UPDATE Menopause

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IN THIS ARTICLE

Coverage and expert comment on new insights on HT and Alzheimer disease risk, HT route and sexuality outcomes, mortality in WHI participants, and USPSTF recommendations that may adversely impact HT prescribing for menopausal symptoms

Our knowledge regarding the benefits and risks of systemic menopausal hormone therapy (HT) has continued to evolve since the 2002 publication of the initial findings of the Women's Health Initiative (WHI). In late 2017, the US Preventive Services Task Force (USPSTF) issued its recommendation against the use of menopausal HT for the prevention of chronic conditions. In this Menopause Update, Dr. JoAnn Manson, Dr. JoAnn Pinkerton, and I detail why we do not support the Task Force's recommendation. In a sidebar discussion, Dr. Manson also reviews the results of 2 WHI HT trials, published in September 2017, that analyzed mortality in trial participants over an 18-year follow-up.

In addition, I summarize an observational study that assessed the association of HT and Alzheimer disease (AD) as well as a clinical trial that compared the impact of oral versus transdermal estrogen on sexuality in recently menopausal women.

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Patrick Duff, MD
July 2018

What's the impact of long-term use of systemic HT on Alzheimer disease risk?

Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study. Neurology. 2017;88(11): 1062–1068.

Data from the WHI HT randomized trials have clarified that initiation of oral HT among women aged 65 and older increases the risk of cognitive decline. By contrast, an analysis of younger WHI participants found that oral HT had no impact on cognitive function. Recently, Imtiaz and colleagues conducted a prospective cohort study of postmenopausal HT and AD in women residing in a Finnish county, with 25 years of follow-up. A diagnosis of AD was based on administrative health records and use of medications prescribed specifically to treat dementia. Use of systemic HT was identified via self-report. Overall, among more than 8,000 women followed, 227 cases of AD (mean age, 72 years) were identified.

In an analysis that controlled for factors including age, body mass index, alcohol use, smoking, physical activity, occupation status, and parity, up to 5 years of HT use was not associated with a risk of being diagnosed with AD. Five to 10 years of HT use was associated with a hazard ratio (HR) of 0.89, an 11% risk reduction that did not achieve statistical significance. By contrast, more than 10 years' use of systemic HT was associated with an HR of 0.53, a statistically significant 47% reduction in risk of AD.[1]

Other studies found conflicting results

Three large randomized trials found that HT initiated early in menopause and continued for less than 7 years had no impact on cognitive function.[2-4] The Cache County (Utah) long-term prospective cohort study, however, found that HT started early in menopause and continued for 10 years or longer was associated with a significant reduction in risk of AD.[5]

Of note are results from the 2017 report of 18-year cumulative mortality among WHI participants (see the box on page 30). In that study, mortality from AD and other dementia was lower among participants who were randomly assigned to treatment with estrogen alone versus placebo (HR, 0.74; 95% confidence interval [CI], 0.59–0.94). With estrogen-progestin therapy, the HR was 0.93 (95% CI, 0.77–1.11), and the pooled HR for the 2 trials was 0.85 (95% CI, 0.74–0.98).[6]

NAMS guidance

The North American Menopause Society (NAMS) HT position statement recommends that prevention of dementia should not be considered an indication for HT use since definitive data are not available.[7] The statement indicates also that estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause and taken until the average age of menopause to prevent health risks seen with early loss of hormones.

FAST TRACK

In more than 8,000 women, use of systemic HT for 10 or more years was associated with a statistically significant 47% reduction in risk of AD

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Definitive data from long-term randomized clinical trials are not likely to become available. Observational trials continue to have methodologic issues, such as "healthy user bias," but the studies are reassuring that initiating HT close to menopause does not increase the risk of dementia. The long-term Finnish study by Imtiaz and colleagues and the Cache County study provide tentative observational data support for a "critical window" hypothesis, leaving open the possibility that initiating systemic HT soon after menopause onset and continuing it long term may reduce the risk of AD. Discussion is needed on individual patient characteristics, potential benefits and risks, and ongoing assessment over time.

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18 Years of WHI follow-up data on menopausal HT and all-cause mortality provide reassurance

JoAnn E. Manson, MD, DrPH, NCMP

A new analysis from the Women's Health Initiative (WHI) randomized trials examined all-cause and cause-specific mortality during the intervention and postintervention follow-up periods.[1] We followed more than 27,000 postmenopausal women aged 50 to 79 (mean age, 63) who were recruited to 2 randomized WHI trials of HT between 1993 and 1998. The trials continued until 2002 for the estrogen-progestin trial and to 2004 for the estrogen-alone trial. The trials ran for 5 to 7 years' duration, with post-stopping follow-up for an additional 10 to 12 years (total cumulative follow-up of 18 years).

The participants were randomly assigned to receive active treatment or placebo. The interventions were conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) versus placebo for women with an intact uterus and CEE alone versus placebo for women who had a hysterectomy.

All-cause mortality did not increase with HT use

The primary outcome measure was all-cause mortality in the 2 pooled trials and in each trial individually. We found that there was no link between HT and all-cause mortality in the overall study population (ages 50–79) in either trial. However, there was a trend toward lower all-cause mortality among the younger women in both trials. In women aged 50 to 59, there was a statistically significant 31% lower risk of mortality in the pooled trials among women taking active HT compared with those taking placebo, but no reduction in mortality with HT among older women (*P* for trend by age = .01).

Notably, all-cause mortality provides a critically important summary measure for interventions such as HT that have a complex matrix of benefits and risks. We know that HT has a number of benefits in menopausal women. It reduces hot flashes and other menopausal symptoms. It lowers the risk of hip fracture, other types of bone fractures, and type 2 diabetes. However, HT increases the risk of venous thrombosis, stroke, and some forms of cancer.

A summary measure that assesses the net effect of a medication on serious and life-threatening health outcomes is very important. As such, all-cause mortality is the ultimate bottom line for the balance of benefits and risks. This speaks to why we conducted the mortality analysis—WHI is the largest randomized trial of HT with long-term follow-up, allowing detailed analyses by age group. Although there have been previous reports on individual health outcomes in the WHI trials, no previous report had specifically focused on all-cause and cause-specific mortality with HT, stratified by age group, over long-term follow-up.

Hopefully the results of this study will alleviate some of the anxiety associated with HT because, as mentioned, there was no increase in overall total mortality or specific major causes of death. In addition, the younger women had a trend toward benefit for all-cause mortality.

We think that these findings support the recommendations from The North American Menopause Society and other professional societies that endorse the use of HT for managing bothersome menopausal symptoms, especially when started in early menopause. These results should be reassuring that there is no increase in mortality with HT use. Although these findings do not support prescribing HT for the express purpose

Oral vs transdermal estrogen therapy: Is one preferable regarding sexuality?

Taylor HS, Tal A, Pal L, et al. Effects of oral vs transdermal estrogen therapy on sexual function in early post menopause: ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). JAMA Intern Med. 2017;177(10):1471–1479.

If route of administration of systemic HT influences sexuality outcomes in menopausal women, this would inform how we counsel our patients regarding HT.

Recently, Taylor and colleagues conducted a randomized clinical trial to examine the effects of HT's route of administration on sexual function.[8] The 4-year Kronos Early Estrogen Prevention Study (KEEPS) ancillary sexual study randomly assigned 670 recently menopausal women to 0.45 mg of oral conjugated equine estrogens (CEE), an 0.05-mg estradiol transdermal patch, or placebo (with oral micronized progesterone for those on active treatment). The participants were aged 42 to 58 years and were within

of trying to prevent cardiovascular disease, dementia, or other chronic diseases (due to some potential risks), they do support an important role of HT for management of bothersome hot flashes, especially in early menopause.

Cause-specific mortality

Regarding cause-specific mortality and HT use, we looked in detail at deaths from cardiovascular causes, cancer, dementia, and other major illness. Overall, we observed no increase or decrease in cardiovascular or cancer deaths. In the estrogen-alone trial, there was a surprising finding of a 26% reduction in dementia deaths. In the estrogen-progestin trial, the results were neutral for dementia deaths.

Overall, the cause-specific mortality results were neutral. This is surprising because even for total cancer deaths there was no increase or decrease, despite a great deal of anxiety about cancer risk with HT. It appears that for cancer, HT has complex effects: it increases some types of cancer, such as breast cancer, and decreases others, such as endometrial cancer (in the estrogen-progestin group), and possibly colorectal cancer. Moreover, CEE alone was associated with a reduction in breast cancer mortality, but it remains unclear if this applies to other formulations. HT's net effect on total cancer mortality was neutral in both trials, that is, no increase or decrease.

Cautions and takeaways

We need to keep in mind that in current clinical practice, lower doses and different formulations and routes of administration of HT are now often used, including transdermal estradiol patches, gels, sprays, and micronized progesterone. These formulations, and the lower doses, may have an even more favorable benefit-risk profile. We need additional research on the long-term benefits and risks of these newer formulations and lower dosages.

Generally, these findings from the WHI trials indicate that for women who have significant hot flashes, night sweats, or other bothersome menopausal symptoms, it's important to discuss their symptoms with their health care provider and understand that hormone therapy may be an option for them. If it's not an option, many other treatments are available, including nonhormonal prescription medications, nonprescription medications, and behavioral approaches.

These findings should alleviate some fear about HT use, especially in younger women who have an overall favorable trend in terms of all-cause mortality with treatment, plus a much lower absolute risk of adverse events than older women. In a woman in early menopause who has bothersome hot flashes or other symptoms that disrupt her sleep or impair her quality of life, it's likely that the benefits of HT will outweigh the risks.

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36 months from their last menstrual period.

Participants were evaluated using the Female Sexual Function Inventory (FSFI) questionnaire, which assessed desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI is scored using a point range of 0 to 36. A higher FSFI score indicates better sexual function. An FSFI score less than 26.55 depicts low sexual function (LSF).

Transdermal estrogen improved sexual function scores

Treatment with oral CEE was associated with no significant change in FSFI score compared with placebo, although benefits were seen for lubrication. By contrast, estrogen patch use improved the FSFI score (mean improvement, 2.6). Although improvement in FSFI score with transdermal estrogen was limited to participants with baseline LSF, most participants in fact had LSF at baseline.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Oral estrogen increases the liver's production of sex hormone–binding globulin, resulting in lower free (bioavailable) testosterone. Transdermal estrogen does not produce this effect. Accordingly, sexuality concerns may represent a reason to prefer the use of transdermal as opposed to oral estrogen.

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The USPSTF recommendation against menopausal HT use for prevention of chronic conditions: Guidance that may confuse—and mislead

US Preventive Services Task Force; Grossman DC, Curry SJ, Owens DK, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. JAMA. 2017;318(22):2224–2233.

FAST TRACK

We are concerned that the USPSTF recommendation will be misconstrued as suggesting that the use of HT is not appropriate for any indication, including bothersome menopausal symptoms

In late 2017, the USPSTF issued its recommendation against the use of menopausal HT for prevention of chronic conditions.[9] We are concerned that this recommendation will be misconstrued as suggesting that the use of HT is not appropriate for any indication, including treatment of bothersome menopausal symptoms.

Although the Task Force's report briefly indicated that the guidance does not refer to HT use for treatment of symptoms, this important disclaimer likely will be overlooked or ignored by many readers. The result may be increased uncertainty and anxiety in decision making regarding HT use. Thus, we might see a further decline in the proportion of menopausal women who are prescribed appropriate treatment for symptoms that impair quality of life.

HT use improves menopausal symptoms

According to the 2017 NAMS Position Statement, for symptomatic women in early menopause (that is, younger than age 60 or within 10 years of menopause onset) and free of contraindications to treatment, use of systemic HT is appropriate.[7] Currently, clinicians are reluctant to prescribe HT, and women are apprehensive regarding its use.[10] Unfortunately, the USPSTF guidance may further discourage appropriate treatment of menopausal symptoms.

Findings from randomized clinical trials, as well as preclinical, clinical, and epidemiologic studies, clarify the favorable benefit-risk profile for HT use by recently menopausal women with bothersome vasomotor and related menopausal symptoms.[7,10–12]

Notably, the USPSTF guidance does not address women with premature or early menopause, those with persistent (long-duration) vasomotor symptoms, or women at increased risk for osteoporosis and related fractures. Furthermore, the prevalent and undertreated condition, genitourinary syndrome of menopause, deserves but does not receive attention. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In recent decades, our understanding regarding HT's benefits and risks has advanced substantially. Guidance for clinicians and women should reflect this evolution and underscore the individualization and shared decision making that facilitates appropriate decisions regarding the use of HT.

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