NAMS Practice Pearl

Extended Duration Use of Menopausal Hormone Therapy

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Although providing guidance to patients regarding duration of hormone therapy represents a topic surrounded by controversy, clinicians often encounter this issue in practice. As pointed out in the NAMS 2012 Hormone Therapy (HT) Position Statement, determining the optimal duration of HT is challenging both for clinicians and for patients. This Practice Pearl addresses clinical situations for which long-term HT might be appropriate and provides practical guidance regarding prudent therapeutic choices for women using HT for an extended duration.

Use of Systemic HT to Treat Vasomotor Symptoms (VMS). Moderate to severe VMS represent the most common indication for systemic combination estrogen-progestin (EPT) or estrogen-only (ET) HT, and HT represents the most effective treatment for VMS.[1] Some experts' recommendations regarding HT duration of use 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."[2,3] However, VMS persist for longer than many have assumed. For instance, The Penn Ovarian Aging Study was conducted specifically to estimate the duration of moderate-to-severe VMS and found that median duration of such symptoms was 10.2 years. In this landmark cohort study, the median duration of VMS that started near the entry into the menopause transition was greater than 11.57 years.[4] In a population of older postmenopausal women (mean age and years since menopause 67 and 19 years, respectively), 11.8% of women reported "clinically significant" hot flushes and "…more than half of these women who complained of significant hot flushes at baseline continued to report persistently bothersome symptoms after 3 years."[5] These observations underscore that in many women, short-term (3-5 years) use of HT will not be sufficient to control bothersome VMS.

Use of Systemic HT to Prevent Osteoporosis. Standard dose (eg, conjugated equine estrogens 0.625 mg, micronized estradiol 1.0 mg or transdermal estradiol 0.05 mg) HT prevents osteoporosis,[1] with many HT formulations approved for the prevention of this condition. Randomized trial data from the Women's Health Initiative (WHI) have likewise clarified that this dose of HT also prevents fractures.[1] Very low doses of ET can maintain or improve bone mineral density (BMD). Use of the weekly estradiol 0.14 mg patch is associated with serum estradiol levels that remain in the menopausal range.[6] In women mean age 66 with an intact uterus, use of this ultra-low dose estrogen patch for two years without progestin was not found to increase the risk of endometrial hyperplasia.[6] However, use of this patch does appear to increase the incidence of endometrial proliferation.[7] Accordingly, periodic endometrial monitoring may be appropriate in women using the 0.14 mg estradiol patch long-term. Package labeling for the estradiol 0.014 patch recommends that women who have a uterus be given a progestogen for 14 days every 6-12 months.[8]

Although the ultra-low dose estradiol patch is approved to prevent osteoporosis, this formulation was not shown to reduce VMS in the largely asymptomatic study population (women age 60-80)[9] and is not approved to treat VMS. In one other study, however, the ultra-low-dose patch did relieve VMS.[10] Data assessing the risks of osteoporotic fractures in women using the ultra-low dose estradiol 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 prevention generally is not recommended, though may be considered for a woman at high risk for fracture when alternative treatments are not tolerated. The FDA's package labeling for systemic hormone therapy indicates: "When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered."[11] NAMS 2012 HT Position Statement indicates: "Provided that the woman is well aware of the potential benefits and risks and has clinical supervision, extending EPT 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 EPT, and (2) for the woman at high risk of fracture for whom alternate therapies are not appropriate or cause unacceptable adverse effects."[1] As detailed above, the doses of HT lower than used to treat VMS can prevent loss of BMD. Accordingly, clinicians prescribing HT for the sole indication of osteoporosis prevention should use lower than standard HT doses. Likewise, clinicians who are prescribing HT to prevent osteoporosis should recognize that given the elevated risk of breast cancer with EPT, extended use of HT to prevent osteoporosis is more appropriate in selected high-risk women post-hysterectomy than in women with an intact uterus. Clinicians should also be aware that, in contrast with bisphosphonates, loss of BMD occurs rapidly after women discontinue HT, and alternative agents to maintain BMD should be considered.[12] Finally, clinicians should also be aware that most clinical guidelines for osteoporosis do not recommend prescription therapy for prevention. Ensuring adequate intake of vitamin D and calcium represents preventive measures. Prescription therapy is indicated for a diagnosis of osteoporosis (by DXA or by history of fracture) or those with high risk of fracture, such as determined by FRAX score.[12]

Extended Duration Use of Systemic HT: Safety Concerns. Breast cancer and mortality from breast cancer increase with more than 3 to 5 years of EPT use, and the elevated risk of stroke persists throughout the duration of therapy.[1] Accordingly, women with an intact uterus who choose to extend duration of EPT use beyond 5 years for control of VMS or protection against osteoporosis need to be candidly counseled regarding these concerns. No elevation in risk of breast cancer was observed in the ET arm of the WHI randomized clinical trial (mean duration of conjugated equine estrogen [CEE] use 7.1 years). When use of ET (largely CEE) was extended beyond 15 years in the observational Nurse's Health Study, an increased risk of breast cancer was observed. In the observational Million Women Study, among current users of estrogen-only formulations (the majority of which were estradiol), there was little or no increase in risk of breast cancer if use began 5 years or more after menopause but risk was increased in women who started ET within 5 years after menopause. Whether the difference between these findings and the WHI ET arm reflects differences in the timing of ET initiation, the types of ET, study populations, increased mammographic surveillance of women using HT, or other factors not controlled for in an observational study has not been determined.[1]

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), though follow up in clinical trials has not extended beyond 7 years for EPT, and midlife may bring increases in baseline cardiovascular risks.[1] However, women in their 70s who initiate oral ET or EPT, particularly those with VMS, experience an increased risk of CHD,[13] underscoring the need for caution and individualization in this patient population. Oral HT increases the risk of venous thromboembolism (VTE) and stroke. (NAMS) Age also represents an independent risk factor for these two outcomes. In contrast with oral ET, transdermal HT does not appear to increase risk for VTE in observational studies, but randomized trial evidence is lacking.[14-19] Likewise one observational study suggests that low dose ($\leq$0.05 mg estradiol) transdermal estradiol does not appear to increase the risk of stroke,[20] but trial data are again unavailable. Transdermal ET may have safety advantages over oral ET in long-term users. However, higher endogenous levels of estrogen have been associated with increased risk of stroke in women 65 and older.[21]

Discontinuation of Systemic HT. VMS may recur in approximately one half of women discontinuing HT. The likelihood of subsequently experiencing VMS does not appear to differ whether the dose is tapered or HT is abruptly discontinued.[1] Some HT users, particularly those who experienced severe VMS previously, may be reluctant to reduce their dose or discontinue HT. In my clinical experience, many women reluctant to discontinue HT may be receptive to a trial of lower dose HT, particularly if they have an understanding with their clinician that they will be able to resume their original (higher) HT dose should bothersome VMS reoccur. Individualized assessment of HT benefits and risks and shared decision-making play important roles in the management of such 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), are best addressed with vaginal ET.

Extended Use of Vaginal Estrogen. Although low dose local/vaginal ET has not been studied in clinical trials for longer than one year, it is thought to carry significantly fewer risks than systemic HT. Several studies have confirmed that serum E levels in women using low dose vaginal ET remain in the postmenopausal range. In addition to treating vaginal dryness and dyspareunia, low dose vaginal estrogen may also improve overactive bladder and reduce the incidence of recurrent urinary tract infections.[22.23] In contrast with VMS, untreated genital atrophy may continue to progress as women age, sometimes necessitating extended use of vaginal ET. The registration trials for vaginal ET have not found an elevated risk of endometrial hyperplasia, and routine use of progestin to prevent endometrial proliferation in women with an intact uterus using vaginal ET is generally not recommended.[1] However, these trials have been too short to assure long-term endometrial safety. All postmenopausal women using vaginal ET should be advised to report any vaginal bleeding, and this should be thoroughly evaluated.

Summary:

Systemic HT. Although providing guidance to women regarding duration of HT remains controversial, clinicians caring for menopausal women routinely encounter this issue in practice. Because extended use of EPT increases the risk of breast cancer, the benefit-risk ratio for extended use is less favorable than for ET. In women who seek use of EPT for an extended duration, periodic discussions between the clinician and woman regarding the elevated risk of breast cancer associated with long-term use of EPT are appropriate. Although women age 70 or older who initiate oral HT experience an elevated CHD risk, randomized trial data does not address CHD or other risks in women

who begin HT at the time of menopause and continue use for decades. In older women using HT for an extended duration, transdermal estrogen may be safer with respect to risk of VTE and stroke.

Vaginal ET. Extended use of low dose vaginal ET may be necessary to treat symptoms of vulvovaginal atrophy (VVA) as, unlike vasomotor symptoms, symptoms of VVA often worsen with time since menopause. Women using long term low dose local ET should be advised to report any vaginal bleeding and this should be thoroughly evaluated.

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Disclosures

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