



MENOPAUSE

The North American Menopause Society has updated hormone therapy guidelines; herein, what you need to know. Plus, a continued call for the boxed warning to be removed from low-dose vaginal estrogen.



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Since publication of initial findings of the Women’s Health Initiative (WHI) in 2002, use of systemic menopausal hormone therapy (HT) has declined by some 80% among US women.¹ Against this backdrop, this year’s Menopause Update highlights the “hot off the press” updated position statement on menopausal HT from The North American Menopause Society (NAMS), summarized by Dr. JoAnn V. Pinkerton. Although this guidance is chock full of practical, evidence-based guidance, the take-home message that Dr. Pinkerton and I would like to leave readers

of OBG MANAGEMENT with is that for women with bothersome menopausal symptoms aged in their 50s or within 10 years of the onset of menopause who are free of contraindications, use of systemic HT is appropriate.

Although menopausal vasomotor and related symptoms improve as women age, in untreated women, vulvovaginal atrophy (VVA, also known as genitourinary syndrome of menopause, or GSM) tends to progress, causing vaginal dryness and sexual dysfunction, among other symptoms. When symptomatic GSM represents the

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only indication for treatment, low-dose local vaginal estrogen, ospemifene, or dehydroepiandrosterone (DHEA; prasterone) is safe and effective. However, as with systemic HT, specific treatments for GSM are substantially underutilized.² The current package labeling

for low-dose vaginal estrogen deters many appropriate candidates from using this safe, effective treatment. In this Update, Dr. JoAnn E. Manson reviews the rationale for updating this labeling as well as recent efforts to accomplish the task.

Guidelines on HT have been updated by The North American Menopause Society

The 2017 hormone therapy position statement of The North American Menopause Society [published online ahead of print June 2017]. Menopause.

The North American Menopause Society Hormone Therapy (HT) Position Statement Advisory Panel, composed of more than 20 experts in menopausal women's HT, including clinicians, researchers, and epidemiologists, reviewed the 2012 HT Position Statement, evaluated prior and new literature and used levels of evidence to identify the quality of the evidence and strength of the recommendations and to find consensus for the guidelines. The following information comes from the NAMS 2017 Hormone Therapy Position Statement.³

What are the major findings?

HT is the most effective treatment for vasomotor symptoms (VMS) and GSM and has been shown to prevent bone loss and fracture. Risks of HT may differ for women depending on type, dose, duration, route of administration, and timing of initiation and whether or not a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation about benefits and risks of continuing or discontinuing HT.

For women who are younger than age 60 or within 10 years of menopause and have no

contraindication, the clearest benefit of HT is for the treatment of VMS and prevention of bone loss in those at elevated risk.

The clinical guidelines were presented to NAMS audience at the 2016 annual clinical meeting, where NAMS recommended "determining the most appropriate type, dose, formulation, and duration of HT."⁴

When to initiate HT and duration of use

In its soon-to-be-published 2017 guidelines on HT, NAMS affirms the safety and efficacy of HT for symptomatic menopausal women or those at high risk for bone loss who are under age 60 or within 10 years of menopause. NAMS encourages practitioners to employ shared decision making with their patients to find the appropriate type, dose, formulation, and duration of HT, making individualized decisions based on evidence-based information, the unique health risks of women, and with periodic reassessment.

In the clinical guidelines presented in the 2016 NAMS annual meeting,⁴ key recommendations taken from the 2017 Hormone Therapy Position Statement³ include the following: For women who are aged younger than 60 years or within 10 years of menopause and have no contraindications, the benefit/risk ratio appears favorable for treatment of bothersome VMS and in those at elevated risk for bone loss or fracture.

For women who initiate HT more than



NAMS recommends individual decision making and using the most appropriate type, dose, duration, and formulation of HT

10 years from menopause or after age 60, this benefit/risk ratio appears less favorable because of greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.

What about extended use of hormone therapy? There is no evidence to support routine discontinuation of HT after age 65. Decisions about longer durations of HT should be individualized and considered for indications such as persistent VMS or bone loss, with shared decision making, documentation, and periodic reevaluation. Longer duration is more favorable for estrogen therapy than for estrogen-progestin therapy, based on the Women's Health Initiative (WHI) randomized controlled trials.⁵

What about only vaginal symptoms? For bothersome GSM not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal estrogen therapy or other therapies are recommended and can be continued as long as indicated since there is minimal systemic absorption of estrogen, with serum levels remaining within the normal postmenopausal range.^{6,7} For women with estrogen sensitive cancer, oncologists should be included in decision making, particularly for women on aromatase inhibitors.

Considerations for special populations

Early menopause. For women with hypogonadism, primary ovarian insufficiency, or premature surgical menopause without contraindications, HT is recommended until at least the median age of menopause (52 years), as studies suggest that benefits outweigh the risks for effects on bone, heart, cognition, GSM, sexual function, and mood.⁸

Family history of breast cancer. Observational evidence suggests that use of HT does not further alter the risk for breast cancer in women with a family history of breast cancer. Family history is one risk, among others, that should be assessed when counseling women regarding HT.

Women who are BRCA-positive without breast cancer. For women who are BRCA-positive (higher genetic risk of breast cancer,

primarily estrogen-receptor-negative), and have undergone surgical menopause (bilateral salpingo-oophorectomy), the benefits of estrogen to decrease health risks caused by premature loss of estrogen need to be considered on an individual basis.⁹ On the basis of limited observational studies, consider offering systemic HT until the median age of menopause (52 years) with longer use individualized.³

Survivors of endometrial and breast cancer with bothersome VMS. For women with prior estrogen-sensitive cancers, non-HTs should be considered first, particularly those agents studied through randomized controlled trials in this population and found to be effective. If systemic estrogen is considered for persistent symptoms after non-HT or complementary options have been unsuccessful, decisions should be made for compelling reasons and after detailed counseling, with shared decision making and in conjunction with their oncologist.³

Bothersome GSM. On the basis of limited observational data, there appears to be minimal to no demonstrated elevation in risk for recurrence of endometrial or breast cancer using low-dose vaginal estrogen,^{3,10} but decisions should be made in conjunction with an oncologist.

The importance of relaying the new guidelines to patients

It is important for clinicians to talk to women about their menopausal symptoms and their options for relief of symptoms or prevention of bone loss. Discussion should take into account age and time from menopause, include evidence-based information¹¹⁻¹³ about benefits and risks of different types of therapy, and employ shared decision making to choose the most appropriate therapy to maximize benefits and minimize risks for the individual woman.

Following the WHI initial release in 2002, both women and providers became fearful of HT and believed media hype and celebrities that compounded bioidentical HT was safer than FDA-approved HTs. However, compounded products lack safety and



For women who are BRCA-positive with no breast cancer, consider offering systemic HT until approximately age 52, with longer use individualized



efficacy data, are not monitored or regulated by the FDA, and have unique risks associated with compounding, including concerns

about sterility, impurities, and overdosing or underdosing, which could increase cancer risk.³

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The bottom-line takeaways for clinicians are:

- Hormone therapy for symptomatic menopausal women is safe and effective for those under age 60 or within 10 years of menopause.
- Identify the most appropriate type, dose, formulation, and duration of hormone therapy for an individual woman based on evidence.
- We want to remove the fear of using hormone therapy for healthy symptomatic women who are under age 60 or within 10 years of menopause.
- Age at initiation of hormone therapy matters.
- NAMS endorses use of FDA-approved hormone therapy over compounded therapies.

Physicians continue to underwhelmingly prescribe low-dose vaginal estrogen for GSM

Kingsberg SA, Krychman M, Graham S, Bernick B, Mirkin S. The Women's EMPOWER survey: identifying women's perceptions on vulvar and vaginal atrophy and its treatment. J Sex Med. 2017;14(3):413-424.

of women with GSM symptoms received treatment.

GSM is seriously underrecognized and undertreated.^{2,6,14} It has a major impact on women's lives—a silent epidemic affecting women's quality of life, sexual health, interpersonal relationships, and even physical health in terms of increased risk of urinary tract infections and urinary symptoms. Unfortunately, patients are reluctant to mention the problem to their clinicians, and they do not clearly recognize it as a medical condition that has available treatment options. Clinicians also rarely receive adequate training in the management of this condition and how to discuss it with their patients. Given busy schedules and time constraints, addressing this topic often falls through the cracks, representing a missed opportunity for helping our patients with safe and effective treatments. In a recent study by Kingsberg and colleagues, an astoundingly low percentage

Details of the study

The study authors evaluated women's perceptions of GSM and available treatment options. US women aged 45 and older who reported GSM symptoms were surveyed. Of 1,858 women with a median age of 58 (range, 45-90), the study authors found that 50% had never used any treatment; 25% used over-the-counter medications; 18% were former users of GSM treatments; and 7% currently used prescribed GSM therapies.

When GSM was discussed, women were more likely than their clinicians to initiate the conversation. The main reason for women not mentioning their symptoms was the perception that GSM symptoms were a natural and inevitable part of aging. Hormonal products were perceived by women as having several downsides, including risk of systemic absorption, messiness of local creams, and the need to reuse an applicator. Overall, clinicians recommended vaginal estrogen



Half of the surveyed 1,858 US women aged 45 and older never used any treatment for their reported GSM

therapy to only 23% and oral HTs to 18% of women.

The results of the study are consistent with results of earlier surveys of menopausal women. Although the survey included nearly 2,000 women, it has the potential for selection biases inherent to most Internet-based surveys. In addition, the respondents tended to be white and have higher socioeconomic status, with limited representation from other groups.

Calls for the current boxed warning to be revised

GSM is highly prevalent among postmenopausal women; the condition has adverse effects on quality of life and sexual health.^{2,8,14} Safe and effective treatments are available but are underutilized.^{1,8,15,16} A current boxed warning appears on low-dose vaginal estrogen—class labeling that appears on all medications in the class of estrogen or HT, regardless of dose or route of administration. These warnings are based on findings from the WHI and other studies of systemic estrogen or estrogen plus progestin, which demonstrated a complex pattern of risks and benefits of HT (including increased risk of venous thrombosis or pulmonary embolism, stroke, and breast cancer [with estrogen plus progestin]).

These findings, however, do not appear to be relevant to low-dose vaginal estrogen, given minimal if any systemic absorption and much lower blood levels of hormones than found with systemic HT. Blood levels of estradiol with low-dose vaginal estrogen remain in the normal postmenopausal range, compared to several-fold elevations in hormone levels with systemic HT.^{8,15,16} Additionally, observational studies of low-dose vaginal estrogen, as well as short-term randomized clinical trials, show no evidence of an increased risk of venous thromboembolic events, heart disease, stroke, breast cancer, or dementia—the listed possible adverse effects in the boxed warning. The current warning is based on extrapolating findings from systemic HT, which is inappropriate and not evidence-based for low-dose vaginal estrogen.¹⁵

The inappropriate boxed warning contributes to the problem of undertreatment of GSM in women by discouraging clinicians from prescribing the medication and dissuading patients from taking it even after purchase. Testimonials from many clinicians caring for these women have underscored that women will fill their prescription, but after seeing the boxed warning will often become alarmed and decide not to take the medication. Clinicians reported that patients often say at their next appointment: “No, I never took it. I got very scared when I saw the boxed warning.” As a result, clinicians often have to spend a great deal of time explaining the limitations of, and lack of evidence for, the boxed warning on low-dose vaginal estrogen.

Recommended label revisions

A modified label, without a boxed warning, would be safer for women because the key messages would not be obscured by the large amount of irrelevant information. Our Working Group recommended that the label explain that the listed risks were found in studies of systemic HT and their relevance to low-dose vaginal estrogen is unknown. The Group also recommended that warning text should be added in bold font to advise patients to seek medical attention if they have vaginal bleeding or spotting while taking the medication. In addition, patients who have a history of breast cancer or other hormone-sensitive cancer should discuss the use of the medication with their oncologist.

Status update on efforts to revise label.

A citizen’s petition was filed in the Spring of 2016, with signatures from more than



Unlike systemic HT, low-dose vaginal estrogen results in estradiol blood levels in the normal postmenopausal range

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

GSM continues to be underrecognized and undertreated, despite recent educational initiatives. Suboptimal communication between clinicians and patients, reluctance to prescribe available treatments, and product labeling that is not evidence based contribute to this problem. Ultimately, we hope that a modified label that better reflects the safety profile of treatment will facilitate the safe and effective treatment of GSM.



600 clinicians and patients and representatives of medical and professional organizations endorsing a more appropriate evidence-based

label for low-dose vaginal estrogen. The FDA is continuing to review and deliberate on these issues but has not yet made a final decision.

Did you read “Focus on treating genital atrophy symptoms” from Dr. Andrew Kaunitz from January 2017? Find it in the archive at obgmanagement.com

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