Drug Administration's Role in Advancing Therapeutics for Midlife and Menopausal Women

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The presentation will provide an overview of FDA's role in advancing the development of safe and effective therapeutics for women during midlife and menopause. It will discuss regulatory science in women's health and how the evidence base informs the evaluation, approval, and labeling of FDA-regulated products. The presentation will also highlight efforts by FDA's Office of Women's Health (OWH) to identify and address critical knowledge gaps, support research relevant to midlife and menopausal health, foster scientific collaboration, and promote reliable, science-based health information. Finally, it will explore opportunities for clinicians, researchers, and other stakeholders to engage with FDA and help strengthen the evidence base for therapies that address the health needs of women during midlife and menopause.