Update: Management of menopausal and postmenopausal symptoms

By Donna Duvall, RN, MN, WHCNP and David M. Plourd, MD, FACOG

Faculty

Donna Duvall, RN, MN, WHCNP
Private Practice
San Diego, California

David M. Plourd, MD, FACOG
Clinical Instructor, Department of OB/GYN
University of California San Diego
San Diego, California

Continuing education (CE) material

This activity provides practical education for clinicians who manage the health of midlife and older women. The evidence-based content will facilitate clinicians' management of their patients' menopausal and postmenopausal symptoms.

CE approval period

Now through February 28, 2015

Educational objectives

- Evaluate specific menopausal and postmenopausal symptoms as they pertain to the individual patient
- Assess treatment options, dosage, and route of delivery of hormone therapy to meet the individual patient's needs
- Discuss the use of other agents to address the individual patient's menopausal and postmenopausal symptoms

Accreditation statement

This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit, including 1.0 contact hour of pharmacology content.
Estimated time to complete this activity: 1 hour

Faculty disclosures

NPWH policy requires all faculty to disclose any affiliation or relationship with a commercial interest that may cause a potential, real, or apparent conflict of interest with the content of a CE program. NPWH does not imply that the affiliation or relationship will affect the content of the CE program. Disclosure provides participants with information that may be important to their evaluation of an activity. Faculty are also asked to identify any unlabeled/unapproved uses of drugs or devices made in their presentation. The faculty reports the following:

- Ms. Duvall has nothing to disclose. Dr. Plourd serves on the Speakers Bureau for Teva Women's Health.

Participating faculty members determine the editorial content of CE activities; this content does not necessarily represent the views of NPWH or Novo Nordisk. This content has undergone a blinded peer review process for validation of clinical content. Although every effort has been made to ensure that the information is accurate, healthcare practitioners are responsible for evaluating this information in relation to generally accepted standards in their own communities and integrating the information in this activity with that of established recommendations of other authorities, national guidelines, FDA-approved package inserts, and individual patient characteristics.

Successful completion of the activity

Successful completion of this activity, 13-09J, requires participants to: (a) read the learning objectives, disclosures, and disclaimers; (b) study the material in the learning activity; (c) during the approval period (now through February 28, 2015): 1. click on the link to the course and log on to the NPWH Online Continuing Education Center (**https://npwhcourses.globalclassroom.us/stratus/course/view.php?id=56**); 2. complete the online posttest and evaluation; 3. earn a score of 70% or better on the posttest; 4. print out the CE certificate.

Commercial support

This publication is sponsored in part by an unrestricted educational grant from Novo Nordisk to NPWH.

To participate in this CE program, go to click here.

Before reading the article, click here to take the pretest.

Although use of hormone therapy (HT) has a long history, demonstrating safety and efficacy since the 1980s, HT use became controversial in the mid-2000s following reports from the Women's Health Initiative (WHI). This study was designed not to assess the utility of HT in women at and after menopause but, rather, to further evaluate data suggesting the potential benefit of HT in protecting the heart, as had been suggested in numerous animal studies. As we know, the WHI results did not show a cardioprotective benefit in a population of women significantly older than that representative of typical HT users. Media reports focused on the potential cardiovascular and breast cancer risks associated with first-time HT use in this older population. The goal of this article is to put the risks and benefits of HT into perspective using a series of case reports and a review of recent study findings and new national and international guidelines and recommendations. This information can help clinicians adopt counseling strategies that increase patients' understanding of HT's benefits and risks. In addition, this article can help clinicians evaluate the impact of a patient's symptoms—particularly the under-reported and undertreated symptoms related to vulvovaginal atrophy—on her quality of life.

KEY WORDS: **menopausal symptoms, postmenopausal symptoms, hormone therapy, HT, vaginal hormone therapy**

Hormone therapy: what your patients need to know

The initial report of the Women's Health Initiative (WHI),[1] released more than a decade ago, had a profound, and some would say extremely adverse, impact on women who experience moderate to severe menopausal and postmenopausal symptoms. Use of hormone therapy (HT), the most effective treatment for menopause-related symptoms that affect quality of life (QOL), has declined precipitously since that time. Many healthcare practitioners (HCPs) have been reluctant to return to the prescribing of HT to relieve these types of symptoms.

Results of the WHI, a prevention study, cannot be applied—and should *never* have been applied—to typical menopausal and postmenopausal women for whom HT provides relief from symptoms that adversely affect QOL. As a trial assessing the cardioprotective effects of HT, the WHI has no relevance to the average 51-year-old with hot flashes or the average 58-year-old with vulvovaginal atrophy (VVA) symptoms.

Of note, the WHI was a well-designed study for its purpose. The researchers had no reason to enroll women experiencing menopause-related symptoms; after all, many studies had already demonstrated the safety and efficacy of estrogen used in this regard.

The goal of *this* article is to put the risks and benefits of HT into perspective using a series of case reports. The article can help HCPs adopt counseling strategies that increase patients' understanding of the benefits and risks of HT. The article can also help HCPs evaluate the impact of troubling menopause- and postmenopause-related symptoms—particularly those related to VVA, which tend to be under-reported and undertreated—on the individual patient and her QOL.

Case 1. Linda: Patient is concerned about HT use and cardiovascular risk

This 51-year-old woman has been your patient for 5 years. For the past 3 years, she has been experiencing hot flashes of increasing severity and frequency (on average, >10 episodes/day). At her current visit, Linda reports irregular menses. Other than high total cholesterol levels, her health is good. You tell her that she is a good candidate for HT, but she immediately rejects that treatment option out of a fear of cardiovascular health risks. She tells you that her father died last year of a heart attack and that she has heard that HT increases the risks for heart attack and stroke.

How do you assess Linda's health status?

Linda's history clearly indicates she is perimenopausal. Further

Key facts about the WHI

Despite a reassessment of the findings, many key facts about the WHI have been ignored—and serve as useful discussion points to share with patients who may remain fearful or misinformed about HT use. In counseling patients and in making clinical decisions about when to recommend HT, HCPs should keep in mind that:

- Only one arm of the WHI—the oral conjugated equine estrogen (CEE)/medroxyprogesterone (MPA) arm, not the CEE-only arm—was terminated prematurely.
- The study was designed to evaluate the effects of estrogen in promoting cardiovascular health and in retarding the progression of cognitive decline.
- Because of the study goals—to assess long-term chronic disease typically manifested in women long past menopause—the WHI researchers enrolled an older cohort of women who had never previously used HT to start this form of treatment.
- The study was designed only to measure the utility of long-term interventions to prevent future chronic disease.
- Because the study was intended to evaluate disease prevention, not treatment, the Data Safety Monitoring Board tolerated a level of risk much lower than that applied to treatment studies.
- The study was not designed to:
  - Assess the safety or efficacy of established FDA-approved formulations.
  - Evaluate the impact of treatment on postmenopausal symptoms such as those related to VVA.
  - Review the effect of treatment on QOL indicators.
  - Describe the effects of HT on typical women who use this therapy for relief of menopausal symptoms; women experiencing such symptoms were excluded from the trial.[1]

testing is not warranted; however, you would consider assessing follicle-stimulating hormone levels in a much younger woman who experiences both irregular periods and hot flashes. Such symptoms at a younger age could suggest conditions ranging from thyroid dysfunction to psychological problems to tuberculosis (night sweats could be confused with hot flashes).

Is Linda's family history a potential concern?

No. In this respect, both patients and HCPs sometimes confuse the risks associated with high hormone doses found in oral contraceptives with the much lower doses used in HT to treat menopause-related symptoms.

What are appropriate treatment options for Linda's symptoms?

There is no question that HT will be of value for Linda, as demonstrated by the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study.[2] Results of this 12-week study showed that the number of hot flashes declined dramatically with administration of oral CEE/MPA at 0.625/2.5 mg/day, 0.45/1.5 mg/day, or 0.3/1.5 mg/day. All three dosages reached similar efficacy at 12 weeks. A regimen of CEE alone showed considerable efficacy, although greater relief was seen with the 0.625 mg/day regimen than the two lower-dose formulations. Other oral and transdermal HT formulations have shown excellent efficacy in managing such symptoms.

If Linda remains uncomfortable with the use of oral or transdermal estrogen, does she have other therapeutic options?

Serotonin norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors (SSRIs) have shown consistent efficacy in combating menopausal vasomotor symptoms (VMS) in trials.[3,4] These agents target neurotransmitters that affect hypothalamic thermoregulation, thereby reducing the severity and frequency of hot flashes.

A systematic review and meta-analysis showed that SSRI use is associated with a modest improvement in hot flash severity and frequency (these agents have the typical profile of SSRI adverse effects).[5] Escitalopram may be superior to the other SSRIs in terms of efficacy.[5] A 7.5-mg formulation of paroxetine, recently approved by the FDA for VMS management, has been shown to be effective and well tolerated in phase III studies of 12 and 24 weeks' duration.[6]

Selective estrogen-receptor modulators (SERMs) have selective estrogen agonist and antagonist effects, depending on the target tissue. A combination of CEE and the SERM bazedoxifene has recently received FDA approval to treat moderate to severe VMS associated with menopause and to prevent postmenopausal osteoporosis.[7,8] Fa-

vorable tolerability profiles, no increase in uterine bleeding or breast tenderness, and favorable effects on metabolic parameters and QOL have been noted. CEE/bazedoxifene will be available as a treatment option in the near future.

Most herbal products have shown little or no benefit or inconclusive benefits in clinical trials. Black cohosh, red clover, St. John's wort, and omega-3 fatty acids have shown some benefit, although research has not indicated optimal dosing and safety.[9-12]

In counseling Linda, which studies might you discuss to demonstrate the safety of HT?

A brief review of recent study data may help Linda better understand that for her, the risks of HT use are extremely low and should be weighed against the impact of untreated VMS on her QOL. She may be interested in these key study findings:

WHI. Despite the adverse publicity surrounding the WHI, annual disease rates initially reported for all women, regardless of age, who received combined oral HT (i.e., CEE/MPA), as compared with placebo, were as follows:

- 7 additional cases of coronary heart disease per 10,000 woman-years;
- 8 additional cases of stroke per 10,000 woman-years;
- 8 additional cases of breast cancer (BrCA) per 10,000 woman-years;
- 14 additional cases of venous thromboembolism (VTE) per 10,000 woman-years;
- 6 fewer cases of colorectal cancer per 10,000 woman-years;
- 5 fewer hip fractures per 10,000 woman-years; and
- no difference in mortality.[1]

In the oral CEE-only arm, annual disease rates for estrogen recipients, as compared with placebo recipients, were as follows:

- 12 additional cases of stroke per 10,000 woman-years;
- 6 fewer cases of hip fracture per 10,000 woman-years;
- no difference in coronary heart disease rates;
- no difference in BrCA rates; and
- no difference in colorectal cancer rates.[13]

HT is hypothesized to be cardioprotective for women who have been menopausal for less than 10 years.

Linda might be interested in knowing that HT is hypothesized to be cardioprotective for women who have been menopausal for less than 10 years. Multiple studies support this timing hypothesis.[14-19] For example, Rossouw et al[18] performed a secondary analysis of the WHI data, which demonstrated reduced cardiovascular risk for women in the study who had been menopausal for less than 10 years and who used either CEE/MPA or CEE-only. A slightly elevated risk of cardiovascular disease was noted in women who used CEE/MPA or CEE and who had been menopausal for 10-20 years prior to initiating HT. An elevated risk was noted in women who were more than 20 years postmenopause when starting HT. Only two studies do not support this timing hypothesis.[20,21]

ESTHER. The Estrogen and Thromboembolism Risk study was a case–control investigation; the cases were women with VTE and the controls were women who had never had a VTE.[22] Compared with estrogen therapy (ET) nonusers, oral ET users had an adjusted odds ratio (OR) for VTE of 3.5 and transdermal ET users had an adjusted OR for VTE of 0.9; that is, the oral group had nearly a 4 times greater risk for VTE than did the transdermal group. Many other studies have shown that the use of transdermal ET, unlike oral ET, does not increase VTE risk.[23-30]

Danish cohort study. Løkkegaard et al[31] followed approximately 700,000 women in Denmark for 7 years, during which time nearly 5000 of the women experienced a myocardial infarction (MI). Overall, there was no increased risk for MI among current HT users versus never-users. However, the greatest MI risk occurred in continuous HT users; no increased risk was noted in users of unopposed estrogen or cyclic combined therapy. A significantly lower MI risk was found among transdermal ET users than among oral ET users.

KEEPS. The Kronos Early Estrogen Prevention Study has recently provided encouraging data regarding cardiovascular safety (using surrogate markers)

in a younger population.[32] Participants in KEEPS have been randomized to receive oral or transdermal estrogen or placebo; those receiving active estrogens are also given oral micronized progesterone, which has a better safety profile than MPA (the progestogen used in the WHI), to protect the uterus. To date, oral estrogen use has been associated with beneficial increases in high-density lipoprotein cholesterol and decreases in low-density lipoprotein cholesterol. However, triglycerides and C-reactive protein levels have increased with oral ET. By contrast, transdermal ET has had no effect on cardiovascular markers. Compared with placebo, neither oral nor transdermal estrogen has had apparent effects, either beneficial or deleterious, on atherosclerosis progression assessed by carotid ultrasound, but they have been linked to a nonsignificant trend toward less accumulation of coronary artery calcium. Mood has improved to a greater degree with oral estrogen and libido has improved to a greater degree with transdermal estrogen.

ELITE. The Early Versus Late Intervention Trial With Estradiol is evaluating the impact of treatment with 17-beta estradiol on atherosclerosis and cognition in women less than 6 years postmenopause and in those more than 10 years postmenopause.[33] This study is ongoing; results have not yet been reported.

What are current recommendations from national and international societies?

In its 2012 Hormone Therapy Position Statement, The North American Menopause Society (NAMS) noted that:

- Current evidence supports the use of HT for perimenopausal and postmenopausal women when the risk/benefit profile is favorable for the individual woman.
- HT is the most effective treatment available for VMS and effects that reduce QOL.
- Estrogen/progestogen therapy should be limited in duration; long-term use is associated with an increased risk for BrCA.
- Transdermal administration of estrogen, compared with the oral route, appears to reduce VTE risk.[34]

The British Menopause Society notes that HT, if prescribed in women within a decade of reaching menopause, has a favorable health profile.[35] Prescribed after age 60, HT can have some adverse effects; at that time, transdermal administration is preferable.

Case 2. Lisa: Patient is concerned about HT use and BrCA risk

Lisa, Linda's twin sister, has been a patient in your practice for 5 years. Like her twin, she has experienced an average of >10 hot flashes per day for the past 3 years. Her concern about use of HT to treat her

Osteoporosis and HT

Estrogen is approved for the prevention—but not the treatment—of osteoporosis. Bisphosphonates are very effective not only for prevention but also for treatment of osteoporosis. These agents specifically target the pathophysiology of osteoporosis. Like estrogens, they are antiresorptive and inhibit the action of osteoclasts. I would prescribe estrogen as osteoporosis prophylaxis only if a woman were seeking concomitant relief of VMS and/or VVA symptoms and if she had related QOL concerns.

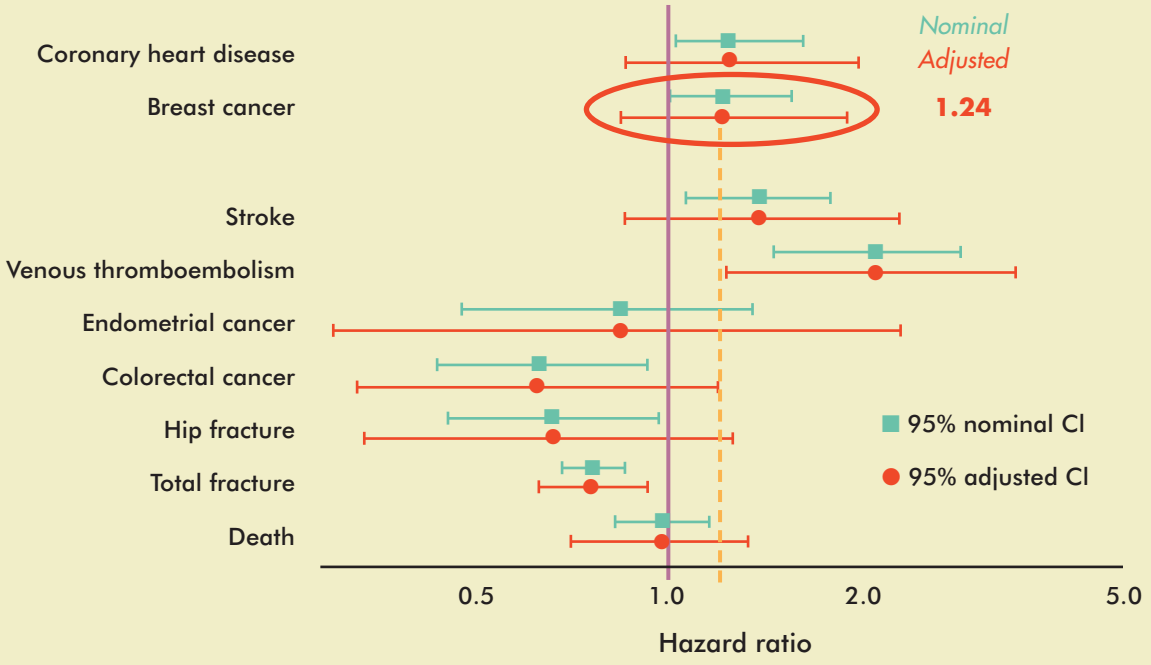
– David Plourd, MD

Long-term HT and risks in perspective

Data concerning BrCA and HT indicate that there is a stronger association with longer-term use. This association does not imply causation. The goal is to use the lowest effective dose of HT for the shortest duration of time. Decisions should be made within the context of a patient's risk/benefit profile and personal situation. The question to be asked initially is "Why did she start using menopausal hormone therapy?" If she started HT at age 51 and she is now 56, it is appropriate to reassess her need for systemic therapy. But what about the patient who has been using HT for more than 10 years and does not want to discontinue it? She is aware of the association between long-term use and increased risk for breast disease. Should she worry about increased cardiovascular risk? No. She initiated HT at age 51. The WHI data and risk profile apply to women who initiated use much later in life. Other data indicate that the highest risk for cardiovascular events is in the first few years of use. Therefore, I would not actively discourage her from continuing use.

– David Plourd, MD

Figure 1. Women's Health Initiative: Preliminary results with CEE/MPA



Writing Group for the Women's Health Initiative Investigators, *JAMA*. 2002;288(3):321-333.

VMS is related to the recent death of her maternal aunt, who succumbed to BrCA at age 76.

Owing to Lisa's family history, will the use of estrogen increase her BrCA risk?

No. Key risk factors for BrCA are being female, getting older, and having a family history of premenopausal BrCA. Multiple studies have demonstrated that exogenous estrogen use does not initiate breast cancer.[36] Meta-analyses have supported these findings.[37-39] Instead, data suggest that exogenous estrogen is not an initiator but, rather, a promoter of BrCA. Preliminary WHI results revealed a 24%-26% increased BrCA risk with CEE/MPA therapy versus placebo (*Figure 1*), but the confidence interval spanned 1.0.[1] The estrogen-only arm of the WHI showed a 22% reduction in BrCA among women taking CEE alone versus those taking placebo (*Figure 2*).[13]

How should you advise this patient?

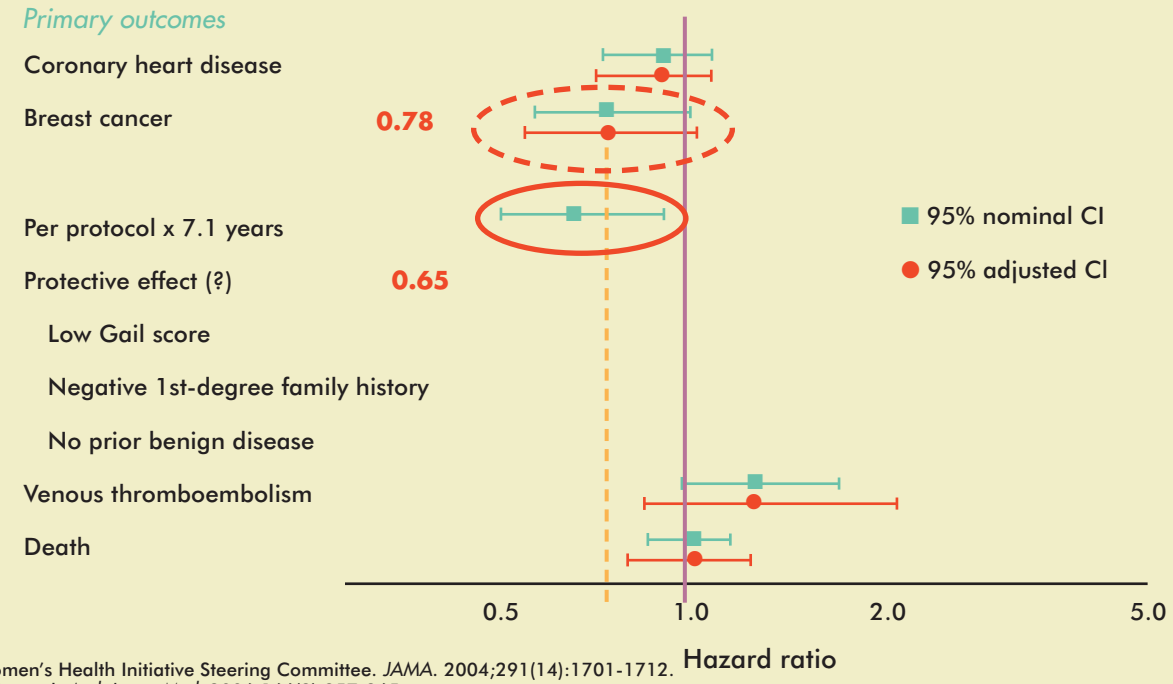
Lisa will probably benefit from 2-3 years of estrogen administration to manage her hot flashes. She should be counseled that, for up to 5 years of use, there is no increased BrCA risk associated with HT. With regard to absolute risk of breast cancer in the general population, for every 100 women aged 50 years who do not take HT or ET, 2.8 will develop BrCA after 10 years.[40] Among 100 women who do take HT, 3.5 will develop BrCA after 10 years (after an average of 5.2 years of HT use).[1] The increase in risk translates into less than one new case after use of much longer duration than Lisa will need.

HCPs' role in improving patients' sexual health and QOL

As indicated in NAMS' 2013 Position Statement, women need to be educated about VVA symptoms.[42] HCPs need to better diagnose and manage these symptoms to meet patient goals. Too few patients know that VVA can be treated effectively.

– Donna Duvall, NP

Figure 2. Women's Health Initiative: Results with CEE alone



Women's Health Initiative Steering Committee. *JAMA*. 2004;291(14):1701-1712.
Hsia et al. *Arch Intern Med*. 2006;166(3):357-365.
Rosenberg et al. *Arch Intern Med*. 2006;166(7):760-765.
Stefanick et al. *JAMA*. 2006;295(14):1647-1657.
Salpeter et al. *J Gen Intern Med*. 2004;19(7):791-804.

What about bioidentical hormones?

Nothing has been proven regarding the safety or efficacy of compounded products.[41] There is no role for individualized estrogen regimens in treatment of menopause-related symptoms because there is no scientific evidence for their efficacy or safety.

Case 3. Mary: Vulvovaginal atrophy is causing discomfort and marital stress

Mary, age 60, has never used HT because of fear instilled by media coverage of the WHI reports. She managed her mild hot flashes and transient sleep problems on her own. Her mood remained good throughout the menopausal transition. She exercises regularly. She uses simvastatin to control her hypercholesterolemia.

At this visit, you ask Mary if everything is okay at home. When she hesitates, you ask if she is experiencing any vaginal symptoms that bother her. She reports dryness and increasing pain with intercourse. She reports that she has started using an over-the-counter (OTC) lubricating product, without much improvement. She experiences vaginal itching and has tried OTC remedies for yeast infections,

Choices among local treatment options

In terms of helping a patient select a vaginal ET product, I may give her a sample of the creams and tablet. I advise her to try each of them for 2 weeks and let me know which one she prefers. The base in each of the cream products differs; many patients have a preference. It is also helpful to counsel the patient that, if she has severe VVA, she may find the tablet less soothing. She may want to try the creams first and then the tablet. This way, when she uses the tablet, the vaginal tissue will be somewhat estrogenized. It is also useful to show her the ring so that she can see the size and better understand how it works in case she wants to try it once her tissues are estrogenized.

– Donna Duvall, NP

Talking to our patients

Because many women incorrectly assume that VVA symptoms are just a part of the normal aging process, they do not broach the subject with their HCPs. Therefore, we need to initiate the conversation. In addition, many patients worry about the risks of HT. So we have two jobs—to help our patients discuss their symptoms and to counsel them concerning the safety of available treatment options. If we do not provide options and allay their fears, they won't fill the prescriptions we write for them.

– Donna Duvall, NP

without improvement. You ask whether these physical problems are having any consequences. She confides that she and her husband used to have sex twice a week, but now only about once a month. They argue frequently, and she is sure her husband is upset about her lack of interest in sex. She also mentions that she has had three urinary tract infections (UTIs) over the past year. She used OTC products to manage the first two UTIs and requested a prescription for the third UTI from a local urgent-care clinic. Her current history and an examination indicate that Mary has severe VVA.

How do you counsel the patient?

First, it may be helpful to show Mary the physical changes that are occurring. You can offer to provide a mirror so that she can see the vulvar effects you describe. Explain the impact of these effects on dyspareunia and other symptoms. Let her know that these symptoms will not improve without treatment and will likely continue to worsen—but that with treatment, she will see rapid improvement. These treatment-related changes may not affect her desire for sex, but they will facilitate her ability to have regular sexual activity.

She may also benefit from learning that her symptoms are extremely common. The recent CLOSER study demonstrated that vaginal discomfort caused 58% of participants to avoid intimacy and 64% to lose their libido.[43] Among their male partners, 79% believed that vaginal discomfort caused the women to avoid intimacy.

Are any nonhormonal options available to treat VVA symptoms?

Ospemifene, an orally administered SERM recently approved by the FDA for the management of dyspareunia, is an option. This agent has been shown to reverse the physiologic signs of VVA, with effects on the superficial and parabasal cells as well as vaginal pH, thereby diminishing dyspareunia.[44] Other treatments include OTC lubricants and moisturizers,[45,46] although Mary has had only limited success with these products. Engaging in more frequent sexual activity can be helpful.

How about vaginal estrogen therapy? Is it safe and effective?

The CLOSER study showed that 56% of women experienced symptom improvement with administration of local ET and 41% reported more satisfying sex with treatment.[43] You can also cite the 2012 NAMS statement, which indicates that vaginal ET has been proven to restore vaginal blood flow, decrease vaginal pH, and improve the thickness and elasticity of vulvovaginal tissue.[34] According to NAMS, if VMS relief or osteoporosis prevention is not required, low-dose vaginal ET is recommended to ease VVA symptoms.

How can you allay Mary's fears about using hormones?

You can reassure her that the health risks shown in the WHI data do not apply to her. Although Mary is almost as old as the typical WHI participant, who faced elevated risks associated with initiation of HT, vaginal ET uses such a low dose of estrogen that no progestogen is required to protect the uterus. Use of a specific progestogen—MPA—was responsible for most of the risk seen in the WHI. Vaginal ET offers rapid local—not systemic—effects on the superficial cells of the epithelium and vaginal pH, reducing susceptibility to infection. Mary may also find that she experiences fewer UTIs.

What are the options for vaginal ET?

Mary is satisfied by these reports concerning the safety of vaginal ET administration and elects to try it. You review the options with her:

- Two rings, which release different levels of estrogen over 90 days, are available. The low-dose formulation is used to manage local symptoms and is appropriate for Mary. The higher-dose formulation, which provides relief of systemic symptoms—and which, as a result of the systemic effects, requires use of a progestogen to protect the

uterus—is not suitable for her.

- Two FDA-approved cream formulations are available; one formulation is used daily and then several times weekly and the other is used daily or twice weekly for 21 days and then discontinued for 7 days. Some patients prefer one over the other.
- One FDA-approved tablet, administered once a day for 2 weeks and then twice a week.

Mary decides to begin using vaginal cream 1-2 g at night for 2 weeks. Then she reduces the dosage to 0.5-1 g 2-3 times a week. If she finds that the cream becomes messy, she can use a smaller quantity. This "messiness" is considered a good sign, because it means that her vaginal tissue is becoming more estrogenized. At a 2-month follow up, Mary has experienced extensive improvement.

Can vaginal ET help relieve Mary's urinary problems?

Because she has recurrent UTIs, Mary may find it useful to apply cream to the area outside of the vagina and around the urethra. This technique is especially helpful for elderly women. Vaginal ET is also likely to decrease the number of UTIs that she experiences.[47] Mary has not reported urinary incontinence, but she may still find it useful to know that vaginal ET may improve urge incontinence and overactive bladder—even though it is not FDA-approved for these indications.

What should Mary expect from her HCP?

As HCPs, we need to feel comfortable in asking our patients whether they experience VVA symptoms, listening to our patients to determine if they feel distress concerning their VVA symptoms, and prescribing estrogen for patients whose VVA symptoms adversely affect their QOL. Many women experience symptoms of menopause-related VVA, but few know that the condition can be treated. In a study of 3520 postmenopausal women in seven countries, investigators noted that:

- 45% reported symptoms of VVA;
- 4% realized that VVA is a progressive postmenopausal problem; and
- 46% knew nothing about vaginal ET.[47]

> Women who start HT at or close to the time of menopause do not incur the same health risks as do those who start HT much later.

Similar data were obtained in an online survey of 3,046 postmenopausal women in the United States:

- 55% experienced vaginal dryness;
- 44% said they experienced pain with intercourse;
- 59% noted that VVA symptoms affected their enjoyment of sex; and
- 24% related these symptoms to menopause and 12% ascribed them to hormonal changes.[48]

What can we assume from these findings? Most women believe that symptoms of VVA are part of the aging process and do not realize that these symptoms occur because of the decreasing amounts of estrogen in their system. They do not know that effective treatment is available. Yet, 85% of women polled in various studies report concerns about safety issues with estrogen.[49]

Conclusion

The three women described in the case studies represent typical menopausal and postmenopausal patients that HCPs see in their practice. These women have unpleasant VMS or VVA-related symptoms that compromise their QOL. Ever since the publication of the WHI results more than 10 years ago, many of these women have refused to use HT or have been discouraged to do so by their well-meaning HCPs.

However, over this period of time, many reanalyses of the WHI data, as well as findings from many other studies, have shown that (1) women who start HT at or close to the time of menopause do not incur the same health risks as do those who start HT much later; (2) the route of HT delivery matters; non-oral HT is safer than oral HT in terms of cardiovascular, cerebrovascular, VTE, and BrCA risks; (3) the type of progestogen used is important; data have shown reduced risk associated with progestogens other than MPA, the progestogen used in the WHI[34]; (4) vaginal ET

contains such a low dose of estrogen that no progestogen is required to protect the uterus; and (5) vaginal ET has rapid local—not systemic—effects on the superficial cells of the epithelium and vaginal pH, reducing susceptibility to infection and possibly reducing UTI frequency. Women experiencing menopausal and postmenopausal symptoms that are distressing and uncomfortable, and who have no contraindications to HT, can feel much better about using it, and HCPs can feel much better about prescribing it.

References

1. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.

2. Utian WH, Shoupe D, Bachmann G, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 2001;75(6):1065-1079.

3. Gordon PR, Kerwin JP, Boesen KG, et al. Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general populations. *Menopause.* 2006;13(4):568-575.

4. Hall E, Frey B, Soares C. Nonhormonal treatment strategies for vasomotor symptoms: a critical review. *Drugs.* 2011;71(3):287-304.

5. Shams T, Firwana B, Habib F, et al. SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. *J Gen Intern Med.* 2013 Jul 26. [Epub ahead of print]

6. 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.

7. FDA. Pfizer Inc. Announces FDA Approval of DUAVEETM (conjugated estrogens/bazedoxifene) for the Treatment of Moderate-to-Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause and the Prevention of Postmenopausal Osteoporosis. www.pfizer.com/news/press-release/press-release-detail/pfizer_inc_announces_fda_approval_of_duaveetm_conjugated_estrogens_bazedoxifene_for_the_treatment_of_moderate_to_severe_vasomotor_symptoms_hot_flashes_associated_with_menopause_and_the_prevention_of_postmenopausal_osteoporosis_1

8. Gennari L, Merlotti D, Valleggi F, et al. Ospemifene use in postmenopausal women. E*xpert Opin Investig Drugs.* 2009;18(6):839-849.

9. Abdali K, Khajehei M, Tabatabaee HR. Effect of St John's wort on severity, frequency, and duration of hot flashes in premenopausal, perimenopausal and postmenopausal women: a randomized, double-blind, placebo-controlled study. *Menopause.* 2010; 17(2):326-331.

10. Freeman EW, Sammel MD, Lin H, et al. Duration of menopausal hot flushes and associated risk factors. *Obstet Gynecol.* 2011;117(5):1095-1094.

11. Geller SE, Shulman LP, van Breeman RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause.* 2009;16(6):1156-1166.

12. Oktem M, Eroglu D, Karahan HB, et al. Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. *Adv Ther.* 2007;24(2):448-461.

13. Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701-1712.

14. Barrett-Connor E. Hormones and heart disease in women: the timing hypothesis. *Am J Epidemiol.* 2007;166(5):506-510.

15. Manson JE, Bassuk SS. Invited commentary: hormone therapy and risk of coronary heart disease why renew the focus on the early years of menopause? *Am J Epidemiol.* 2007;166(5):511-517.

16. Hsia J, Langer RD, Manson JE, et al; Women's Health Initiative Investigators. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med.* 2006;166(3):357-365.

17. Toh S, Hernández-Díaz S, Logan R, et al. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. *Ann Intern Med.* 2010;152(4):211-217.

18. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007;297(13): 1465-1477.

19. Allison MA, Manson JE, Langer RD, et al; Women's Health Initiative and Women's Health Initiative Coronary Artery Calcium Study Investigators. Oophorectomy, hormone therapy, and subclinical coronary artery disease in women with hysterectomy: the Women's Health Initiative coronary artery calcium study. *Menopause.* 2008;15(4 pt 1):639-647.

20. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA.* 1998;280(7):605-613.

21. Grady D, Herrington D, Bittner V, et al; HERS Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).Research Group. *JAMA.* 2002;288(1):49-57.

22. Scarabin PY, Oger E, Plu-Bureau G; EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oes-

trogen-replacement therapy with venous thromboembolism risk. *Lancet.* 2003;362(9382):428-432.

23. Straczek C, Oger E, Yon de Jonage-Canonico MB, et al; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation.* 2005;112(22):3495-3500.

24. Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol.* 2010;30(2):340-345.

25. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost.* 2010;8(5):979-986.

26. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ.* 2010;340:c2519.

27. Laliberté F, Dea K, Duh MS, et al. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause.* 2011;18(10):1052-1059.

28. ACOG Committee Opinion No. 556: Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. *Obstet Gynecol.* 2013;121(4):887-890.

29. Roach RE, Lijfering WM, Helmerhorst FM, et al. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. *J Thromb Haemost.* 2013;11(1):124-131.

30. Sweetland S, Beral V, Balkwill A, et al; The Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *J Thromb Haemost.* 2012 Sep 10. [Epub ahead of print]

31. Løkkegaard E, Andreasen AH, Jacobsen RK, et al. Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J.* 2008;29(21):2660-2668.

32. The North American Menopause Society. KEEPS Results Give New Insight Into Hormone Therapy. 2013. www.menopause.org/annual-meetings/2012-meeting/keeps-report

33. ClinicalTrials.gov. ELITE: Early Versus Late Intervention Trial With Estradiol. November 12, 2013. http://clinicaltrials.gov/ct2/show/NCT00114517

34. North American Menopause Society. 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause.* 2012;19(3):257-271.

35. Panay N, Hamoda H, Arya R, et al, on behalf of The British Menopause Society and Women's Health Concern. The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy. *Menopause Int.* 2013;19(2):59-68.

36. Bush TL, Whiteman M, Flaws JA. Hormone replacement therapy and breast cancer: a qualitative review. *Obstet Gynecol.* 2001;98(3):498-508.

37. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. *Arch Intern Med.* 1991;151(1):67-72.

38. Sillero-Arenas M, Delgado-Rodriguez M, Rodigues-Canteras R, et al. Menopausal hormone replacement therapy and breast cancer: a meta-analysis. *Obstet Gynecol.* 1992;79(2):286-294.

39. Colditz GA, Egan KM, Stampfer MJ. Hormone replacement therapy and risk of breast cancer: results from epidemiologic studies. *Am J Obstet Gynecol.* 1993;168(5):1473-1480.

40. American Cancer Society. Cancer Facts & Figures 2002. www.uhmsi.com/docs/CancerFacts&Figures2002.pdf

41. Pinkerton JV. "Bioidentical" hormones: What you (and your patient) need to know. *OBG Manage.* 2009;21(1):42-52.

42. North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause.* 2013;20(9);888-902.

43. Simon, JA, Nappi RE, Kingsberg SA, et al. 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*; 2013 Jun 3. [Epub ahead of print]

44. New SERM approved for dyspareunia. *Drug Topics.* 2013. http://drugtopics.modernmedicine.com/drug-topics/news/new-serm-approved-dyspareunia.

45. Stika CS. Atrophic vaginitis. *Dermatol Ther.* 2010;23(5):514-522

46. Bachmann GA, Ebert GA, Burd ID. Vulvovaginal complaints. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:195-201.

47. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) – results from an international survey. *Climacteric.* 2012;15(1):36-44.

48. Kingsberg SA, Wysocki S, Magnus L, et al. 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.

49. Lehman RA. Clinical approach to recognizing and managing a patient with vaginal atrophy: a guide for physician assistants. *Internet J Acad Physician Assistants.* 2010;8(1).

To participate in this CE program, click here.