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## Today's approaches to treating the menopause: Risks and benefits of various therapies

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### Menopausal symptoms: Therapeutic options and special considerations

**Genevieve Neal-Perry, MD, PhD**

**M**any symptoms are attributed to the menopausal transition and menopause, but only a few are supported by solid evidence. These include vasomotor symptoms (VMS) and vaginal dryness/atrophy.

#### Vasomotor symptoms

Most common among women during perimenopause and early menopause, VMS are characterized by a reddening of the skin (flushing) and excessive sweating. Unlike the general sweating caused by exercise, sweating associated with VMS is primarily confined to the upper body.

Episodes of hot flashes tend to last from 6 months to 5 years after menopause, but they have been known to persist for several decades. In a survey of 501 self-selected postmenopausal women (ages 29 to 82), 50% of women began experiencing hot flashes before menopause, when the menstrual cycle was still regular or just becoming irregular.<sup>1</sup>

The Study of Women's Health Across the Nation (SWAN) investigated factors associated with menopausal symptoms reported by women in the United States, including age, race/ethnicity, educational attainment, lifestyle factors (smoking, physical activity), and menopausal status.<sup>2</sup> Most of the 12,425 women aged 40 to 55 years included in the analysis reported hot flashes and night sweats, and most were premenopausal or early perimenopausal.

VMS were reported most commonly among African American (45.5%), Hispanic (35.4%) and white women (31.2%), respectively. Women with a higher body mass index were also

more likely to report symptoms.<sup>2</sup> Sociodemographic variables, including lower educational attainment and greater difficulty paying for basic needs, were associated with increased reporting of VMS.<sup>2</sup>

Hot flushes are believed to be caused by a narrowing of the thermoneutral zone in the brain, an effect likely related to changes in patterns of neurotransmitter release and/or responsiveness in the central nervous system subsequent to estrogen withdrawal.<sup>3</sup> Neurotransmitters that are believed to be involved include the serotonergic, histaminergic, noradrenergic, and opioid systems.

### Treatment options: Behavioral interventions, pharmacotherapy

**Nonpharmaceutical interventions** for VMS include lifestyle modifications, such as healthy eating, maintaining normal body weight, smoking cessation, and wearing layers of clothing to allow removal of layers when experiencing a hot flush. Paced breathing, similar to that used to ameliorate the pain of contractions during childbirth, has been shown to be helpful.<sup>4</sup> Weak evidence supports aerobic exercise, yoga, or relaxation as treatment for flushing, however, and data regarding acupuncture are mixed. Nonetheless, regular exercise is encouraged because it will assist with the maintenance of a normal body weight and related benefits.

**Estrogen replacement therapy** is well established as the most effective treatment for severe and persistent menopausal symptoms.<sup>3,5</sup> A randomized, double-blind, crossover study published more than 35 years ago demonstrated a substantial reduction in the average number of hot flushes per week with conjugated equine estrogen (CEE).<sup>6</sup> Today, many options, including low- and ultra-low-dose CEE combinations are available. The recommendation is to use the lowest dose to treat symptoms because of the risk factors associated or identified with estrogen use in older women, and progesterone should be included in women with a uterus.

**The nonhormones** most widely used for treatment of VMS are the **serotonin and norepinephrine reuptake inhibitors (SNRIs)**. These agents are particularly useful in women with depression. The most common side effects of SNRIs are insomnia and anorexia, however, and they are not tolerated by some patients.

**Other** available pharmacotherapies are **gabapentin**, an anticonvulsant that can effectively reduce VMS, and **clonidine**, an  $\alpha$ -adrenergic mediator particularly useful in women who have breast cancer. These drugs may also be difficult to tolerate due to associated side effects.<sup>7</sup>

### Vaginal changes in menopause

Loss of estrogen affects the skin and impacts vaginal health. Reduction of collagen fibers and glycoaminoglycans can affect skin thickness and elasticity. Changes in secretions, particularly

from the vagina, and in vascularity also cause skin thinning. Hair changes occur, typically involving hair loss on the head and growth of unwanted hair on the chin.<sup>8,9</sup>

Vaginal dryness can be a significantly distressing symptom that increases over the course of menopausal change. In a population-based study of 438 women aged 45 to 55 years, 47% of women reported vaginal dryness 3 years postmenopause.<sup>10</sup> Vaginal dryness often impacts patient self-image and negatively affects the ability to have and enjoy sex. Not surprisingly, about 40% of women experience dyspareunia. Alterations in vaginal mucosa are also associated with immune changes that increase risk for infections. Nevertheless, only 25% of women will actually seek help.<sup>10</sup> Given that vaginal dryness is such a common problem for menopausal women, physicians are encouraged to initiate a dialogue with their at-risk patients by querying postmenopausal women at the time of their annual visit.

### Management approaches

Treatment options for vaginal dryness include nonhormonal vaginal lubricants, a temporary fix for problems with intercourse; vaginal moisturizers using a bioadhesive polycarbo-phil-based-polymer, which provides weeks of improvement; or longer-term hormonal intervention (vaginal suppository, tablet, or ring).

Concerns regarding the tolerability and safety of estrogen and estrogen plus progestin treatments have led to investigations of alternative therapies to reduce menopausal symptoms with less potential for bone loss, cardiovascular, and endometrial effects. Promising results have been achieved in phase III trials of a tissue-selective estrogen complex (TSEC) composed of bazedoxifene, a third-generation selective estrogen-receptor modulator (SERM), and conjugated estrogens.<sup>11,12</sup> Significant reductions in frequency and severity of hot flushes and improved measures of vaginal atrophy were achieved versus placebo, suggesting that this combination has potential to be of benefit in treating multiple menopausal symptoms.

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## Treating menopausal osteoporosis: Risk and benefits of various therapies

Presented by Lubna Pal, MBBS, MRCOG, MS

The incidence of osteoporosis-related fractures in women aged 29 and older is higher than the incidence of heart attack, stroke, and breast cancer combined.<sup>1-3</sup> The cost to society, in both human and economic terms, is enormous. Around 20% of elderly people with hip fracture die within the first year.<sup>4</sup> Thus, clinicians have important decisions to make from the skeletal perspective: Who are the patients at risk for fracture? When should I initiate therapy? Should I be thinking prevention or treatment? And which treatment is most appropriate for this patient?

### Risk assessment tools

Several tools are available to identify fracture risk, including the Risk Factor Profile, which combines single-site bone density assessment and selected clinical risk factors to help estimate the risk of osteoporotic fracture for postmenopausal women over the next 5 years; dual-emission x-ray absorptiometry (DXA) to measure bone mineral density (BMD); biomarkers of bone formation and bone resorption to determine status of bone metabolism; and FRAX, a free Web-based tool that quantifies 10-year risk factor for any osteoporotic fracture based on patient-specific parameters.<sup>4,5</sup> The National Osteoporosis Foundation has guidelines as to when to initiate treatment based on FRAX data.

### Risk factors for osteoporosis

Aging is the biggest risk factor for fragility fractures. A 70-year-old woman or man is more likely to experience a fracture than a 50-year-old with the same bone density and bone turnover status. Low body mass index (BMI) is an independent risk factor, and Caucasians are at a higher fracture risk than individuals of other races.

Other risk factors include late menarche and early menopause. Time of menarche is a huge determinant of peak bone gain. Duration of and age at lactation are important considerations, as bone loss may occur during pregnancy and lactation. While pregnancy- and lactation-related bone loss is mostly reversible, long-term concerns may be relevant in the case of teenage pregnancy. Personal and/or family history of fractures helps determine an individual's genetic risk profile.

Environment is a critical but often overlooked consideration for fracture risk. For example, someone who has borderline osteopenia or early stages of osteoporosis is at higher risk for fracture if she lives in an area where tripping and falling is common. Lifestyle issues, such as tobacco use and alcohol consumption, also increase fracture risk. Other factors include poor nutrition and vision impairment in the aging population.

### Therapeutic options for patients at risk for fracture

A variety of antiresorptive agents are available, including estrogens, bisphosphonates, and selective estrogen-receptor modulators (SERMs). Numerous studies have demonstrated that estrogen-based therapy improves bone mineral density. The Women's Health Initiative trials also confirmed fracture risk reduction.<sup>7</sup> With many generic formulations available, estrogen is a cost-effective fracture prevention strategy for appropriate patients.

**Estrogens.** Menopausal hormone therapy (MHT) is recognized as a strategy for fracture risk reduction and osteoporosis *prevention*; its role in the *treatment* of existing osteoporosis, however, is questionable. Given that MHT use is not risk free, and that the magnitude of skeletal benefit from MHT is surpassed by existing alternatives, estrogens should not be considered as a first-line therapy in postmenopausal women with known osteoporosis. In the relatively young and otherwise healthy symptomatic women deemed at fracture risk, use of MHT offers symptom relief as well as skeletal benefit.

**Bisphosphonates.** This class of antiresorptive agents is the most commonly utilized pharmacologic risk-reduction strategy against fracture; these agents are approved for *prevention* as well as *treatment* of osteoporosis. The currently available bisphosphonates offer flexibility in administration (oral or intravenous) and dosing regimen (daily, weekly, 3 times monthly, and yearly). Because these drugs are retained in the bone for years and long-term consequences are not entirely clear, caution is warranted when using bisphosphonates in the relatively young. In recent years, the concept of *drug holiday* has emerged as a strategy to minimize certain risks that may relate to long-term (more than 2 to 3 years) use of bisphosphonates, eg, occurrence of atypical fractures of the femur.

**SERMs.** Raloxifene has been the most widely used SERM in the United States, and its efficacy in vertebral fracture risk reduction is well described.<sup>8</sup> Bazedoxifene, an emerging agent, has shown similar efficacy in vertebral fractures as well as efficacy in a subgroup of patients who are at high risk for nonvertebral fractures.<sup>9</sup>

An asymptomatic menopausal woman who is deemed at risk for breast cancer may be a good candidate for treatment with a SERM from the perspective of skeletal protection; however, it must be appreciated that if she is at risk for hip fracture, raloxifene may not be the right strategy. Nevertheless, until tissue-selective estrogen complexes (TSECs) become available, the main role of SERMs is in the younger population, where this strategy offers the dual benefit of skeletal protection and breast cancer risk reduction.

**Calcitonin.** Use of the naturally occurring hormone calcitonin for its skeletal benefits has waned with the emergence of the more efficacious strategies. Calcitonin, however, may still have a role in the management of patients with existing vertebral fractures, in whom calcitonin use has been shown to offer analgesic benefit for severe back pain.

**Denosumab.** A newer antiresorptive agent that has shown promise in risk reduction for vertebral and nonvertebral fractures, denosumab is a humanized monoclonal antibody directed against the receptor activator of nuclear factor kappa beta ligand (RANKL). It specifically binds to RANKL and inhibits osteoclast activity, decreasing bone resorption and increasing BMD, and thereby confers fracture risk reduction. Its infrequent dosing regimen and proven efficacy against vertebral and nonvertebral fractures make this drug an attractive alternative to the bisphosphonates; denosumab is administered every 6 months by subcutaneous injection, and its effects last up to 6 months.<sup>10</sup> Denosumab is indicated for the treatment of osteoporotic postmenopausal women who are deemed at high risk for fracture when the alternative agents are either ineffective or are poorly tolerated.

**Parathyroid hormone (PTH).** The lone anabolic agent available in the United States is PTH. Parathyroid hormone is the most efficacious and robust available agent in reducing risk of vertebral and nonvertebral fractures.<sup>11</sup> While relatively well tolerated, PTH requires daily administration by subcutaneous injection. The recommended duration of therapy is about 18 months to a maximum of 2 years. PTH may be an appropriate agent to start with in a patient at high risk for fracture or who has existing fractures. Efficacy drops rapidly after treatment cessation; a long-term management strategy with an alternative agent thus must be considered to ensure ongoing skeletal

benefit after PTH therapy is discontinued. Sequential combination therapy (PTH course followed by maintenance antiresorptive therapy) has been shown to be superior to the concomitant approach (a combination of PTH and an antiresorptive agent) in offering long-term skeletal protection.

**Miscellaneous. Vitamin D** supplementation is recommended for all deemed at risk for low BMD and skeletal fragility. Of particular relevance is that the efficacy of the various bone-sparing agents discussed earlier is compromised in the setting of concomitant vitamin D deficiency. In select populations, vitamin K may also be important because of its effects at the level of maturation of the bone collagen. Strontium has both anabolic and resorptive properties; its mechanism of action, however, remains unclear, and it is not available in the United States.<sup>12</sup>

In summary, numerous pharmaceutical options are available for the prevention and treatment of menopausal osteoporosis. Promising new agents such as TSECs are in development and offer a hope of targeted skeletal benefit. Nonpharmacologic interventions, such as lifestyle modifications, physical therapy, fall prevention, optimizing vision, and improving balance, all play an important role in fracture risk reduction.

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# Today's approaches to treating the menopause: Case studies

Presented by Cynthia K. Sites, MD

Apply your understanding of therapeutic options for menopausal symptoms and osteoporotic fracture risk in the following cases.

## Case 1

A 52-year-old woman presents with complaints of hot flashes and decreased interest in her usual activities. Her mammograms have been normal, and her last menstrual period was 2 years ago. Which treatment is best for this patient?

- A. Tibolone
- B. Bioidentical progesterone cream
- C. Tissue-selective estrogen complex (TSEC)
- D. Venlafaxine

**The correct answer is D, venlafaxine.**

Decreased interest in sexual activity can be interpreted as a symptom of depression. As a selective norepinephrine reuptake inhibitor (SNRI), venlafaxine is used to treat depression and it has also been shown to reduce hot flashes. Tibolone, bioidentical progesterone cream, and TSECs are not recognized treatments for depression.

## Case 2

A 54-year-old woman has hot flashes and difficulty sleeping. She was diagnosed with estrogen-receptor positive breast cancer 2 years ago for which she takes tamoxifen. Her last menstrual period was 1 year ago. Which treatment is best?

- A. Paroxetine
- B. Bioidentical estrogen cream
- C. Gabapentin
- D. Tissue-selective estrogen complex (TSEC)

**The correct answer is C, gabapentin.**

Gabapentin contains no hormones and has been shown to relieve hot flashes. A side effect of gabapentin is drowsiness, which may be helpful in patients who have difficulty sleeping. Paroxetine can cause insomnia, and bioidentical estrogens are not the best choice for a patient who has estrogen-receptor positive breast cancer and is taking tamoxifen.

## Case 3

A 53-year-old woman whose last menstrual period was 1 year ago presents with poor sleep quality due to frequent hot flashes. A recent mammogram was normal, and she is generally healthy, with a body mass index (BMI) of 24 kg/m<sup>2</sup>. A bone mineral scan revealed a T score of -2.0 at the lumbar spine. She has not had a hysterectomy. What is the best treatment?

- A. Oral estradiol and progesterone
- B. Risedronate
- C. Raloxifene
- D. Teriparatide (parathyroid hormone, PTH)

**The correct answer is A, oral estradiol and progesterone.**

Hormonal therapy is still the gold standard for treatment of vasomotor symptoms in an otherwise healthy, newly menopausal woman. It also reduces risk for bone fractures in women with reduced bone density. Risedronate, raloxifene, and teriparatide provide no benefit for hot flashes.

## Case 4

A 73-year-old woman presents with evidence of osteoporosis on bone density assessment (T score of -2.8 at the lumbar spine and T score of -2.6 at the hip). She cannot tolerate the side effects of bisphosphonates and does not want daily subcutaneous injections. Which treatment is most appropriate?

- A. Calcitonin
- B. Denosumab
- C. Tamoxifen
- D. Teriparatide (PTH)

**The correct answer is B, denosumab.**

This patient has severe osteoporosis at the spine and hip and does not want daily injections. Denosumab is injected once every 6 months. Calcitonin does not reduce risk of nonvertebral fractures, and tamoxifen is more effective in younger postmenopausal women.

## Case 5

A 49-year-old woman has symptoms of vaginal dryness and occasional hot flashes. Her last menstrual period was 1 year ago. Her mother had a hysterectomy for endometrial cancer. What is the best potential treatment for this patient?

- A. Oral estradiol and progesterone
- B. Tissue-selective estrogen complex (TSEC)
- C. Gabapentin
- D. Bioidentical estrogen cream

**The correct answer is A, oral estradiol and progesterone.**

The best treatment for this patient is oral estradiol and progesterone. A family history of endometrial cancer is not a contraindication for menopausal hormone therapy. TSECs represent an emerging pharmacotherapeutic intervention for treatment of hot flashes and they do not stimulate the endometrium. Short-term data regarding TSECs have been submitted to the FDA and are currently under review for clinical use, with relief of VMS as the primary indication. TSECs may offer an alternative therapy for patients who experience depressive-like symptoms in response to progesterone. Gabapentin is not beneficial for vaginal dryness. Bioidentical estrogen cream may stimulate the endometrium.