A SUPPLEMENT TO

OBG MANAGEMENT

MAY 2016

ADVANCES IN MENOPAUSE TRANSITION MANAGEMENT

SeleneTouch

An Innovative Solution for Intimate Health

50% of post-menopausal women, after childbirth, hormonal changes and medications, experience a diverse range of symptoms and side effects including: dryness, itching, and painful intercourse, which affect Quality of Life.

The SeleneTouch micro-ablative laser energy is dispensed in a controlled and uniform distribution into the vaginal wall tissue. The superior design allows the SeleneTouch laser to ablate small micro spots of tissue, while leaving the adjacent tissue intact, thus promoting faster tissue regeneration. This natural tissue regeneration process promotes the restoration of pre-menopausal metabolic activity including new collagen, elastin, and vascularization of the vaginal mucosa.

Increased collagen production, thicker vaginal mucosa, and natural restoration of the ablated vaginal tissue allow post-menopausal women to return to their normal lifestyle with comfort, confidence, and improved Quality of Life.

Call now for a representative: 877.275.8760

www.SeleneTouch.com

ACOG 2016
Washington, DC
Booth #138

Benefits

- ★ Immediate Improved Quality of Life
- ★ No Anesthesia—Outpatient Procedure
- ★ Fast, Safe, and Effective
- ★ Painless
- ★ 2nd Generation CO_2 Technology
- ★ Clinically Studied—Expert Approved
- ★ 3, 5 Minute Treatments, 6 Weeks Apart
- ★ Fast Return on Investment

Call Now: 877.275.8760

FOCUS MEDICAL

Not enough women are receiving treatment for bothersome menopausal symptoms

The objective of this special issue is to enhance how you respond to and manage patients' sexuality and menopausal symptom concerns

Andrew M. Kaunitz, MD

"Help! My patients are asking me about sex and menopause concerns. What do I tell them?" I often receive this query from young ObGyns who, as they transition from training, encounter clinical scenarios different from those stressed during residency. Staying up to date and feeling comfortable addressing sexuality and menopausal symptom management in midlife women is a challenge not just for young ObGyns but for all of us,[1] and unfortunately women with bothersome menopausal symptoms often are not evaluated or treated.[2,3] With this in mind, I believe you will find the 4 articles in this special issue of OBG MANAGEMENT, authored by nationally-prominent expert clinician/researchers, brimming with recent evidence combined with authorative clinical recommendations.

Two fundamental truths regarding menopause are that, while vasomotor symptoms (VMS) improve over time, vulvovaginal atrophy (also referred to as genitourinary syndrome of menopause, or GSM) worsens in untreated women.[4] In their article on page S2, Drs. Sheryl Kingsberg and Michael Krychman provide expert advice regarding recognition and practical management of GSM.

While homone therapy (HT) remains the gold standard approach to treating menopausal VMS,[2] some patients either have contraindications to use of HT or prefer non-HT strategies. On page S10, Drs. Juliana Kling and JoAnn Manson use 2 cases to update readers on the latest evidence addressing US Food and Drug Administration (FDA)–approved as well as off-label prescription medications, over the counter supplements, and nonmedication-based strategies to address bothersome VMS.

Five selective estrogen receptor modulators are now FDA approved for a diverse array of indications. In their review on page S18, Drs. James Liu and Gretchen Collins update readers regarding this increasingly important class of medications.

We often hear our midlife patients say, "My sex life is down in the cellar. What can be done about this?" In her article on page S30 addressing sexuality concerns of midlife women, Dr. Kellogg Spadt offers among others, tips for handling arousal concerns and addressing pelvic floor disorders with the goal of helping their midlife patients, "bring intimacy back into their relationships."

I am confident that you will find this special issue not only hones your knowledge and skills regarding sexuality and menopausal management but also will lead to satisfied midlife patients in your practices.

References

1. Manson JE, Kaunitz AM. Menopause management—getting clinical care back on track. N Engl J Med. 2016;374(9):803–806.
2. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(11):3975–4011.
3. Santen RJ, Stuenkel CA, Burger HG, Manson JE. Competency in menopause management: whither goest the internist? J Womens Health (Larchmt). 2014;23(4):281–285.
4. Kaunitz AM, Manson JE. Management of menopausal symptoms. Obstet Gynecol. 2015;126(4):859–876.

Dr. Kaunitz is Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine–Jacksonville. Dr. Kaunitz serves on the OBG MANAGEMENT Board of Editors and is the Guest Editor for this special issue.

Dr. Kaunitz reports that his department at the University of Florida receives clinical trial support from Bayer and TherapeuticsMD and that he serves on the contraception advisory boards for Allergan, Bayer, and Pfizer.

Mitigating the impact of genitourinary syndrome of menopause on sexuality

Up to half of postmenopausal women may experience symptoms of GSM that adversely affect their lifestyle, sexual function, and relationships. An array of treatments are available to help alleviate your patients' discomfort and improve their vaginal and sexual health.

Sheryl Kingsberg, PhD, and Michael Krychman, MD

Women with GSM need not suffer in silence, since a wide variety of treatments are available to reduce symptoms and restore function

Genitourinary syndrome of menopause (GSM) is defined as a collection of symptoms and signs associated with declining levels of estrogen and other sex steroids during the menopause transition that impacts the labia majora and minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. Symptoms may include genital dryness, burning, irritation, lack of lubrication despite sexual arousal, pain during sexual activity, impaired sexual function, and urinary tract symptoms.[1] The term vulvovaginal atrophy (VVA) is subsumed under the more comprehensive GSM definition in which all the genitopelvic anatomic structures are considered. The North American Menopause Society (NAMS) has published practice guidelines that illustrate clinical assessment, diagnosis, and treatment options for GSM.[2]

Dr. Kingsberg is Division Chief, Ob/Gyn Behavioral Medicine, University Hospitals Case Medical Center, and Professor, Reproductive Biology and Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio.

Dr. Krychman is Executive Director, Southern California Center for Sexual Health and Survivorship Medicine Inc., Newport Beach, California.

Dr. Kingsberg reports that she has served as a consultant for Acerus, EndoCeutics, Materna, Novo Nordisk, Nuelle, Pfizer, and TherapeuticsMD and has stock options for Viveve.

Dr. Krychman reports that he has served as a consultant and on the speakers bureau for Noven Therapeutics, Pfizer, and Shionogi and has received research support from NERI Science.

CASE Pain during sexual activity is affecting her relationship

A 55-year-old married woman presents to you, her gynecologist, for her well-woman visit. She has no chronic medical illnesses and currently is not taking any medications. During review of symptoms you uncover that, since about 1 year after her last menstrual period 5 years ago, she has been experiencing increasing discomfort during sexual intercourse. Sexual activity is now very painful. She describes the pain as "tearing" but she "grins and bears it." Her genital sensations are also muted, and she reports a decrease in orgasmic intensity and increase in latency. She wants to enjoy intercourse again and is worried that her symptoms are causing marital problems with her husband of 20 years. The patient is apprehensive about using any hormone therapy because of her family history; both her mother and her maternal aunt had breast cancer at age 68 and 73 years, respectively.

How would you further evaluate and counsel this patient, and what treatment options would you recommend?

CONTINUED ON PAGE S5

Divigel®
(estradiol gel) 0.1%
0.25 mg 0.5 mg 1 mg

Give your patients a sigh of relief

Eliminates 90% of hot flashes by week 12 (1 mg/day)[1]

- Divigel® provides the **LOWEST COST** to patients*[2]

Important Safety Information for Healthcare Providers

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See Full Prescribing Information for complete Boxed Warning

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia
- The WHI estrogen plus progestin substudy reported increased risks of
- stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI)
- The WHI estrogen plus progestin study reported increased risks of invasive breast cancer
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

Divigel® should not be used in women with undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to Divigel®; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; or known or suspected pregnancy.

Estrogens increase the risk of gallbladder disease.

Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs.

Monitor thyroid function in women on thyroid replacement therapy.

The most common adverse reactions (incidence ≥ 5 percent) are breast tenderness, metrorrhagia, vaginal mycosis, nasopharyngitis, and upper respiratory tract infection.

Patients should be started with the lowest effective dose and the dose should be evaluated periodically.

Alcohol-based gels are flammable. Patients should avoid fire, flame or smoking until the gel has dried.

Please see Full Prescribing & Safety Information. For more information visit www.divigel.com.

You may report side effects by calling: 1-877-95-VERTI (1-877-958-3784) or calling 1-800-FDA-1088

Please see accompanying Brief Summary on adjacent page.

*Divigel® provides Preferred Brand coverage for more patients than any other topical non-patch estrogen therapy

1. Divigel® (package insert) Sayerville, NJ: Vertical Pharmaceuticals, LLC; 2014
2. Data on File

Portable, premeasured sachets for accurate dosing

VERTICAL PHARMACEUTICALS, LLC

To Order Samples:
or visit www.divigel.com/professional/

Divigel® (estradiol gel) 0.1%

Brief Summary of Prescribing Information

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo.

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

Divigel is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

CONTRAINDICATIONS

Divigel® should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema to Divigel
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

WARNING AND PRECAUTIONS

Cardiovascular Disorders- An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately. *Stroke* - In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years). In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) .The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. *Coronary Heart Disease*- In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2]. Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years)[1]. In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years)[1]. An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5. In postmenopausal women with documented heart disease (n=2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. *Venous Thromboembolism*- In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. **Malignant Neoplasms**- *Endometrial Cancer*- An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. *Breast Cancer*- The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[2]. The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups[6]. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial date on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration. The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. *Ovarian Cancer* - The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 [95 percent CI, 0.77-3.24]. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association. **Probable Dementia-** In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8]. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 womenyears[8]. When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Gallbladder Disease-** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. **Hypercalcemia -**Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **Visual Abnormalities-** Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued. **Addition of a Progestin When a Woman Has Not Had a Hysterectomy-** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. **Elevated Blood Pressure-** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. **Hypertriglyceridemia-** In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. **Hepatic Impairment and/or Past History of Cholestatic Jaundice-** Estrogens may be poorly metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. **Hypothyroidism-** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range. **Fluid Retention-** Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed. **Hypocalcemia-** Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur. **Exacerbation of Endometriosis-** A few cases of malignant transformation of residual endometrial implants have been reported in women treated post hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered. **Hereditary Angioedema** Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. **Exacerbation of Other Conditions** Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions. **Photosensitivity/Photoallergy** The effects of direct sun exposure to Divigel application sites have not been evaluated in clinical trials. **Application of Sunscreen and Topical Solutions** Studies conducted using other approved topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels. The effect of sunscreens and other topical lotions on the systemic exposure of Divigel has not been evaluated in clinical trials. **Flammability of Alcohol-Based Gels - Alcohol based gels are flammable.** Avoid fire, flame, or smoking until the gel has dried. Occlusion of the area where the topical drug product is applied with clothing or other barriers is not recommended until the gel is completely dried. **Potential for Estradiol Transfer and Effects of Washing** There is a potential for drug transfer from one individual to the other following physical contact of Divigel application sites. In a study to evaluate transferability to males from their female contacts, there was some elevation of estradiol levels over baseline in the male subjects; however, the degree of transferability in this study was inconclusive. Patients are advised to avoid skin contact with other subjects until the gel is completely dried. The site of application should be covered (clothed) after drying. Washing the application site with soap and water 1 hour after application resulted in a 30 to 38 percent decrease in the mean total 24-hour exposure to estradiol. Therefore, patients should refrain from washing the application site for at least one hour after application. **Laboratory Tests-** Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms. **Drug - Laboratory Test Interactions -** Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning]*.
- Malignant Neoplasms *[see Boxed Warning]*.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted for Divigel. **Metabolic Interactions -** *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort *(Hypericum perforatum)* preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy Divigel should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy. **Nursing Mothers-** Divigel should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when Divigel is administered to a nursing woman. **Pediatric Use-** Divigel is not indicated in children. Clinical studies have not been conducted in the pediatric population. **Geriatric Use-** There have not been sufficient numbers of geriatric women involved in studies utilizing Divigel to determine whether those over 65 years of age differ from younger subjects in their response to Divigel. *The Women's Health Initiative Studies* In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

The Women's Health Initiative Memory Study In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Renal Impairment-** The effect of renal impairment on the pharmacokinetics of Divigel has not been studied. **Hepatic Impairment-** The effect of hepatic impairment on the pharmacokinetics of Divigel has not been studied.

OVERDOSAGE

Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Divigel therapy with institution of appropriate symptomatic care.

REFERENCES

1. Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA.* 2007;297:1465-1477.
2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med.* 2006;166:357-365.
3. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med.* 2006;166:772-780.
4. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA.* 2004;292:1573-1580.
5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Post-menopausal Women With Hysterectomy. *JAMA.* 2006;295:1647-1657.
6. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmeno-pausal Women. *JAMA.* 2003;289:3234-3253.
7. Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA.* 2003;290:1739-1748.
8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA.* 2004;291:2947-2958.

Distributed by
Vertical Pharmaceuticals, LLC, All rights reserved.
2500 Main Street, Sayreville, NJ 08872

See www.divigel.com for more information.

Rev 0514
106637.01
107179.01

CONTINUED FROM PAGE S2

TABLE 1 Signs of GSM on genital examination[6]

General	External	Internal
• Pale, dry, shiny appearance • Petechiae • Ulcerations • Friability of tissue • Loss of elasticity/turgor of tissue	• Thinning of vulvar skin • Loss of fat pads (labia majora/mons pubis) • Diminished labia minora (possible fusion) • Receded prepuce • Sparse pubic hair	• Thinning of vaginal epithelium • Narrowed/shortened vagina • Diminished rugae • Reduced secretions • Erythema indicating inflammation

Abbreviation: GSM, genitourinary syndrome of menopause.

Half of postmenopausal women have GSM

GSM may affect 50% of postmenopausal women.[2] Symptoms are progressive and do not resolve without treatment. Vaginal dryness and dyspareunia are the most bothersome symptoms reported both in clinical trials and in the largest US survey of women with VVA.[3,4] In another survey of 1,000 postmenopausal women with VVA, almost two-thirds of respondents reported both dyspareunia and loss of sexual desire.[5]

Diagnosing GSM

Be proactive regarding the possible presence of GSM when providing care for perimenopausal and postmenopausal women. Women experiencing GSM may not report symptoms because they are embarrassed, are unaware that their symptoms are related to menopause, or believe that their symptoms are an inevitable part of aging.[4]

Upon genital examination, detailed assessment may reveal various external and internal changes (**TABLE 1**).[6] Although it is not essential to assess the vaginal maturation index and vaginal pH to make a diagnosis, some clinicians recommend assessing the vaginal pH (typically >5.0) to confirm the presence of vaginal atrophy.[2]

CASE Continued

History and physical exam reveal that the patient has many GSM symptoms, including vaginal and vulvar irritation, pelvic area burning, and pain with sexual activity, particularly intercourse.

Recall that GSM encompasses urinary tract changes, which can impact sexual function and confidence. Low estradiol levels are linked to recurrent urinary tract infections due to the decline in lactobacilli, rise in vaginal pH, increased urinary frequency/incontinence, residual urine, and reduction in urine flow.[7] Physical and functional urinary tract changes include mucosal thinning in the urethra and bladder, urethral shortening, reduced periurethral collagen, urethral caruncle, weakened sphincter, reduced bladder storage capacity, and residual urine volume.[8]

Some medications (oral contraceptives, antihistamines, aromatase inhibitors, chemotherapy drugs, and methotrexate) may exacerbate GSM symptoms, such as vaginal dryness. It is therefore important to review current medications when evaluating women with symptoms suggestive of GSM.

Be proactive about the potential presence of GSM in menopausal patients because they may not report symptoms

CASE Continued

The patient reports that her orgasmic intensity and latency have been a problem and her marital relationship is being negatively impacted. These issues may be manifestations of GSM.

Based on the patient's symptoms and results of the physical examination, you diagnose GSM.

Treatment should be multidimensional

Counsel on lifestyle

Treatment begins with educating and counseling the patient about the cause of

GSM, its symptoms, and management approaches. Incorporate shared decision making with regard to treatment. Review simple behavioral changes the patient can make to improve vulvovaginal health, and offer practical suggestions, such as avoiding tight clothing; using mild, unscented laundry detergent; using plain soft, white, unscented toilet paper to gently pat the vulvar area dry with only light pressure; and avoiding perfumed or harsh soaps, creams, or feminine hygiene products. Also advise that she choose breathable cotton underwear and remove a wet bathing suit and damp exercise clothing promptly. You also can advocate simple sitz baths in lukewarm or even chilled or cool water to relieve vulvar burning and irritation.

Mild vulvar washes can be used to help soothe a dry, irritated vulvar area. In is essential that postmenopausal patients understand the importance of skin health and how the hygiene products that they choose can impact GSM.

Making simple lifestyle changes and using OTC vaginal moisturizers and lubricants are initial treatment approaches for patients with GSM

Over-the-counter options

Although prescription therapies are approved as first-line treatment for GSM, if the patient's physical signs and symptoms appear mild, it is reasonable for you to suggest initial use of nonhormonal treatments, including vaginal moisturizers and lubricants, and perhaps the use of vaginal stretching activities (regular sexual activity or dilators).

Over-the-counter (OTC) treatments are often suggested as simple solutions to mitigate discomfort from vaginal dryness or lack of lubrication. Vaginal moisturizers support and hydrate the vaginal and pelvic tissue. Consistent application of a vaginal moisturizer 1- to 3-times weekly helps restore the ridges, folds, and elasticity and stretchability of the vaginal tissues. Moisturizers are placed within the vagina, and sometimes on the vulva, independent of sexual activity, whereas lubricants are used only during sexual activity.

Dozens of brands of lubricants are available, and the products are distinguished by their base, composed of water, oil, silicone, or petroleum.[9] Some women prefer organic or water-based lubricants for lovemaking, while others prefer silicone-based products. Some lubricant brands offer glycerin- and paraben-free options, which may be less irritating than alternatives. Water-based lubricants are nonstaining and harmless with latex. They rarely cause irritation but do dry up quickly and often need to be reapplied during sexual activity. (See **TABLE 2**).[9–18]

Silicone-based lubricants are long lasting, sleek, silky slick, and slippery (and may cause slippery floor surfaces). They are often tasteless, odorless, and have no stickiness or tackiness, but they can stain fabrics. For some women with fragile vaginal tissues, silicone-based lubricants can sometimes irritate the vagina.

Petroleum-based lubricants are not a good option; however, natural oil-based lubricants are nonirritating and latex friendly.

Hybrid vaginal products are a recent addition to the OTC product options for GSM. Hybrids have the properties of both a water- and a silicone-based lubricant.[10] They work as a soothing gel/cream that transforms into a silky layer, coating and soothing the vaginal lining while also acting as a form of liquid lubrication. Hybrid products are meant to deliver long-lasting vaginal moisture with the easy clean up of a water-based lubricant. Hybrids are often made with nonirritating ingredients, designed for women with allergies and skin sensitivities.

Despite the accessibility and safety of vaginal moisturizers and lubricants, women may be concerned about cost, excessive leakage, harmful chemical additives, and even exacerbation of symptoms.[4] Many women do not understand the difference between a moisturizer and a lubricant. The vast number of product options available can overwhelm even the most experienced consumer.

Regardless of which products a patient may try initially, instruct her to read all product labels and to consider avoiding products that contain parabens, chlorhexidine, and glycerin. Spermicides, bactericides, color and flavor additives, and warming or cooling

TABLE 2 Nonprescription and prescription first-line treatment for GSM and VVA[9–18]

Treatment	Comments	Available products
OTC nonhormonal topicals		
Vaginal lubricants	For use during sex; apply at vaginal or anal entrance and on external genitals of both partners	
Water based[9]	Ingredients: deionized water, glycerin, propylene glycol; latex safe; rare irritation; dry out with extended sexual activity	Astroglide, Good Clean Love, Natural, Organic, Pink, Sliquid, Yes
Oil based[9]	Ingredients: avocado, olive, peanut, corn; latex safe; can be used with silicone products; staining; safe (unless peanut allergy); nonirritating	Vegetable oil, coconut oil, vitamin E oil
Silicone based[9]	Ingredients: silicone polymers; staining; typically nonirritating; long lasting; waterproof; should not be used with silicone dilators, sexual toys, or gynecologic products	Astroglide X, Oceanus Ultra Pure, Pink Silicone, Pjur Eros, Replens Silky Smooth, Silicone Premium JO, SKYN, Wet Premium
Petroleum based[9]	Staining; ingredients: mineral oil, petroleum jelly, baby oil; irritating; not latex safe and not for use with cervical caps or intravaginal diaphragms	Rarely recommended
Hybrids[10]	Properties of water- and silicone-based lubricants; nonirritating; for daily use; designed for women with allergies and skin sensitivities[10]	Lubrigyn, Luvena
Vaginal moisturizers	For maintenance use 1 to 3 times weekly; can benefit women with dryness, chafing with ADL, and recurrent vaginal infections irrespective of sexual activity timing	Emerita, Hyalogyn, KY Liquibeads, Rephresh, Replens, vitamin E
Vulvar washes	For daily use for intimate hygiene	Lubrigyn Lotion, Luvena Therapeutic Wash
Prescription local estrogen preparations		
Vaginal creams		
CE (0.625 mg/g)[11]	For use twice weekly 0.5 g/d	Premarin
Estradiol (0.01%)[12]	• Initial dosing: 2–4 g/d (1–2 times/wk), gradually reduced to half the initial dose for a similar period • Maintenance dosing: 1 g, 1–3 times/wk	Estrace
Vaginal ring[13]		
Estradiol (7.5 µg released per 24 h)	1 ring replaced every 3 mo	Estring
Vaginal tablet[14]		
Estradiol (10-µg tablet)	• Initial dosing: 1 tablet/d for 2 wk • Maintenance dosing: 1 tablet/d twice weekly	Vagifem
Prescription oral nonestrogen		
Ospemifene (60-mg tablet)	For daily use to treat moderate to severe dyspareunia[15]; SERM shown to have estrogenic action in the vaginal epithelium and neutral effect on endometrium[16–18]	Osphena

Abbreviations: ADL, activities of daily life; CE, conjugated estrogens; GSM, genitourinary syndrome of menopause; OTC, over the counter; SERM, selective estrogen receptor modulator; VVA, vulvovaginal atrophy.

CONTINUED ON PAGE S8

CONTINUED FROM PAGE S7

Treating GSM in women with a personal history of breast cancer

Many women have become fearful of using any hormonal treatments, including local estrogens. The package inserts for local estrogen therapies, which carry the same warnings as systemic estrogen formulations, likely contribute to this fear. You can offer patients, including women with a history of breast cancer, a more accurate and balanced perspective regarding the use of local estrogen therapies. The American College of Obstetricians and Gynecologists has published practice guidelines supporting the use of minimally absorbed local vaginal estrogen products, and NAMS has supported a change in product labeling for low-dose vaginal estrogen.[1,2]

References

1. American College of Obstetricians and Gynecologists Committee Opinion No. 659: the use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. Obstet Gynecol. 2016:127(3):e93–e96.
2. Manson JE, Goldstein SR, Kagan R, et al; Working Group on Women's Health and Well-Being in Menopause. Why the product labeling for low-dose vaginal estrogen should be changed. Menopause. 2014;21(9):911–916.

products may be problematic to the sensitive vaginal and vulvar mucosa.

Low-dose local vaginal estrogen products and an oral nonestrogen alternative are available for women who do not obtain sufficient symptom relief with OTC products

Available prescription medications

For many women with symptoms of GSM, OTC products may not provide sufficient symptom relief and do not treat the underlying pathology. Fortunately, an array of prescription medications approved by the US Food and Drug Administration (FDA) are available, including minimally absorbed low-dose local vaginal estrogen products (creams, rings, and intravaginal tablets) and an oral selective estrogen receptor modulator (SERM). See TABLE 2 on page S7.[11–18]

Conjugated estrogen or estradiol creams may provide excellent coverage of the vagina, but use of excessive amounts may lead to leakage, systemic absorption, and patient discontinuation. Vaginal estradiol tablets are an ultra-low-dose treatment with almost no systemic escape, but they may not provide adequate coverage to the lower third of the vagina, and some women may continue to report introital or insertional dyspareunia. The estradiol-containing vaginal ring is a long-acting product that may remain within the vagina for 3 months, with almost no systemic absorption. The ring does not have pessary-like benefits, and it may be expelled during defecation. Some women may be aware of the ring during coitus.

The SERM ospemifene is a tissue-specific estrogen agonist/antagonist, an oral nonestrogen alternative approved for the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause.[15] Ospemifene has estrogenic action in the vaginal epithelium and a neutral effect on the endometrium. Three phase 3 clinical trials have demonstrated ospemifene's efficacy and safety for the treatment of VVA in postmenopausal women.[16–18] Ospemifene has been associated, however, with an increased incidence of hot flushes. NAMS considers ospemifene, along with local estrogen preparations, a first-line treatment option.[2,19] For a detailed discussion of ospemifene, see "SERMs in menopause: Matching agents to symptoms and attributes" on page S18.

As with all patients who are treated with estrogen, women treated with ospemifene who experience abnormal vaginal bleeding should undergo a comprehensive evaluation that includes transvaginal ultrasonography and/or an endometrial biopsy.

Vaginal laser therapy

A variety of laser types have been used to treat VVA and GSM. Although lasers may have indications for nonspecific gynecologic interventions, further evaluation is warranted before they can be recommended for GSM. The website ClinicalTrials.gov describes an upcoming "multi-centered, randomized prospective single blinded clinical trial comparing CO_2 fractionated vaginal laser therapy and vaginal estrogen cream therapy in the treatment of vulvovaginal atrophy/GSM."[20]

Products on the horizon

A number of therapies to treat VVA and GSM are in development, including an applicator-free intravaginal estradiol softgel that has been assessed in a phase 3 clinical trial.[21]

A dehydroepiandrosterone intravaginal suppository is presently under review at the FDA. The published data demonstrate that this formulation has excellent efficacy and safety,

and researchers report that there is no systemic release of estradiol because of the product's intracellular biomechanical physiology.[22]

Another promising option is the investigational SERM lasofoxifene, for which regulatory approval is being sought in the United States and Europe. (See "SERMs in menopause: Matching agents to symptoms and attributes" on page S18.)

CASE Resolved

Your patient is concerned about taking hormones, even vaginal estrogen and ospemifene, because of her family history of breast cancer. You counsel her about the minimal systemic absorption of low-dose vaginal estrogen; however, her concerns are not allayed. You discuss nonhormonal options, such as lubricants, moisturizers, dilators, and vibrators, and focus on shared decision making.

Add adjunctive treatments when necessary

Severe vaginal atrophy and advanced symptomatology of GSM not only may be associated with dyspareunia but also may trigger pelvic floor hypertonus (PFH), muscular contraction, and levator ani spasm. If severe, levator spasm and intravaginal hypertonus may lead to chronic pelvic pain and vaginismus. Use of adjunctive progressive dilators coupled with genitopelvic floor physical therapy may be helpful in the overall treatment paradigm. (See "Tips for counseling women about intimacy after menopause" on page S30.)

Regardless of which treatment option(s) a patient eventually chooses, the universal first step is to take a GSM-specific history and physical examination. By discussing the issues with your patient, you will open the door to an appropriate diagnosis and helpful treatment. ■

References

1. Portman DJ, Gass M. Genitoruinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause. 2014;21(10):1063–1068.
2. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society. Menopause. 2013;20(9):888–902.
3. Ettinger B, Hait H, Reape KZ, Shu H. Measuring symptom relief in studies of vaginal and vulvar atrophy: the most bothersome symptom approach. Menopause. 2008;15(5):885–889.
4. Kingsberg SA, Wysocki S, Mangus L, Krychman M. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (Real Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med. 2013;10(7):1790–1799.
5. Simon JA, Nappi RE, Kingsberg SA, Maamari R, Brown V. Clarifying vaginal atrophy's impact on sex and relationships (CLOSER) survey: emotional and physical impact of vaginal discomfort on North American postmenopausal women and their partners. Menopause. 2014;21(2):137–142.
6. Minkin MJ, Guess MK. Diagnosis and treatment of the non–sex-related symptoms of vulvovaginal atrophy. Female Patient. 2012;37:33–41.
7. Luthje P,Hirschberg AL, Brauner A. Estrogenic action on innate defense mechanisms in the urinary tract. Maturitas. 2014;77(1):32–36.
8. Chism LA. Overcoming resistance and barriers to the use of local estrogen therapy for the treatment of vaginal atrophy. Int J Women's Health. 2012;4:551–557.
9. Hutcherson HY, Kingsberg SA, Krychman ML, et al. A positive approach to female sexual health: a summary report. Female Patient. 2009;(suppl April):1–6.
10. Donders GG, Bellen G. Cream with cutaneous fibroblast lysate for the treatment of provoked vestibulodynia: a double-blind randomized placebo-controlled crossover study. J Low Genit Tract Dis. 2012;16(4):427–436.
11. Premarin [package insert]. Philadelphia, PA: Pfizer Inc; May 2012.
12. Estrace [package insert]. Rockaway, NJ: Warner Chilcott; September 2013.
13. Estring [package insert]. New York, NY: Pharmacia and Upjohn Company; September 2014.
14. Vagifem [package insert]. Princeton, NJ: Novo Nordisk Inc; April 2013.
15. Osphena [package insert]. Florham Park, NJ: Shionogi Inc; 2015.
16. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480–486.
17. Portman DJ, Bachmann G, Simon J; The Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause. 2013;20(6):623–630.
18. Goldstein SR, Bachmann GA, Koninckx PR, Lin VH, Portman DJ, Ylikorkala O; The Ospemifene Study Group. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric. 2014;17(2):173–182.
19. Cui Y, Zong H, Yan H, Li N, Zhang Y. The efficacy and safety of ospemifene in treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy: a systematic review and meta-analysis. J Sex Med. 2014;11(2):487–497.
20. Comparison of vaginal laser therapy to vaginal estrogen therapy (VeLVET). ClinicalTrials.gov web site. https://clinicaltrials.gov/ct2/show/NCT02691936?term=CO2+fractionated+vaginal+laser+therapy&rank=1. Updated February 22, 2016. Accessed April 16, 2016.
21. Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized controlled trial evaluating the safety and efficacy of a novel vaginal estradiol softgel capsule for symptomatic vulvar and vaginal atrophy (VVA). Poster presented at: 2016 ENDO Annual Meeting; April 1–4, 2016; Boston, MA.
22. Labrie F, Archer DF, Koltun W, et al. Efficacy of dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vaginal atrophy, and the genitourinary syndrome of menopause. Menopause. 2016;23(3):243–256.

Nonhormonal treatment options for vasomotor symptoms of menopause

Your patient's preferences, medical and family history, and symptom severity direct her treatment choices. When her optimal choice is hormone-free, here are current and best options.

Juliana M. Kling, MD, MPH, and JoAnn E. Manson, MD, DrPH

A discussion of managing menopausal symptoms can include on- and off-label, over-the-counter, and alternative nonhormonal options

CASE 1 When hormone therapy is contraindicated or otherwise unacceptable

Your 52-year-old patient wants to discuss treatment options for her frequent and bothersome vasomotor symptoms (VMS). Her last menstrual cycle was 6 months ago. She has had mild VMS for the past year, but they recently increased in frequency and magnitude, occurring every 1 to 2 hours.

Two years ago she experienced an unprovoked deep vein thrombosis (DVT) for which she received anticoagulation therapy for 3 months. DVT also has occurred in one of her uncles and a cousin but in no other first-degree relatives. She did not complete testing for an inherited thrombophilia. Her medical and family histories are otherwise unremarkable.

She is not interested in hormone therapy because of her medical history and for other personal reasons.

Dr. Kling is Assistant Professor of Medicine and Senior Associate Consultant, Division of Women's Health Internal Medicine at Mayo Clinic in Scottsdale, Arizona. Dr. Kling is a NAMS Certified Menopause Practitioner.

Dr. Manson is Chief, Division of Preventive Medicine, Brigham and Women's Hospital, and Professor of Medicine and the Michael and Lee Bell Professor of Women's Health, Harvard Medical School, Boston, Massachusetts. Dr. Manson is a NAMS Certified Menopause Practitioner.

The authors report no financial relationships relevant to this article.

What options are available for your patient who cannot or will not take hormone therapy?

Vasomotor symptoms are the most common reason women seek medical care during or after the menopause transition.[1] Some women have contraindications to hormone therapy, such as a history of hormone-responsive cancer or venous thromboembolism; a history of or active arterial thromboembolic disease, such as stroke or myocardial infarction; or liver impairment. Other women simply may prefer to avoid hormone therapy. Although estrogen remains the most effective treatment for VMS,[2] there are alternatives that offer relief of hot flashes (**TABLE**, page S12).

For women whose symptoms are less bothersome or milder, lifestyle interventions to lower core body temperature or facilitate heat dissipation can be recommended.[3] These interventions include, but are not limited to, dressing in layers, using a handheld fan, keeping the room temperature low, avoiding triggers such as warm drinks and spicy foods, and reducing stress and obesity. These interventions have minimal to no adverse effects and are low cost. However, apart from weight loss, these approaches only have limited or inconclusive data to support their efficacy. For this reason, lifestyle interventions are not recommended by the North American Menopause Society (NAMS) for management of VMS.[5]

CONTINUED ON PAGE S12

COMFORT COMES EASIER.

Every body changes. From enhancing intimate moments to soothing everyday dryness, Astroglide offers a variety of personal lubricants to help your patients live comfortably with menopause.

Visit **Astroglide.com/healthcarepros** to request samples for your patients.

ASTROGLIDE®

CONTINUED FROM PAGE S10

TABLE. Nonhormonal treatment options for vasomotor symptoms of menopause

Treatment type	Treatment	Details
Medications		
	SSRIs	
	*Paroxetine mesylate***	7.5 mg/d (no titration needed)
	Paroxetine	10–25 mg/d
	Citalopram	10–20 mg/d
	Escitalopram	• 10–20 mg/d • Can start with 5 mg/d for older women or those with drug hypersensitivity
	SNRIs	
	Venlafaxine	37.5–150 mg/d
	Desvenlafaxine	• 100–150 mg/d • Start 25–50 mg/d then titrate up by that amount/day
	Gabapentinoids	
	Gabapentin	• 900–2,400 mg/d • Start with 300 mg at night (100 mg if concerned about sensitivity), then increase by 300 mg as tolerated. Can add day dose.
	Pregabalin	150–300 mg/d
	Clonidine	0.1 mg/d (transdermal gives more stable blood levels)
Lifestyle		
	Cooling techniques	• Clothing (dressing in layers, cotton) • Environment (fans, cold pack under pillow, lowering room temperature)
	Avoid triggers	Possible triggers: alcohol, spicy food, hot food/drink
	Exercise	Regular aerobic exercise
	Yoga	Many types (Iyengar, traditional Indian, integrated, Yogasana, and Tibetan) and durations have been evaluated
	Weight loss	
Mind-body techniques		
	Cognitive behavioral therapy	Self-guided and group formats including relaxation and paced breathing
	Clinical hypnosis	
	Mindfulness-based stress reduction	Includes acupuncture, yoga, and mindfulness meditation to handle stress
	Paced respiration and relaxation	
Complementary/alternative medicines		
	Supplements and herbs such as black cohosh, magnesium oxide, red clover, soy products, vitamin E	
Other options requiring further study		
	S-equol	Derivative of soy isoflavones
	Stellate ganglion block	Via image-guided injection of local anesthetic (bupivacaine) at the C6 level

*Italicized treatments are therapies recommended by the North American Menopause Society in its 2015 position statement.[5]

**The only nonhormonal medication approved by the US Food and Drug Administration for use in alleviating vasomotor symptoms of menopause.

Abbreviations: RCT, randomized controlled trial; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VMS, vasomotor symptoms.

*, 3–5,8,14–16,18

	Adverse effects, comments	References
	• Drowsiness (administer at night), headache, dizziness, decreased libido, constipation, dry mouth • CYP2D6 inhibitor: use caution with tamoxifen	3,8
	• Drowsiness, insomnia, diaphoresis, nausea, dry mouth • Minimal CYP2D6 inhibition	3,5
	• Headache, insomnia, drowsiness, nausea, anorgasmia • Expensive • CYP2D6 inhibitor: use caution with tamoxifen	3,5
	Nausea, dizziness (usually subside in 1–2 weeks)	3,5
	Nausea, dizziness (usually subside in 1–2 weeks)	3,5
	• Dizziness, sedation, impaired balance • Sedation and lethargy may limit its use to nighttime, but good option for women with disruptive sleep	4,5
	• Dizziness, sedation, peripheral edema, headache, weight gain, dry mouth, blurred vision, impaired memory • Less well studied	4,5
	Appears less effective than the SSRI/SNRIs and gabapentinoids, with more side effects (hypotension, lightheadedness, headache, dry mouth, sedation, constipation)	3,5
	• Can be recommended for mild or less bothersome hot flashes • No clinical trial evidence to support • Low cost and low risk	3,5
	No clinical trial evidence to support	5
	Randomized trials do not support benefit, but has many health benefits	5,14
	Randomized trials do not support benefit	5,15
	Reductions in weight, body mass index, and abdominal circumference decrease hot flash bother	5,16
	• Expertise important • Reduces hot flash severity, but not frequency	5,14,18
	Expertise important	5
	Limited evidence, additional studies warranted	5
	Limited or inconsistent evidence to support its benefit	5
	RCTs have not shown them to be more effective than placebo (mixed results, small participant numbers, short study durations)	3,5,7,13
	RCTs have been criticized for limited scope and other design limitations	5
	• Small RCT found reduction in moderate to severe VMS • Rare risk of bleeding complications or transient seizure	4,21

CONTINUED ON PAGE S14

CONTINUED FROM PAGE S13

For women whose symptoms are more bothersome or frequent, pharmacologic options include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or clonidine. These medications have been shown in randomized controlled trials (RCTs) to decrease VMS,[4] usually within 2 weeks of treatment initiation. However, with most of these medications, treatment for VMS is off label. The only nonhormonal prescription medication approved by the US Food and Drug Administration (FDA) for this purpose is low-dose paroxetine mesylate.

SSRIs/SNRIs

In large, randomized, placebo-controlled clinical trials of paroxetine mesylate, citalopram, escitalopram, venlafaxine, and desvenlafaxine, hot flash frequency has been reduced by 25% to 69%; sertraline and fluoxetine have yielded inconsistent and statistically insignificant results.[3,5,6] Paroxetine mesylate and venlafaxine are the best studied of these antidepressants.[7] No trials have directly compared the relative efficacy of these medications. Therefore, use a patient's history and preference, as well as drug adverse effects and contraindications, to guide your choice of therapy.

Low doses of SSRIs/SNRIs can decrease vasomotor symptoms of menopause within 2 weeks of treatment

SSRI/SNRI doses used for VMS treatment are lower than those used to treat psychiatric disorders. For example, compared with paroxetine doses of 20 mg to 40 mg for psychiatric purposes, data from 2 RCTs showed that a paroxetine mesylate dose of just 7.5 mg was effective in treating VMS,[8] without the need for dose escalation. Moreover, in contrast to higher doses, the 7.5-mg paroxetine mesylate formulation appears not to contribute to weight gain or cause sexual adverse effects.[9] Many of the antidepressant drug adverse effects are dose dependent, and effects such as nausea and headache subside after several weeks of treatment.[7] Overall, these medications appear to be well tolerated.[3] See TABLE on page S12.

Precautions. Whether indicated for VMS or psychiatric conditions, SSRIs and SNRIs should not be used in women with a history of neuroleptic syndrome or serotonin syndrome or who are taking a monoamine oxidase inhibitor. Use these medications with caution and monitor them closely in women with bipolar disease, liver or kidney problems, uncontrolled seizures, hypertension, or hyponatremia or in those already using an SSRI or SNRI for another indication.[5]

Because paroxetine and other potent SSRIs inhibit the hepatic enzyme Cyp2d6, they should be avoided in women taking tamoxifen. This is important for women with a history of breast cancer or at a high risk for breast cancer, who commonly require VMS management and are not candidates for hormone therapy. Instead, use venlafaxine, desvenlafaxine, gabapentin, or pregabalin.[4]

Gabapentinoids

Both gabapentin and pregabalin are effective in treating hot flashes,[4,5,7] although pregabalin is less well studied. Gabapentin is FDA approved as an antiepileptic, but it is commonly used off label to treat diabetic neuropathy and other neuropathic pain symptoms. Studies of symptomatic menopausal women have found that doses of 900 mg to 2,400 mg are effective in treating VMS.[5,7,10] Although higher doses of gabapentin have been as effective as estrogen, the resulting adverse effects—including headache, disorientation, and dizziness—limit its use.[5] Therefore, it is recommended to start with a dose of 300 mg at night and titrate up, as tolerated, by 300 mg to a maximum 2,400 mg daily in 3 divided doses. Gabapentin's sedative effects work well at night to help promote sleep and reduce night sweats.[3] These same adverse effects, however, may limit its daytime use.

Clonidine

Clonidine, an α-2-adrenergic receptor agonist used to treat hypertension, has been shown in several RCTs to reduce hot flashes. However, it appears less effective than the SSRI/SNRIs and the gabapentinoids and causes more adverse effects such as hypotension, bradycardia, dizziness, headache, constipation, and dry mouth, as well as rebound hypertension following cessation.[11,12] Therefore, it is not

CONTINUED ON PAGE S16

Lumenis®
Energy to Healthcare

FemTouch™ Laser Treatment

For vaginal health in post-menopausal and post-natal women
Serving the OBGYN laser market since 1979

Lumenis, a leader in the medical laser industry, has been providing solutions to OBGYN practices for 37 years. The FemTouch™ by Lumenis offers a vaginal and skin workstation. With just a five-minute vaginal health procedure, the vaginal canal achieves remodeling of the mucous epithelium layer. The FemTouch offers maximum versatility, from the surgical suite to standalone private practices.

The FemTouch treats post-menopausal and post-natal symptoms, including:

- Endometriosis
- Vaginal health
- Cone biopsies
- Condyloma
- Uneven pigmentation and dyschromia
- Pigmentation
- Fine lines and scars

Contact your dedicated Lumenis representative to find out more about the FemTouch, or call:
1877.LUMENIS I WWW.LUMENIS.COM

"I have used many devices and lasers for women's vaginal health and I find the Lumenis FemTouch is very user friendly. It delivers the best results for treatment of vaginal atrophy, urinary incontinence and vaginal laxity. The treatment takes about 3-5 minutes. Patient's tolerate the treatment well and experience no pain. I am very happy with my overall experience with the Lumenis FemTouch Laser."

– Darush Mohyi, M.D., Gynecology & Reproductive Medicine
La Jolla Cosmetic Laser Clinic, La Jolla, CA

PB-2005117 rev A

Lumenis®
Energy to Healthcare

CONTINUED FROM PAGE S14

recommended as an initial choice for treatment of VMS and must be used with caution to minimize adverse effects.

CASE 1 Resolved

For the patient in this case, starting with an SSRI or SNRI such as paroxetine mesylate would be appropriate and likely would help to alleviate her VMS, without increasing her risk of blood clots.

CASE 2 A patient with VMS who refuses prescription medication of any kind

Your 56-year-old patient wants to discuss her options for treating her VMS that occur approximately 5 times per day. She went through menopause 9 years ago and has been "toughing it out" since then because she did not want to start hormones. Previous clinicians have offered her antidepressants for her symptoms but she does not want to take any prescription medications. She tells you that she prefers a more natural approach and would like to discuss those options.

What alternative-treatment options are available to women with VMS?

Both cognitive-behavioral therapy and clinical hypnosis have shown efficacy to reduce bothersome hot flashes

Many women seek natural therapies to help with their menopausal symptoms. Over-the-counter therapies include black cohosh, soy, omega-3 fatty acid supplements, and other botanicals, and they have been used widely to treat VMS. However, studies have shown them to be no more effective than placebo.[3,5,7,13] Soy isoflavonoids have been evaluated as a potential promising therapy for VMS treatment. S-equol, a nonsteroidal estrogen isoflavonoid derivative that has a high affinity for estrogen-β receptors acting as an agonist, has shown the most promise. However, studies demonstrating reduction of VMS with s-equol have been criticized because of their limited scope and other study design limitations.[5] Additional research is needed before this isoflavonoid can be recommended widely for VMS treatment.

Cognitive-behavioral therapy

Behavioral approaches that have been evaluated for VMS treatment, but have limited or inconsistent evidence for efficacy, include acupuncture, yoga, mindfulness-based stress reduction, exercise, paced respiration, and relaxation training.[7,14–16] The 2 non–medication therapies for which good evidence supports efficacy in treating VMS are cognitive-behavioral therapy (CBT) and clinical hypnosis.[5] Data from 2 RCTs demonstrated that CBT reduced VMS problem ratings that were maintained for 26 weeks, though it did not decrease VMS frequency.[17,18] Specific CBT interventions included education on paced breathing, relaxation techniques, and psycho-education on VMS physiology, stress as a trigger, and sleep hygiene. Both self-guided and group CBT yielded similar results,[18] and either format can be recommended for VMS treatment. Critical to success with this therapy is expert guidance, which can be intensive, including regular meetings with a clinical psychologist, homework, and daily practice on relaxation techniques over many weeks.

Clinical hypnosis

Clinical hypnosis, a mind-body treatment that incorporates a relaxed state and mental imagery has been found to reduce hot flash frequency.[5,19] RCTs that evaluated clinical hypnosis involved a weekly therapist-directed hypnosis session and at-home self-hypnosis practice over 5 weeks. For the 187 women evaluated in one of the studies, clinical hypnosis reduced hot flashes by 74.2% compared with only 17.1% reduction in the control arm.[19] Similar findings were seen for physiologically monitored hot flashes. As with CBT, expertise in the area of VMS hypnosis is required to assure success.

Stellate ganglion block

Another therapy that may be beneficial is stellate ganglion block. This procedure is administered by a pain specialist to block the cervical sympathetic chain and has been used to treat certain pain syndromes.[20] It has been studied in women with VMS and found to reduce the frequency of moderate-to-

severe hot flashes compared with sham.[21] It is believed that the interruption to the sympathetic nervous system affects norepinephrine levels within the thermoregulatory areas of the brain, thereby decreasing hot flashes. However, the exact physiologic mechanism is unknown. Larger sham-controlled RCTs are needed to confirm this intervention as an effective nonhormonal therapy for VMS, as well as to evaluate its safety.

CASE 2 Resolved

You offer this patient CBT or clinical hypnosis, after you identified local providers with expertise in VMS treatment. You also further review with her the nonhormonal prescription medications to see if she may reconsider them as an option. See TABLE on page S12.

Additional resources

Guidelines from NAMS and the Endocrine Society can help guide your approach to choosing nonhormonal treatment options for women with VMS.[3,5] Another available tool is the free MenoPro mobile app that can be downloaded to your smart phone or tablet device.[22] This app, developed in collaboration with NAMS, provides an algorithm for clinical decision making for both clinicians and patients and links to many online resources for menopausal symptom management. ■

References

1. Nelson HD. Menopause. Lancet. 2008;371(9614):760–770.
2. North American Menopause Society. The 2012 hormone therapy position statement of: the North American Menopause Society. Menopause. 2012;19(3):257–271.
3. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(11):3975–4011.
4. Sideras K, Loprinzi CL. Nonhormonal management of hot flashes for women on risk reduction therapy. J Natl Compr Can Netw. 2010;8(10):1171–1179.
5. North American Menopause Society. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015;22(11)1155–1172.
6. Shams T, Firwana B, Habib F, et al. SSRI for hot flashes: a systematic review and meta-analysis of randomized trials. J Gen Intern Med. 2014;29:204–213.
7. Kaunitz AM, Manson JE. Management of menopausal symptoms. Obstet Gynecol. 2015;126:859–876.
8. Simon JA, Portman DJ, Kaunitz AM, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause. 2013;20(10):1027–1035.
9. Portman DJ, Kaunitz AM, Kazempour K, et al. Effects of low-dose paroxetine 7.5 mg on weight and sexual function during treatment of vasomotor symptoms associated with menopause. Menopause. 2014;21(10):1082–1090.
10. Hayes LP, Carroll DG, Kelley KW. Use of gabapentin for the management of natural or surgical menopausal hot flashes. Ann Pharmacother. 2011;45(3):388–394.
11. Rada G, Capurro D, Pantoja T, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev. 2010;9:CD004923.
12. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA. 2006;295(17):2057–2071.
13. Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med. 2006;145(12):869–879.
14. Daley A, Stokes-Lampard H, Thomas A, et al. Exercise for vasomotor symptoms. Cochrane Database Syst Rev. 2014;11:CD006108.
15. Cramer H, Lauche R, Langhorst J, et al. Effectiveness of yoga for menopausal symptoms: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2012;Nov 7. doi: 10.1155/2012/863905.
16. Thurston RC, Ewing LJ, Low CA, et al. Behavioral weight loss for the management of menopausal hot flashes: a pilot study. Menopause. 2015;22(1):59–65.
17. Mann E, Smith M, Hellier J, et al. A randomised controlled trial of a cognitive behavioural intervention for women who have menopausal symptoms following breast cancer treatment (MENOS 1): trial protocol. BMC Cancer. 2011;11:44.
18. Ayers B, Smith M, Hellier J, et al. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. Menopause. 2012;19(7):749–759.
19. Elkins GR, Fisher WI, Johnson AK, et al. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. Menopause. 2013;20(3):291–298.
20. Lipov EG, Joshi JR, Sanders S, et al. A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD). Med Hypotheses. 2009;72(6):657–661.
21. Walega DR, Rubin LH, Banuvar S, et al. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. Menopause. 2014;21(8):807–814.
22. Manson JE, Ames JM, Shapiro M, et al. Algorithm and mobile app for menopausal symptom management and hormonal/non-hormonal therapy decision making: a clinical decision-support tool from the North American Menopause Society. Menopause. 2015;22(3):247–253.

SERMs in menopause: Matching agents to patients' symptoms and attributes

Knowing how selective estrogen receptor modulators may vary from one another in affecting specific tissues helps to optimize treatment choices. Additionally, the available SERM-estrogen combination offers benefits to some individuals in lieu of traditional hormone therapy.

James H. Liu, MD, and Gretchen Collins, MD

Treatment of menopausal symptoms with SERMs can benefit various target tissues, but clinicians need to know the agents' limitations

CASE Should this woman continue hormone replacement therapy?

A 56-year-old woman (G3P3) requests an examination due to irregular vaginal spotting. For the past 4 years, she has been taking conjugated estrogens 0.45 mg on days 1 through 30 and micronized progesterone 200 mg on days 1 through 12. She has had good relief of menopausal symptoms during the estrogen phase, but feels moody and has joint aches and fatigue during the estrogen-progesterone phase. She admits to skipping the progesterone medication for more than 5 months. On examination, her body mass index is 21 kg/m^2. Her breast and pelvic examinations are normal. Her endometrial thickness measures 13 mm. An endometrial biopsy revealed simple and focal hyperplasia without atypia. The patient would like to remain on hormone therapy but also wants to know her options.

Dr. Liu is Professor and Chair, Department of Reproductive Biology, Case Western Reserve University, Department of Obstetrics and Gynecology, University Hospital Case Medical Center, Cleveland, Ohio.

Dr. Collins is an Instructor, Department of Reproductive Biology, Case Western Reserve University, and Department of Obstetrics and Gynecology, University Hospital Case Medical Center, Cleveland.

Dr. Liu reports being a consultant to Pfizer and Sermonix. Dr. Collins reports no financial relationships relevant to this article.

Selective estrogen receptor modulators (SERMs) are compounds that were developed to block the action of estrogen at its receptor. However, in vivo these agents exhibit both agonist and antagonist properties, depending on the target tissue; thus they are also called estrogen receptor agonists/antagonists. For menopausal women, the ideal SERM would act as an estrogen agonist in bone and the brain, preventing osteoporosis and hot flashes. And it would act as an antagonist or be neutral to estrogen in the uterus, blood, and breast, preventing endometrial proliferation, venous thromboembolism (VTE), and breast cancer. Because no ideal SERM exists, physicians must understand the benefits and limitations of each agent to treat a patient's symptoms while minimizing risks.

Pharmacodynamics of SERMs

Estrogens and SERMs are lipid-soluble steroid hormones that bind to 2 specific hormone receptors, estrogen receptor α and

CONTINUED ON PAGE S22

Studied in over 100 clinical trials worldwide[1*]

*Only EstroGel 0.06% is approved for use in the U.S. Products marketed and prescribed in other countries may have different indications and dosages from that approved in the U.S.

ESTROGel® 0.06%
(estradiol gel)
The *Modern* Classic

The only non-patch transdermal estrogen therapy that treats both moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar/vaginal atrophy due to menopause[2a]

- One pump per day provides steady serum concentration levels within 3 days[2]
- Significant reduction in severity score of hot flashes vs placebo at week 4 (P=0.005)[2b]
- Significant reduction in frequency of moderate to severe hot flashes vs placebo at week 4 (P=0.019)[2]

ESTROGEN PLUS PROGESTIN THERAPY MAY INCREASE THE RISKS OF DEEP VEIN THROMBOSIS, PULMONARY EMBOLISM, STROKE AND MYOCARDIAL INFARCTION IN POSTMENOPAUSAL WOMEN.

[a]When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

[b]Data based on last observation carried forward.

PLEASE SEE IMPORTANT RISK INFORMATION AND BOXED WARNING ON THE FOLLOWING PAGES.
PLEASE SEE FULL PRESCRIBING INFORMATION AT **www.estrogel.com**

REFERENCES: 1. Data on file, ASCEND Therapeutics. **2.** EstroGel 0.06% [package insert]. Herndon, VA: ASCEND Therapeutics; 2014.

ASCEND THERAPEUTICS

ESTROGel® 0.06%
(estradiol gel)

℞ only

This is only a brief summary of prescribing information. For current Full Prescribing Information, please visit www.estrogel.com.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed, persistent or recurring abnormal genital bleeding *[see Warnings and Precautions]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions* and *Use in Specific Populations]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions]*.

The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions* and *Use in Specific Populations]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause. Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause.

Limitation of Use

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

DOSAGE FORMS AND STRENGTHS

EstroGel 0.06% is an estradiol transdermal gel. One pump depression delivers 1.25 g of gel that contains 0.75 mg estradiol.

CONTRAINDICATIONS

EstroGel is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema to EstroGel
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analysis of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n = 2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted.

Should a VTE occur or be suspected, therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before any surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.8]*.

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA.

In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women- years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increase in the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable

dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years *[see Use in Specific Populations]*.

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years *[see Use in Specific Populations]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Use in Specific Populations]*.

Gallbladder Disease
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Addition of a Progestin when a Woman has not had a Hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

Elevated Blood Pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia
In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hepatic Impairment and/or Past History of Cholestatic Jaundice
Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid-replacement therapy. These women should have their thyroid function monitored in order to maintain an acceptable range.

Fluid Retention
Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed.

Hypocalcemia
Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Exacerbation of Endometriosis
A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Hereditary Angioedema
Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

Exacerbation of Other Conditions
Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Alcohol-based Products are Flammable
Avoid fire, flame, or smoking until the gel has dried.

Moisturizer Lotion Application
Use of moisturizing lotion one hour after application of EstroGel 0.06% significantly increased estradiol absorption.

Laboratory Tests
Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

Drug-Laboratory Test Interactions
Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and T_3 concentrations are unaltered. Women on thyroid-replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum (for example, corticosteroid-binding globulin [CBG], sex hormone-binding globulin [SHBG]), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, and Warnings and Precautions]*
- Malignant Neoplasms *[see Boxed Warning, and Warnings and Precautions]*

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

EstroGel was studied in 2 well-controlled, 12-week clinical trials. Incidence of adverse drug reactions ≥5 percent for 1.25 g EstroGel 0.06% and placebo is given in Table 1.

TABLE 1: Incidence of Adverse Drug Reactions ≥5 Percent Occurrence in the EstroGel Treatment Group for the Intent-to-Treat Safety Population in 2 Well-controlled Clinical Studies (Expressed as Percent of Treatment Group)

Body System/ Adverse Drug Reactions	EstroGel 0.06% 1.25 g /day (n=168)	Placebo (n=73)
BODY AS A WHOLE		
Headache	**9.5**	**2.7**
DIGESTIVE SYSTEM		
Flatulence	**5.4**	**4.1**
UROGENITAL SYSTEM		
Breast pain	**10.7**	**8.2**

In 2 controlled clinical trials, application site reactions were reported by 0.6 percent of patients who received 1.25 g of EstroGel. Other skin reactions, such as pruritus and rash, were also noted.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of EstroGel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary system: Endometrial cancer

Breast: Pain; tenderness; breast cancer

Cardiovascular: Deep vein thrombosis; myocardial ischemia; phlebitis

Gastrointestinal: Nausea; abdominal distension; diarrhea; stomach discomfort

Skin: Alopecia; rash; pruritus; application site: dryness, pain, discoloration, reaction, rash

Eyes: Retinal vein occlusion

Central nervous system: Headache; dizziness; insomnia; hypoesthesia; meningioma; aphasia; bradyphrenia; paresthesia

Miscellaneous: Drug ineffective; hot flush; arthralgia; night sweats; drug effect decreased; pain in extremity; fatigue; weight increased; pain; hypersensitivity; dyspnea; malignant mesenchymoma; angioedema; hepatitis acute; face edema; accidental exposure; myoclonus; gait disturbance; flushing

DRUG INTERACTIONS
No drug-drug interaction studies have been conducted for EstroGel.

Metabolic Interactions
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's wort *(Hypericum perforatum)* preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogen and may result in side effects.

USE IN SPECIFIC POPULATIONS
Pregnancy
EstroGel should not be used during pregnancy *[see Contraindications]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

Nursing Mothers
EstroGel should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogen have been identified in the milk of women receiving estrogen therapy. Caution should be exercised when EstroGel is administered to a nursing woman.

Pediatric Use
EstroGel is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use
There have not been sufficient numbers of geriatric women involved in studies utilizing EstroGel to determine whether those over 65 years of age differ from younger subjects in their response to EstroGel.

The Women's Health Initiative Studies
In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age.

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

The Women's Health Initiative Memory Study
In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions]*.

Renal Impairment
The effect of renal impairment on the pharmacokinetics of EstroGel has not been studied.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of EstroGel has not been studied.

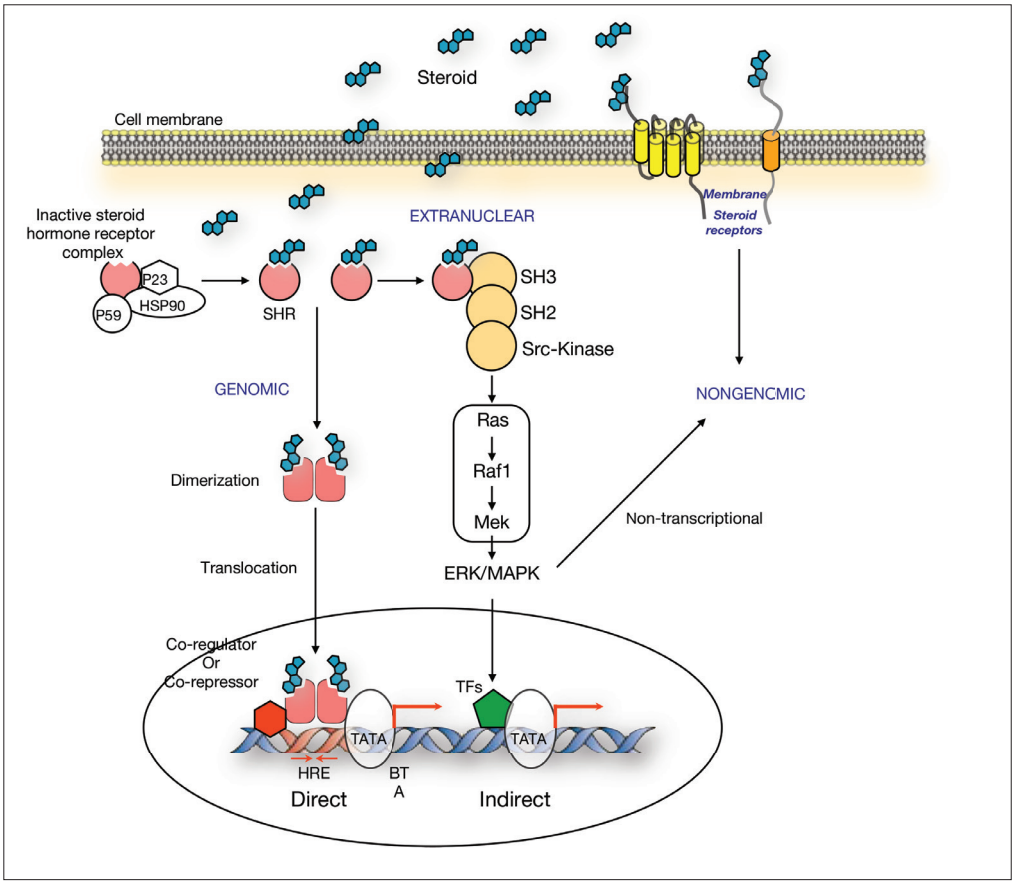
OVERDOSAGE
Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of EstroGel together with institution of appropriate symptomatic care.

Keep out of reach of children.

This brief summary is based on the EstroGel full Prescribing Information.

CONTINUED FROM PAGE S18

Steroid hormone receptor signaling pathway



Hormone binding at the cell surface receptor activates the Ras-GTP pathway. When the hormone binds to its intracellular receptor, the latter undergoes conformational change that releases a heat-shock protein and exposes the DNA-binding domain. The receptor-hormone complex (1) forms a dimer; (2) translocates to the nucleus; (3) binds to a specific hormone receptor sequence-DNA to modulate gene expression; (4) undergoes mRNA transcription in the presence of coactivators and corepressors; and (5) initiates downstream protein synthesis that alters cellular function.

Courtesy of S. Mesiano.

For menopausal women with a uterus, combining an estrogen with a SERM allows for the benefits of estrogen therapy while minimizing negative effects

estrogen receptor β, either on the cell surface or inside the cell (**FIGURE**). Estrogen receptors are present in various tissues, including the brain, breast, lung, liver, bone, and uterus. However, each of these tissues contains unique transcriptional coactivators and corepressors that distinctively influence the transcriptional efficacy of the hormone-receptor complex, thereby modifying the transcriptional efficiency within the target tissue. It is also believed that SERMs exert different effects depending on the ratio of α-to-β estrogen receptors in specific tissues and on the varying concentrations of coactivators and corepressors in these tissues.[1,2]

Given our understanding of how SERMs interact with the estrogen receptor in various tissues, therapeutic efforts have aimed to optimize the desirable properties of receptor modulation by combining an estrogen with a SERM, forming a tissue selective estrogen complex (TSEC). This new combination allows for the benefits of estrogen therapy while minimizing its negative effects in women with a uterus. Understanding the different tissue effects of each SERM and TSEC helps to guide their use in menopausal management.

CONTINUED ON PAGE S24

Reclaim. Restore. Revive.

THERMIva®

Non-surgical vulvovaginal rejuvenation.

Worldwide, women want to reclaim their younger or "pre-baby" bodies, restore their satisfaction, and revive their vulvovaginal youthfulness and well-being.

"Given the safety, simplicity and ease of treatment associated with TTCRF (Transcutaneous Temperature Controlled Radiofrequency) as well as the remarkable results and high patient satisfaction with virtually no risk, downtime, or discomfort, this novel therapy shows much promise in both the medical and aesthetic arenas in an increasingly accepting social climate."

- Red Alinsod, MD

ThermiVa Electrode and Hand Piece

To learn more about ThermiVa® , visit **Thermi.com**.

866.981.5017

THERMI™

CONTINUED FROM PAGE S22

Table Effects of SERMs vary in target tissues[3–21, 23–26]

SERM	Bone	Brain	Breast	Endometrium-uterus	Vagina	Cardiovascular	FDA indication
Tamoxifen[3–7]	Agonist	Antagonist	Antagonist	Agonist	Agonist, variably	Agonist	Prevention of breast cancer in high-risk women
Raloxifene[8–14]	Agonist	Antagonist	Antagonist	Neutral	Neutral	Agonist	Treat and prevent osteoporosis; prevention of breast cancer in high-risk postmenopausal women
Bazedoxifene[15,16]	Agonist	Weak antagonist	Antagonist	Antagonist	Antagonist	Neutral	None as monotherapy
Ospemifene[17–21]	Agonist	Antagonist	Neutral	Partial agonist	Agonist	Agonist	Moderate-to-severe dyspareunia in VVA
Lasofoxifene[23,24]	Agonist	Weak antagonist	Antagonist	Neutral	Agonist	Agonist	None; in development
BZA/CE[25,26]	Agonist	Agonist	Neutral	Neutral	Agonist	Agonist	Vasomotor symptoms and prevention of osteoporosis

Abbreviations: BZA/CE, bazedoxifene/conjugated estrogen; FDA, US Food and Drug Administration; SERM, selective estrogen receptor modulator; VVA, vulvovaginal atrophy.

FDA-approved SERMs

Tamoxifen

Tamoxifen acts as an estrogen agonist in the liver, bone, and uterus and as an estrogen antagonist in the breast (**TABLE**). Its beneficial effects include a reduced risk of breast cancer, lower low-density lipoprotein (LDL) and higher high-density lipoprotein (HDL) levels, and a decrease in bone mineral turnover and loss. However, tamoxifen increases the risks of endometrial polyps and cancer, VTE, and pulmonary embolism. Approved in 1978 by the US Food and Drug Administration (FDA) for the adjuvant treatment of estrogen-receptor-positive breast cancer in pre- and postmenopausal women, tamoxifen has been widely used for this indication.[3] In 1999, tamoxifen was approved for the primary prevention of breast cancer in high-risk pre- and postmenopausal women based on the results of the Breast Cancer Prevention Trial, which demonstrated that tamoxifen can reduce the risk of invasive estrogen-receptor–positive breast cancer in high-risk women by 49%.[4]

Although tamoxifen acts as an estrogen agonist in the bone and has been shown to prevent bone loss in the lumbar spine and hip, it is not as effective as estrogen alone and is not FDA approved for this indication.[5] Up to 50% of women taking tamoxifen reported hot flashes after starting the medication.[6] The use of tamoxifen for breast cancer chemoprophylaxis in high-risk women is limited because of hot flashes and an increased risk of endometrial hyperplasia and endometrial cancer.[7]

Raloxifene

Raloxifene is a second-generation SERM developed to treat osteoporosis. See TABLE. It exerts estrogenic action on bone, neutral actions on the uterus, and antiestrogenic effects on the breast. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial—a multicenter, double-blind, placebo-controlled study of postmenopausal women with osteoporosis—raloxifene increased bone mineral density (BMD) in the spine

and femoral neck and reduced risk of vertebral fracture.[8] This led to FDA approval of raloxifene 60 mg/day for the prevention and treatment of postmenopausal osteoporosis. In this study raloxifene was also associated with an increased risk of VTE (relative risk [RR], 3.1; 95% confidence interval [CI], 1.5–6.2)[8] and fatal stroke (RR, 1.49; 95% CI, 1.00–2.24).[9] The increase in lumbar spine and femoral neck BMD with raloxifene therapy was conserved after 2, 3, and 4 years of treatment.[10]

Raloxifene decreases the incidence of invasive breast cancer in postmenopausal women with osteoporosis. In the MORE trial, the incidence of invasive breast cancer was reduced by 76% after 3 years and 72% after 4 years.[11] In the 4-year follow-up study to the MORE trial, the risk of invasive breast cancer was significantly reduced by 59% after 8 years (hazard ratio [HR], 034; 95% CI, 0.18–0.66).[12] The results of the MORE trial were supported by the Study of Tamoxifen and Raloxifene (STAR) trial, which showed that both tamoxifen and raloxifene decreased the risk of breast cancer by approximately 50% in postmenopausal women at risk for the disease.[13] The study also showed that women who took raloxifene (vs tamoxifen) daily for 4 years had 36% fewer uterine cancers and 29% fewer blood clots.[13] Adverse events were also lower with raloxifene, including decreased risk of uterine cancer, VTE, and cataracts.[13] However, raloxifene was associated with an increased risk of hot flashes and leg cramps. Following this study, raloxifene was also FDA approved for prevention of invasive breast cancer in high-risk postmenopausal women.

Clinical pearl: Alone, raloxifene does not have any effect on genitourinary syndrome of menopause (GSM), also known as vulvovaginal atrophy or VVA, and has no effect on the vaginal maturation index; however, raloxifene may improve VVA when used with local vaginal estrogen cream or estrogen ring.[14] It should not be used in combination with systemic estrogen due to increased endometrial stimulation. Raloxifene is not approved for treatment of VVA.

Bazedoxifene

Bazedoxifene is a third-generation SERM that acts as an estrogen antagonist in the breast and endometrium and as an estrogen agonist in bone. See TABLE. In a 3-year randomized controlled trial, bazedoxifene (20 or 40 mg/day) significantly improved BMD and reduced bone marker levels compared with placebo ($P<.001$). It also significantly reduced the risk of new vertebral fractures in postmenopausal women with osteoporosis ($P<.05$) and reduced the risk of nonvertebral fracture in patients at high fracture risk.[15] Bazedoxifene is approved for treatment of osteoporosis in Europe. It is awaiting approval as a single agent in the United States, although the FDA has approved it as part of a combination formulation (discussed on page S26). Bazedoxifene is associated with mild hot flashes and an increase in VTE but does not increase endometrial thickness, breast tenderness, or risk of breast cancer.[16] It also has no effect on symptoms of VVA.

Ospemifene

Ospemifene was originally developed to prevent and treat osteoporosis, but to date no large human trials have been performed to evaluate its effectiveness for this indication. Preclinical data in a mouse model noted reduced bone turnover and increased bone strength.[17]

Ospemifene has been well studied for treatment of VVA and dyspareunia. In a 12-week clinical trial, 60 mg of ospemifene increased the number of superficial cells, decreased the number of parabasal cells, and improved vaginal pH, vaginal dryness, and dyspareunia. However, there was an increase in hot flashes compared with placebo (9.6% versus 3.4%), which persisted throughout the 1-year extension study.[18,19]

Ospemifene received FDA approval in 2013 for the treatment of moderate-to-severe dyspareunia. After 1 year of treatment, women taking ospemifene had more uterine polyps (5.9 vs 1.8 with placebo), an increase in proliferative endometrium (86 patients taking ospemifene vs 13 with placebo), and an increase in endometrial

Tamoxifen and raloxifene are both associated with a reduced risk of invasive breast cancer and bone loss and an increased risk of hot flashes

thickness greater than 5 mm (60 patients taking ospemifene vs 21 taking placebo). Although clinical trials have found no increase in endometrial cancer or hyperplasia in women taking ospemifene, they have not assessed endometrial impact beyond 1 year of use.[20] Ospemifene also is associated with a slight increase in hemorrhagic (not thrombotic) stroke and VTE,[21] and the ospemifene labeling contains a black box warning regarding concerns for endometrial stimulation, VTE, and stroke.

Toremifene

Toremifene is a second-generation SERM similar to tamoxifen. See TABLE on page S24. It is used primarily to treat advanced estrogen-sensitive breast cancer and as adjuvant treatment of early breast cancer. Compared with tamoxifen, toremifene lowers the risk of endometrial cancer and may lower the risk of VTE. Its positive effects on BMD and lipid profiles are similar to that of tamoxifen.[22]

SERMS in development

Lasofoxifene

Lasofoxifene is a third-generation SERM that has demonstrated clinical efficacy in preventing and treating osteoporosis and in treating VVA in postmenopausal women. Lasofoxifene at a dose of 0.5 mg/day decreased vertebral fractures by 42% ($P<.001$) and nonvertebral fractures by 24% ($P = .002$) at 3 years.[23] Moreover, the signs and symptoms of VVA, as well as vaginal pH and maturation, improved with lasofoxifene compared with placebo.[23] Additional studies of lasofoxifene were put on hold due to the concern for increased endometrial thickness, even though there was no increase in endometrial hyperplasia or cancer among postmenopausal women treated with lasofoxifene.[24]

Bazedoxifene plus conjugated estrogen is the first TSEC approved for treatment of vasomotor symptoms and prevention of osteoporosis

Tissue selective estrogen complex

For women with a uterus, traditional hormone therapy to treat menopausal symptoms has been estrogen combined with a progestin to protect the uterus from unopposed estrogen stimulation. The consensus among many societies, including the North American Menopause Society, the American College of Obstetricians and Gynecologists, the International Menopause Society, the Endocrine Society, and the American Society for Reproductive Medicine, is that "New data and reanalyses of older studies by women's age show that, for most women, the potential benefits of menopausal hormone therapy given for a clear indication are many and the risks are few when initiated within a few years of menopause. The benefits are more likely to outweigh the risks for symptomatic women before the age of 60 years or within 10 years after menopause."[25] However, combination estrogen-progestin therapy may result in unscheduled bleeding, additional endometrial diagnostic procedures, breast pain/tenderness, and increased mammographic breast density that can lead to additional breast imaging. These unwanted effects have spurred the need to develop new, less risky forms of hormone therapy.

A new formulation, the tissue selective estrogen complex (TSEC), pairs a specific SERM with a specific estrogen and appears to be a favorable alternative to traditional hormone therapy, taking advantage of the estrogen-antagonistic properties of the SERM while offering the benefits of estrogen therapy. In 2013, the FDA approved bazedoxifene (BZA) combined with conjugated equine estrogen (CE) (at a dose of 20 mg BZA/0.45 mg CE) to relieve hot flashes and prevent osteoporosis.[26] This combination is the first TSEC marketed in the United States. BZA was selected as the SERM because it possesses sufficient antagonist effect on uterine tissue to be paired with a conjugated estrogen.

What have we learned from SMART?

The Selective Estrogens, Menopause, and Response to Therapy (SMART) trials were a series of multicenter, randomized controlled studies designed to assess the effects of the TSEC BZA/CE in postmenopausal women.

CONTINUED ON PAGE S28

The medications that cause dry mouth, May also be the leading cause of **Vaginal Dryness**

INTRODUCING LUVENA®

The Closest You Can Get to Natural Moisture

Restorative + Hydrating

No Parabens. No Glycerin.
Just long-lasting soothing comfort
with advanced odor control.

From the Creators of biotène® **

THE #1 RECOMMENDED BRAND FOR DRY MOUTH

Luvena® utilizes similar enzyme technology as in Biotène®.

Natural, Innovative & Effective

Compare Ingredients	Luvena® 6 CT	RepHresh* Vaginal Gel	Replens* Vaginal Moisturizer 14 CT
Lactoferrin	✔ YES	NO	NO
Cranberry Extract	✔ YES	NO	NO
Natural Enzyme Protection	✔ YES	NO	NO
Paraben Free	✔ YES	NO	NO
Glycerin Free	✔ YES	NO	NO

*RepHresh and Replens are registered trademarks of Church & Dwight
**Biotene® is trademark owned by GlaxoSmithKline

Most women will experience dryness...
NEW products NOW available to help.

For information and professional samples: 1-877-522-5333 | **www.luvenacare.com**

CONTINUED FROM PAGE S26

Each SMART trial focused on evaluating different menopausal end points. The SMART 2 trial evaluated 332 women aged 40 to 65 years with a uterus who had at least 50 hot flashes a week of moderate or severe intensity. BZA 20 mg/CE 0.45 mg significantly reduced the number and severity of hot flashes at 4 and 12 weeks (P<.001). At week 12, BZA/CE reduced hot flashes from baseline by 74% (from 10.3 hot flashes per week to 2.8), compared with a 51% reduction with placebo (10.5 vs 5.4). There was also a significant reduction in the severity of hot flashes with BZA/CE compared with placebo (37% vs 17%). The safety profile was similar between BZA/CE and placebo, and no unexpected safety findings were reported.[27]

The SMART 3 trial evaluated 664 healthy postmenopausal women aged 40 to 65 years with VVA for changes in vaginal maturation, vaginal pH, and severity of the most bothersome symptom of VVA at 4 and 12 weeks of treatment with either placebo or BZA/CE. Vaginal atrophy was measured by the percentage of super, intermediate, and parabasal cells on vaginal wall smear. BZA/CE stimulated an estrogen-dominant change in the vaginal mucosa with significantly increased superficial cells and decreased parabasal cells compared with placebo (P<.01). It also significantly improved vaginal pH, vaginal dryness, and the most bothersome VVA symptom (P<.05).[28]

The SMART trials studied BZA/CE's effects on hot flashes, VVA, and osteoporosis prevention; improvements were seen for each end point and no unexpected safety findings were reported

Finally, the SMART 1, 4, and 5 studies evaluated the effects of BZA/CE on osteoporosis prevention. Lumbar spine and total hip BMD increased significantly from baseline at years 1 and 2 with BZA/CE compared with placebo (P<.001). SMART 5 noted similar rates of amenorrhea, breast tenderness, and adverse events between BZA/CE and placebo. There was also a low incidence of endometrial hyperplasia (<1%), endometrial proliferation, asymptomatic endometrial polyps, and endometrial thickening.[29] Importantly, although these trials were not powered to assess impact on breast cancer, the incidence of breast cancer across all 5 SMART trials with data up to 5 years was no different between BZA/CE and placebo.

In summary, SMART study participants reported a low incidence of breast pain/tenderness and a high rate of amenorrhea; they exhibited a low incidence of endometrial hyperplasia and no changes in mammographic breast density.

Clinical pearl: The BZA/CE combination would be an ideal option for women taking estrogen therapy for the treatment of vasomotor symptoms who do not tolerate progesterone therapy or who have a history of irregular bleeding or a thickened endometrial stripe. BZA/CE is also a good first option for symptomatic menopausal women with a uterus who have hot flashes, night sweats, or VVA and desire bone loss prevention without monthly vaginal bleeding.

CASE Resolved

You prescribed cyclic estrogen and progestin therapy for 3 months, and a repeat endometrial biopsy confirmed resolution of the patient's endometrial hyperplasia. Because of her desire not to have monthly bleeding, you prescribe the BZA/CE combination.

Summary guidance on clinical choices

For patients who have had a hysterectomy, estrogen alone would likely be the treatment of choice for vasomotor symptoms, while either low-dose vaginal estrogen or ospemifene could be considered for treatment of VVA in women free of vasomotor symptoms.

For a patient who has a uterus (as presented in our case example), either an estrogen-progestin combination or a TSEC would be appropriate hormonal management for vasomotor symptoms. The TSEC formulation may be more favorable for some women than estrogen-progestin, given that it decreases breast tenderness, has a neutral effect on breast density, and produces a higher rate of amenorrhea.

Ospemifene is an alternative to low-dose local vaginal estrogen for the treatment of dyspareunia associated with VVA. However, unlike vaginal estrogen, ospemifene

is associated with systemic adverse effects.

Raloxifene can be used for the prevention and treatment of osteoporosis and for chemoprophylaxis of breast cancer in high-risk postmenopausal women.

Tamoxifen continues to play an important role in the adjuvant treatment of receptor-positive breast cancer. Tamoxifen also can be used for breast cancer chemoprophylaxis in high-risk pre- and postmenopausal women. ■

References

1. Lonard DM, O'Malley BW. The expanding cosmos of nuclear receptor coactivators. Cell. 2006;125(3):411–414.
2. Dutertre M, Smith CL. Molecular mechanisms of selective estrogen receptor modulator (SERM) action. J Pharmacol Exp Ther. 2000;295(2):431–437.
3. Jordan VC. Tamoxifen treatment for breast cancer: concept to gold standard. Oncology. 1997;11(2 suppl):7–13.
4. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst. 1998;90(18):1371–1388.
5. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med. 1992;326(13):852–856.
6. Bouchard C. Selective estrogen receptor modulators and their effects on hot flashes: a dilemma. Menopause. 2011;18(5):477–479.
7. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the national surgical adjuvant breast and bowel project (NSABP) B-14. J Natl Cancer Inst. 1994;86(7):527–537.
8. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. JAMA. 1999;282(7):637–645.
9. Mosca L, Grady D, Barrett-Connor E, et al. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke. 2009;40(1):147–155.
10. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab. 2002;87(8):3609–3617.
11. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA. 1999;281(23):2189–2197.
12. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst. 2004;96(23):1751–1761.
13. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727–2741.
14. Parsons A, Merritt D, Rosen A, et al. Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. Obstet Gynecol. 2003;101(2):346–352.
15. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008;23(12):1923–1934.
16. Christiansen C, Chestnut CH, Adachi JD, et al. Safety of bazodoxifene in a randomized, double-blind placebo- and active-controlled phase 3 study of postmenopausal women with osteoporosis. BMC Musculoskeletal Disorders. 2010; 11:130.
17. Kangas L, Unkila M. Tissue selectivity of ospemifene: pharmacologic profile and clinical implications. Steroids. 2013;78(12-13):1273–1280.
18. Bachmann GA, Komi JO; Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480–486.
19. Simon JA, Lin VH, Radovich C, Bachmann GA; Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause. 2013;20(4):418–427.
20. Constantine GD, Goldstein SR, Archer DF. Endometrial safety of ospemifene: results of the phase 2/3 clinical development program. Menopause. 2015;22(1):36–43.
21. Elkinson S, Yang L. Ospemifene: first global approval. R&D Insight Report. Drugs. 2013;73(6):605–612.
22. Harvey HA, Kimura M, Hajba A. Toremifene: an evaluation of its safety profile. Breast. 2006;15(2):142–157.
23. Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med. 2010;362(8):686–696.
24. Goldstein SR, Neven P, Cummings S, et al. Postmenopausal Evaluation And Risk Reduction with Lasofoxifene (PEARL) trial: 5-year gynecological outcomes. Menopause. 2011;18(1):17–22.
25. Board of the International Menopause Society; Pines A, Sturdee DW, Birkhauser MH, Schneider HP, Gambacciani M, Panay N. IMS updated recommendations on postmenopausal hormone therapy. Climacteric. 2007;10(3):181–194.
26. US Food and Drug Administration. FDA approves Duavee to treat hot flashes and prevent osteoporosis. http://www.fda.gov/Drugs/NewsEvents/ucm370679.htm. Accessed March 30, 2016.
27. Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. Menopause. 2009;16(6):1116–1124.
28. Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause. 2010;17(2):281–289.
29. Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab. 2014;99(2):e189–e198.

Tips for counseling women about intimacy after menopause

How can you best approach the conversation about sex with your midlife patients once it begins? These 7 recommendations are a good place to start.

Susan Kellogg Spadt, PhD, CRNP, IF, FCST, CSC

As a sexual medicine specialist and certified sex therapist, Dr. Kellogg Spadt's guidance focuses on practical, evidence-based advice for your midlife patients

Your patients who are perimenopausal or postmenopausal have common reports when it comes to their sexual life: their body and mind do not respond like they used to; they are not as mentally or physically "in the game;" they have trouble getting aroused, are not as lubricated, and their introital tissue does not stretch during penetration. Further, they feel more irritation and pain in their vulva and vagina before, during, and after sex, and they cannot climax as easily (or at all).

Many women feel as though they received "no warning" about these sexual changes…from their health care providers, mothers, friends, or from the books that they consulted about hormone therapy. Investigators note that menopausal symptoms such as hot flushes, lack of sleep, and emotional lability are "expected events," women feel informed and ready for these changes. The sexual changes associated with menopause, however, are often unexpected and women feel ill prepared.[1] During menopause a majority of women and men—69% and 76%, respectively—avoid sex due to female genital changes, including dryness, pain, discomfort, and "tightness or tearing."[2] Dyspareunia can result in increased anxiety, stress, and low sexual desire. It also can affect day-to-day issues like mood, sense of well-being, and partner relationships.

The end of menses does not have to be synonymous with the end of your patients' sex lives. If patients know what to expect—and understand that the decreased hormonal influence and alterations in blood flow to the genitals causes tissues to thin and changes sexual response—and are armed with effective strategies to use, they can maintain and even improve physical intimacy.

Studies suggest that a very small percentage of women initiate discussion about arousal, orgasm, and desire concerns with their clinician.[1] It is your job to address these issues, and women prefer that, as their health care provider, gynecologist specifically, you bring up the topic.[3] When broaching the subject, open-ended questions (vs closed-ended, which many clinicians may be used to using more often) are the most efficient in revealing the clinical picture. Ask her: "What type of questions do you have about your/your partner's sexual health?" You also can start the conversation with, "During menopause, many women have changes in their sexual response, tell me about…." You also could present the

Dr. Kellogg Spadt is Director, Female Sexual Medicine, Center for Pelvic Medicine, Academic Urology of PA, Bryn Mawr, Pennsylvania; Professor, Obstetrics and Gynecology, Drexel University College of Medicine, Philadelphia, Pennsylvania; Professor, Human Sexuality, Widener University, Chester, Pennsylvania; Assistant Professor, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey; and Clinical Associate Faculty, University of Pennsylvania and Thomas Jefferson University, Philadelphia.

The author reports receiving grant or research support from Neogyn and being a consultant to Lelo, MiddlesexMD.com, Neogyn, and Nuelle.

issue as a normal part of aging, with "Sexual concerns are very common…." Use silences when asking questions to allow the patient to speak and monitor their body language and use culture- and age-appropriate words. Practicing the use of sexual terminology is a good activity.[4,5]

Once the conversation begins, most women reveal that they simply are at a loss for where to start to improve their level of comfort and sexual activity. There are several recommendations that you can make that will make a difference in your patients' sex lives.

1: Advise regular activity

One of the best strategies for patients to avoid vulvar and vaginal pain in the early menopausal years (and beyond) does not involve medication. Regularity of sexplay is associated with less likelihood of serious genital tissue thinning and alterations in lubrication. Weekly sexual activity with a partner, self stimulation, or use of a dilator is associated with the effects of genital vasocongestion that occur during arousal, keeping the tissues healthy, lubricated, and able to stretch. Regular sexual activity with a partner or self stimulation and/or use of a dilator can be the best first line defense against genital menopausal changes and sexual pain. (See "Practical use of a dilator to menopausal patients with sexual discomfort" on page S32.)

2: Increase stimulation using vibrators

The menopause transition changes sensory touch and vibratory thresholds for women, who may need more intense stimulation than they did during premenopause to become aroused and orgasm. Advise women that use of a handheld or hands-free vibrator during sexual activity produces a strong sensation that can stimulate blood flow, increase vaginal moisture, and boost sexual response to an intensity to facilitate arousal and orgasm. Consumer survey data posits that the most effective vibrators for the postmenopausal woman are: Fiera, Magic Wand, We-Vibe, Smart Wand.[6] For where to direct patients on purchasing, see the **TABLE.**

3: Guide patients to appreciate and care for their menopausal body

A patient's good feeling about her own body translates into acceptance and optimization of aging. Advise patients to eat a Mediterranean-type diet (fresh fruits, vegetables, whole grains, fish, and olive oil); minimize intake of red meat, high fat dairy products, sugar, and alcohol; and exercise regularly (by walking or swimming), which will increase oxygenated blood flow to the genitals.[7,8]

4: Recommend patients "get sex into daily thoughts"

Research suggests that women are motivated to engage in sex if their thoughts are sexually stimulated. A regular program of attending to erotic thought (relaxation coupled with erotic reading of 20 minutes several times per week) can help a "multitasking woman" slow down and nurture her sensual self.[9]

5: Encourage sex conversation between partners

By getting issues "out in the open" both partners will have less worry about sexual

TABLE. Where to obtain vibrators and dilators

Direct from manufacturer
• Syracuse Medical Devices
• American Med Direct
From an Internet website*
• MiddlesexMD.com
• Medamour.com
From you at the office
• You can purchase products from MiddlesexMD.com or Medamour.com and resell them in your office

*Medically supervised websites.

CONTINUED ON PAGE S32

CONTINUED FROM PAGE S31

Practical use of a dilator to benefit menopausal patients with sexual discomfort

The use of vaginal dilation is warranted with several medical conditions, including superficial dyspareunia, high-tone pelvic floor dysfunction, vaginismus, provoked vestibulodynia, vaginal atrophy, vulvar dermatoses, vaginal agenesis, and postradiation adhesions. Dilation also can be used as deconditioning therapy for psychogenic dyspareunia.[1–4] Dilator therapy can restore sexual function, with treatment considered successful if a patient is able to resume comfortable intercourse or self-stimulation as desired.[1] Vaginal dilation is appropriate to use adjunctively with pelvic floor muscle physical therapy, psychotherapy, sex therapy, local estrogen therapy, intravaginal muscle relaxants, lubricants, moisturizers, and vibrators.

When educating your menopausal patient on using a vaginal dilator, instruct her to[5]:

- choose the correct size—one that does not cause pain but enters the vagina with some resistance. Sizes (circumference) come in extra small (1/2 inch; 13 mm) to large plus (1 5/8 in; 38 mm).
- relax before using a dilator, by taking a bath, breathing deeply, or using a muscle relaxant 30 to 60 minutes before dilation
- use proper lubrication (water-based) and positioning (back on the bed with knees bent apart)
- insert the dilator as far as it will go without causing pain
- dilate daily
- clean the dilator thoroughly between uses
- report her progress with you at regular intervals (once per month is typical).

References

1. Idama TO, Pring DW. Vaginal dilator therapy—an outpatient gynaecologic option in the management of dyspareunia. J Obstet Gynaecol. 2000;20(3):303–306.
2. Gentilcore-Saulnier E, McLean L, Goldfinger C, Pukall CF, Chamberlain S. Pelvic floor muscle assessment outcomes in women with and without provoked vestibulodynia and the impact of a physical therapy program. J Sex Med. 2010;7(2 Pt 2):1003–1022.
3. Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. J Sex Med. 2011;8(2):549–559.
4. Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. Cochrane Database Syst Rev. 2010;(9):CD007291.
5. Spadt SK, Iorio J, Fariello JY, Whitmore KE. Vaginal dilation: When it's indicated and tips on teaching it. OBG Manag. 2012;24(12): 12,15–16, 18.

performance. It is crucial for your patient to always be honest about sexual pain, so that sexplay can be altered, changing intimacy from a threatening to a welcome activity.

6: Advise scheduled pleasure

Your patient and her partner should schedule 20 to 30 minutes per week (ideally at the same time and on the same day each week) for quiet uninterrupted time to be together for the purpose of intimate touch. This might include "cuddling" during a much-needed nap, mutual back massages, external fondling, or intercourse. Encourage the couple to vary the activities that they include in their weekly "touch time." By prioritizing this time together, intimate touch will not be relegated to the "last thing to do on the to do list," and months of no intimacy will not lead to resentment and heightening tensions. This valuable strategy will assure a short time of physical reconnection for the couple in their otherwise hectic lives.

7: Assess and address the pelvic floor muscles

In hypertonic pelvic floor muscle (PFM) dysfunction, the vaginal and pelvic support muscles (superficial and deep levators) are abnormally tight, painful, weak, and unable to relax. This can occur as a result of underlying physical conditions, including: connective tissue disease, musculoskeletal asymmetry, accidents/falls, surgical or obstetric injury, anxiety, or infection. Hypertonic pelvic floor dysfunction can cause pain with penetration and thrusting and interfere with arousal, orgasm, and desire. It is typically treated with specialty pelvic floor muscle physical therapy (see http://www.womenshealthapta.org/ for referrals by

zip code), oral or intravaginal muscle relaxants, and dilator therapy (with options from Soul Source, Syracuse Medical, and Berman Intimate Basics).

Patients with untreated PFM hypertonus should not be instructed to begin an aggressive home strengthening (Kegel exercise) program. This often will intensify pain rather than alleviate it.

Postmenopausal women also benefit from referrals to PFM physical therapy and adjuvant biofeedback or electrical simulation when they have hypotonic PFM dysfunction. This condition is characterized by laxity, urinary and fecal incontinence, prolapse, and poor orgasm amplitude. Hypotonus can be related to multiple deliveries, aging, obesity, connective tissue disease, and chronic cough.

Health care providers can begin instruction for PFM strengthening by advising women on the correct technique for Kegel exercises (the Mayo Clinic offers a good resource[10]) and referring patients to physical therapy. Long-term pelvic floor strength and sexual pleasure is also enhanced by vaginal rehabilitation electrical stimulation devices (such as Apex, Associated Medical, and Liberty Pelvic Floor Stimulation System, Utah Medical Products).[8] ■

References

1. Kingsberg S, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: Findings from the REVIVE (Real Women's Views of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med. 2013;10(7):1790–1799.
2. Domoney C, Currie H, Panay N, Maamari R, Nappi RE. The CLOSER survey: impact of postmenopausal vaginal discomfort on women and male partners in the UK. Menopause Int. 2013;19(2):69–76.
3. Shifrin JL, Johannes CB, Monz BU, Russo PA, Bennett L, Rosen R. Help-seeking behavior of women with self-reported distressing sexual problems. J Womens Health (Larchmt). 2009;18(4):461–468.
4. Lipton RB, Hahn SR, Cady RK, et al. In-office discussions of migraine: results from the American Migraine Communication Study. J Gen Intern Med. 2008;23(8):1145–1151.
5. Hahn SR, Lipton RB, Sheftell FD, et al. Healthcare provider-patient communication and migraine assessment: results of the Americn Migraine Communication Study, phase II. Curr Med Res Opinion. 2008;24(6):1711–1718.
6. Herbenick D, Reece M, Sanders S, Dodge B, Ghassemi A, Fortenberry JD. Prevalence and characteristics of vibrator use by women in the United States: results from a nationally representative study. J Sex Med. 2009;6(7):1857–1866.
7. Esposito K, Giugliano F, Maiorino MI, Giugliano D. Dietary factors, Mediterranean diet and erectile dysfunction. J Sex Med. 2010;7(7):2338–2345.
8. Stein A. Heal Pelvic Pain: The Proven Stretching, Strengthening, and Nutrition Program for Relieving Pain, Incontinence, and I.B.S, and Other Symptoms Without Surgery. New York, New York: McGraw-Hill; 2008.
9. Brotto LA, Krychman M, Jacobson P. Eastern approaches for enhancing women's sexuality: mindfulness, acupuncture and yoga. J Sex Med. 2008;5(12):2741–2748.
10. Kegel exercises: A how-to guide for women. The Mayo Clinic website. http://www.mayoclinic.org/healthy-lifestyle/womens-health/in-depth/kegel-exercises/art-20045283. Published September 25, 2015. Accessed April 19, 2016.

A Revolution in Vaginal Health

A remarkable laser therapy that addresses the issues women experience from declining estrogen.

8 PUBLISHED STUDIES
6 ON GOING U.S. STUDIES

MonaLisa Touch®

For more information: **smilemonalisa.com/obg**

CYNOSURE DEKA The Code of Excellence