

When should a menopausal woman discontinue hormone therapy?

⬇ Although this question is common in clinical practice, the answer isn't clear-cut

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CASE After 3 years of HT, a patient asks whether it's time to quit

My menopausal patient is a 57-year-old woman with a body mass index (BMI) of 21 kg/m². Her mother, who also was slender, suffered a hip fracture at age 74.

When this patient was 53, approximately 8 months after her last menstrual period, she scheduled a problem visit to discuss bothersome hot flashes, which occurred primarily at night. These symptoms were associated with sleep disruption and irritability. At that problem visit, the patient and I discussed the benefits and risks of menopausal hormone therapy

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Dr. Pinkerton and Dr. Simon provided peer review and comments for Dr. Kaunitz's case study.

(HT), and she elected to initiate it, choosing transdermal estradiol using an 0.05-mg patch, combined with oral micronized progesterone 100-mg (one capsule) at bedtime. Two months later, she telephoned my office to report that she was experiencing only moderate relief of her symptoms. I increased the dose of estradiol to 0.075 mg. On her next well-woman visit, the patient remarked that her symptoms were largely resolved and said that she wished to continue the regimen.

Now, as she presents for her well-woman visit 3 years later, she asks how long she should continue the HT.

How would you counsel such a patient?

Although the duration of HT is still marked by controversy, clinicians often encounter the issue in practice. As the North American Menopause Society (NAMS) notes in a recent Practice Pearl and in its 2012 Position Statement on hormone therapy, the determination of the optimal duration of HT can be a challenge for clinicians and patients.^{1,2}

In this article, I discuss indications for HT and consider variables that may influence its duration. I also offer practical guidance on therapeutic options for women who elect to use HT for an extended duration.

Hot flashes can be a long-term concern

Moderate to severe vasomotor symptoms (VMS) are the most common indication for systemic combination estrogen-progestin or

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estrogen-only HT—and HT is the most effective treatment for VMS.²

Some experts have cautioned that “it remains prudent to keep the...duration of treatment short” or that HT “may serve a useful role in short-term symptom management.”^{3,4} However, for many menopausal women, VMS are a long-term concern. The Penn Ovarian Aging Study was conducted to estimate the duration of moderate-to-severe VMS and found a median duration of such symptoms of more than 10 years. In this landmark cohort study, the median duration of VMS, which began near the time of the menopausal transition, was almost 12 years.⁵

In a study of older menopausal women (mean age, 67 years; mean time since menopause, 19 years), 11.8% reported “clinically significant” hot flushes and “more than half of these women who complained of significant hot flushes at baseline continued to report bothersome symptoms after 3 years.”⁶

These observations underscore the fact that, in many women, short-term use (3–5 years) of HT will not be sufficient to control bothersome VMS.

Systemic HT also benefits bone

The standard daily dose of HT (eg, conjugated equine estrogens [CEE], 0.625 mg; micronized estradiol, 1.0 mg; or transdermal estradiol, 0.05 mg) for relief of VMS also prevents osteoporosis,² with many HT formulations approved for prevention of this condition. Randomized trial data from the Women’s Health Initiative (WHI) also have confirmed that a standard dose of HT prevents fractures in menopausal women.²

However, in menopausal women, doses of estrogen therapy substantially lower than those commonly used to treat VMS can still maintain or improve bone mineral density (BMD). For example, serum estradiol levels remain in the menopausal range during use of the weekly estradiol ultra-low-dose patch (0.014 mg).⁷ In a clinical trial of women (mean age, 66 years) with an intact uterus, use of this ultra-low-dose estradiol patch for 2 years without progestin did not increase the risk

of endometrial hyperplasia⁷—although this patch does appear to increase the incidence of endometrial proliferation.⁸ For this reason, periodic endometrial monitoring may be appropriate in women using the 0.014-mg estradiol patch over the long term, including vaginal ultrasound assessment of endometrial thickness. Package labeling for this patch recommends that women with an intact uterus be given a progestogen for 14 days every 6 to 12 months.⁹

Although the ultra-low-dose estradiol patch is approved for the prevention of osteoporosis, its efficacy in treating VMS is uncertain. For instance, in a study of this patch in women aged 60 to 80 years, with skeletal health and safety as the primary outcomes, 16% of participants reported VMS at baseline. The 0.014-mg estradiol patch did not reduce VMS more than placebo.¹⁰ However, in a trial of the 0.014-mg estradiol patch in which impact on VMS was the primary outcome, the ultra-low-dose patch did relieve VMS.¹¹ (The ultra-low-dose patch currently is not approved to treat VMS.) Low-dose CEE (0.3 mg, 0.45 mg) and low-dose oral estradiol (0.5 mg) have been found to be effective in the treatment of VMS.^{12,13}

Data on the risk of osteoporotic fractures among women using the ultra-low-dose estradiol patch are not available.

Use of HT to prevent osteoporosis is appropriate for women who have other indications for HT, such as VMS. For women using HT who no longer experience VMS, long-term use of HT for osteoporosis is controversial. However, it may be considered for women at elevated risk for osteoporosis when skeleton-specific treatments (eg, bisphosphonates) are not tolerated or when such women prefer not to use skeleton-specific therapy.

FDA package labeling for systemic HT indicates that, “When prescribing solely for the prevention of postmenopausal osteoporosis, therapy only should be considered for women at significant risk of osteoporosis, and non-estrogen medications should be carefully considered.”¹⁴

The NAMS 2012 Position Statement on HT states: “Provided that the woman is well



In the Penn Ovarian Aging Study, the median duration of menopausal vasomotor symptoms was almost 12 years

aware of the potential benefits and risks and has clinical supervision, extending [estrogen-progestin therapy] use with the lowest effective dose is acceptable under some circumstances, including 1) for the woman who has determined that the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop [estrogen-progestin therapy], and 2) for the woman at high risk of fracture for whom alternate therapies are not appropriate or cause unacceptable adverse effects.”²

A 2014 Practice Bulletin from the American College of Obstetricians and Gynecologists (ACOG) on the management of menopausal symptoms states: “The decision to continue HT should be individualized and be based on a woman’s symptoms and the risk-benefit ratio, regardless of age. Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, ACOG recommends against routine discontinuation of systemic estrogen at age 65. As with younger women, use of HT and estrogen therapy should be individualized based on each woman’s risk-benefit ratio and clinical presentation.”¹⁵

As I have detailed, doses of HT that are lower than those used to treat VMS can prevent loss of BMD. Accordingly, clinicians prescribing HT for the sole indication of osteoporosis prevention should use doses lower than those for standard HT. Moreover, clinicians prescribing HT specifically to prevent osteoporosis should recognize the elevated risk of breast cancer with estrogen-progestin therapy. Extended use of estrogen-only therapy is more appropriate for this indication.

While estrogen-only therapy is common in women following hysterectomy, ultra-low-dose estrogen therapy with regular endometrial monitoring also can be considered in women with an intact uterus.

Also be aware that BMD declines rapidly after discontinuation of HT (in contrast with bisphosphonates), so alternative agents to maintain BMD should be considered when HT is stopped.¹⁶

How safe is extended use of systemic HT?

The incidence of breast cancer and mortality from breast cancer increase after 3 to 5 years of estrogen-progestin therapy, and the risk of stroke remains elevated throughout use of combination as well as estrogen-only HT.² Women with an intact uterus who choose to extend the duration of combination therapy beyond 5 years for control of VMS or protection against osteoporosis, or both, need to be candidly counseled about these concerns. No increase in the risk of breast cancer was observed in the estrogen-only arm of the WHI randomized, clinical trial (mean duration of CEE therapy of 7.1 years).¹⁷

DR. SIMON *Not only was there no increase in the risk of breast cancer in the estrogen-only arm, but the therapy was associated with a decrease in risk that persisted even following discontinuation of the therapy.*

DR. PINKERTON *Yes, after 7 years of follow-up, women taking CEE (0.625 mg daily) had a reduction in the risk of breast cancer that translated into a decrease in mortality.¹⁷*

Long-term risks of oral estrogen

Among women who initiate HT at the time of menopause, long-term use does not appear to increase the risk of coronary heart disease (CHD), although follow-up in clinical trials has not extended beyond 7 years for estrogen-progestin therapy, and midlife may bring increases in a woman’s baseline cardiovascular risk.² However, in the WHI, women who initiated oral estrogen-only or estrogen-progestin therapy later in menopause experienced an increased risk of CHD,¹⁸ underscoring the need for caution and individualization in this patient population.

Oral HT increases the risk of venous thromboembolism (VTE) and stroke.² In addition, age is an independent risk factor for these two outcomes. Observational studies suggest that, in contrast with oral estrogen, transdermal HT does not increase the risk of VTE.^{19–24} Randomized trial data are lacking.



Be aware of the elevated risk of breast cancer with estrogen-progestin therapy when prescribing HT specifically to prevent osteoporosis

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Similarly, one observational study suggests that low-dose (≤ 0.05 mg) transdermal estradiol does not appear to increase the risk of stroke,²⁵ but, again, clinical trial data are unavailable.

Given these apparent safety advantages, transdermal estrogen therapy would appear to be preferable to oral estrogen in older, long-term users, a perspective supported by ACOG.²⁶

In regard to VTE, oral estradiol appears to be safer than CEE.²⁷ Accordingly, oral estradiol may be preferable for older long-term users who don't tolerate transdermal estradiol due to local skin reactions or costs. Oral estradiol also is less expensive than CEE.

What to expect when your patient discontinues systemic HT

VMS may recur in as many as 50% of women after they discontinue HT. The likelihood of recurring VMS does not appear to vary between abrupt and tapered discontinuation.²

Some HT users may be reluctant to reduce their dose or discontinue HT, particularly those who experienced severe VMS originally. In my clinical experience, many of these women are receptive to a trial of lower-dose HT, especially when I advise them that they can resume their original (higher) dose should bothersome VMS recur.

DR. PINKERTON *I use a similar approach with my patients, advising them to try 3 months off HT with the understanding that they can resume the therapy if they develop bothersome symptoms.*

Individualized assessment of HT benefits and risks and shared decision-making play important roles in the management of these patients. As the dose of HT declines, or systemic HT is discontinued, symptoms of genital atrophy may become more prominent and, in the absence of indications for systemic HT (bothersome VMS or prevention of osteoporosis), may best be addressed with vaginal estrogen therapy or ospemifene.

Extended use of vaginal estrogen

Unlike VMS, untreated genital atrophy may continue to progress as women age,

sometimes necessitating use of vaginal estrogen. Because the clinical trials that served as the basis for FDA approval of vaginal estrogen formulations did not find an elevated risk of endometrial hyperplasia, routine use of a progestin to prevent endometrial proliferation in women with an intact uterus is not recommended.²⁸ However, these trials were too limited in duration to assure long-term endometrial safety. All postmenopausal women using vaginal ET should be advised to report any vaginal bleeding, and that bleeding should be evaluated appropriately.

DR. PINKERTON *I recommend transvaginal ultrasound and endometrial biopsy for women using vaginal estrogen who report spotting or bleeding.*

Although low-dose local or vaginal estrogen therapy has not been studied in clinical trials beyond 1 year, it is thought to carry significantly fewer risks than systemic HT.²⁸ Several studies have confirmed that serum estrogen levels remain in the postmenopausal range in women using low-dose vaginal estrogen, specifically the 3-month estradiol ring (2 mg) or twice-weekly estradiol tablets (10 μ g).²⁸

Besides relieving vaginal dryness and dyspareunia, low-dose vaginal estrogen also may improve overactive bladder and reduce the incidence of recurrent urinary tract infection.^{29,30}

CASE Resolved

The 57-year-old patient has been essentially symptom-free for the past 3 years using an estradiol patch (0.075 mg) with progesterone (100 mg nightly). Now she asks how long she should continue HT, and I explain that the duration of bothersome VMS is different in each woman. I also counsel her that hot flashes do resolve over time in almost all women. When she asks how likely it is that bothersome VMS will recur if she simply stops HT, I explain that bothersome symptoms often last 10 years or longer, and I remind her that her VMS began some 4 years earlier.



The likelihood that vasomotor symptoms will recur after discontinuation of HT does not appear to vary between abrupt and tapered discontinuation

I also briefly review HT benefits (treatment of VMS as well as prevention of vulvovaginal atrophy and osteoporosis) and risks (small increased risk of breast cancer and stroke). I suggest a reduction in her HT dose as a reasonable method to determine her ongoing need for HT, telling her that she should know within about 1 month how she feels on the lower dose (0.05-mg patch). I also advise her to call my office if bothersome VMS recur on the lower dose so that I can increase the dose back to its original level.

After her estradiol dose is reduced, the patient reports only minimal VMS, and she opts to continue the estradiol patch (0.05 mg) with nightly progesterone (100 mg) for another 2 years.

At age 59, during her well-woman visit, she decides to lower the estradiol further, transitioning to a 0.0375-mg patch but maintaining the nightly progesterone (100 mg). She reports no VMS on this new regimen.

At age 61, because of her maternal history of osteoporosis and her own low BMI, the patient undergoes BMD assessment with dual x-ray absorptiometry (DXA). In average-risk women, NAMS recommends that BMD assessment be performed at age 65.³¹ The results of BMD assessment are normal.

After further discussion, the patient agrees to an even lower dose of estradiol, switching to an 0.025-mg patch, with progesterone (100 mg nightly) administered for 2 weeks in every 3-month interval. She reports no VMS or vaginal bleeding on this lower-dose HT regimen.

After 12 months on this new regimen, the patient undergoes vaginal sonography, revealing an endometrial thickness of 3 mm. She continues this regimen, including annual vaginal ultrasound assessment of the endometrium, without problems until her well-woman visit at age 65.

At that visit, I explain that discontinuation of HT is unlikely to trigger recurred VMS but may cause her to lose BMD rapidly for several years, and may also result in unpleasant symptoms from vulvovaginal atrophy including sexual discomfort. She decides to switch to an 0.014-mg estradiol patch without progesterone, and to undergo ultrasound

assessment of her endometrium every 1 to 2 years.

Bottom line: Individualize the duration of HT

Although published data on extended use of HT are few, many clinicians caring for menopausal women are asked to make a recommendation. Because extended use of estrogen-progestin HT increases the risk of breast cancer, estrogen-only HT has a more favorable benefit-risk ratio. If a patient uses estrogen-progestin HT for an extended duration, periodic discussions about the elevated risk of breast cancer are appropriate.

DR. PINKERTON

The risk of breast cancer associated with extended use of estrogen-progestin HT likely is reduced if lower doses are given. Overall, however, the risk appears to be both dose- and duration-dependent.

We lack randomized trial data on CHD and other risks in women who begin HT at the time of menopause and continue it for decades. In older women who use HT for an extended duration, transdermal estrogen may be safer in regard to the risk of VTE and stroke.

As the systemic estrogen dose is lowered, it is possible to reduce the dose of the progestin (the sole function of which is to protect the endometrium from estrogen stimulation). Intermittent dosing can be used, although we lack long-term safety data, and periodic endometrial evaluation should be considered.

Remember also that, with intermittent or daily dosing of a progestin, you are relying on the patient to take this medication to protect the endometrium.

Extended use of low-dose vaginal estrogen HT may be necessary to treat symptoms of vulvovaginal atrophy, which tend to worsen over time. Administration of a progestin is not currently recommended with use of vaginal estrogen, but long-term use may increase the risk of endometrial stimulation. ❌



Because extended use of estrogen-progestin HT increases the risk of breast cancer, estrogen-only HT has a more favorable benefit-risk ratio

Disclosures

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Dr. Simon reports being a consultant to or on the advisory boards of Abbott Laboratories, Amgen, Ascend Therapeutics, Depomed, Lelo, MD Therapeutics, Meda Pharmaceuticals, Merck, Noven, Novo Nordisk, Pfizer, Shionogi, Shippan Point Advisors LLC, Sprout Pharmaceuticals, Teva, Warner Chilcott, and Watson. He also reports receiving (currently or in the past year) grant/research support from Novo Nordisk, Palatin Technologies, Teva, and Warner Chilcott. He reports serving on the speakers bureaus of Noven, Novo Nordisk, Teva, and Warner Chilcott. Dr. Simon was the Chief Medical Officer for Sprout Pharmaceuticals until April 1, 2013.

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