Menopausal Hormone Therapy for Prevention of Chronic Conditions
When Is Enough, Enough?

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Over the past 2 decades, the US Preventive Services Task Force (USPSTF) has issued 5 updates to its recommendation on menopausal hormone therapy (MHT), each time recommending against use of estrogen with or without a progestin for prevention of chronic conditions such as coronary heart disease (CHD). The first of these appeared in 2002, shortly after the first Women’s Health Initiative (WHI) trial enrolling more than 16,000 US women aged 50 to 79 years from 40 clinical centers reported an unfavorable overall benefit-risk ratio of postmenopausal estrogen with progesterin for primary prevention of chronic diseases, followed by another update in 2005 after the WHI estrogen-only trial enrolling more than 10,000 additional women drew similar conclusions for unopposed estrogen. The next was in 2012, after findings from longer-term follow-up and subgroup analyses from the WHI and other smaller trials supported the same conclusions. In 2017, the task force reissued its recommendation, again based on substantially the same evidence.

Now in 2022, after additional review of only 2 additional modest-sized trials as well as ancillary analyses of previous trials, the USPSTF has, for the fifth time, reiterated its guideline. After all this time, some may wonder why a repeat statement of this same recommendation is necessary. Isn’t enough, enough? Are there still clinicians who believe, despite the preponderance of evidence to the contrary, that MHT offers a net preventive benefit for postmenopausal persons? Do any important questions about MHT as a preventive intervention remain?

Arguably not. Some menopausal women and their clinicians continue to ask whether MHT may offer preventive benefits in younger postmenopausal patients, even if the net harms outweighed benefits for older women such as those enrolled in the WHI and similar trials. Most of these persistent questions center on the potential implications of timing of MHT, namely, whether the use of hormones in the first few years after menopause may offer beneficial preventive effects, even if continued use more than 5 or 10 years after menopause may result in net harm. But as the updated review of evidence supporting the 2022 USPSTF recommendation update indicates, there is little rigorous evidence to support this timing hypothesis. Women in the WHI trials who were aged 50 to 59 years did not have a statistically significant increased risk of CHD events (hazard ratio, 0.93 [95% CI, 0.65-1.33]) or stroke (hazard ratio, 1.13 [95% CI, 0.73-1.76]), but the numbers of these events in this subgroup of younger women were small, and no statistically significant differences in event rates by age were detected (P values for trend, 0.16 to 0.62). The 2 most recent trials that were added to the USPSTF evidence base, focusing primarily on the question of cognitive effects of MHT, were modest in size compared with the WHI, focused on surrogate end points rather than clinical events, and have yielded inconsistent findings. And for other conditions such as cancer, analyses of WHI data suggest that use of estrogen worsens cancer risk when initiated in the early rather than later postmenopausal years.

Even if new and robust evidence were to emerge that MHT offers a net preventive benefit when used exclusively within a short period after menopause, the medical community would still be in a quandary. How could clinicians and patients navigate use of an intervention that might initially offer protection against CHD only to reverse its effects at some uncertain (and probably impossible to precisely identify) future time? No precedent exists for starting a preventive medication in a large cross-section of the general population with the expectation of discontinuing it before its effects change diametrically to worsen the same health problems it was designed to prevent.

At the same time, it is important to recognize that the USPSTF, faithful to its mandate, has focused its recommendation on use of MHT for chronic disease prevention, not for treatment of symptoms of menopause. And yet its recommendations, along with the study results on which they are based, have made many women and their clinicians reluctant to consider MHT for treatment of menopausal symptoms. These include vasomotor symptoms (hot flashes and night sweats), which affect up to three-fourths of US menopausal women, persist for more than 10 years in up to 10% of women, and have detrimental effects on sleep, day-to-day activities, mood, and well-being. Despite the efforts of the USPSTF to draw a clear distinction between MHT for prevention vs symptom management, many patients and clinicians conflate these 2 different indications. The notion that “the net harms of MHT outweigh the benefits,” originally intended to explain the limitations of MHT for routine prevention, is now widely adopted as a rationale for forgoing MHT for symptomatic treatment.

For prevention, a pillar of the USPSTF recommendation is that for major chronic conditions for which MHT does offer benefits (such as prevention of osteoporosis), there are effective and safe alternatives (such as bisphosphonates). But for menopausal symptoms like hot flashes and night sweats, nonhormonal treatments that are as efficacious as MHT have not yet been identified. Furthermore, the approach to weighing risks should differ when MHT is used for symptom relief in acutely afflicted individuals as opposed to disease prevention.
in healthy, asymptomatic people. Clinicians routinely prescribe many medications for symptomatic relief in midlife and older adults that carry known risks (eg, nonsteroidal anti-inflammatory drugs, migraine medications, muscle relaxants), and patients are willing to take these risks in exchange for effective symptom relief.

Even for younger, severely symptomatic menopausal patients, many clinicians now preferentially recommend non-hormonal medications such as selective serotonin reuptake inhibitors, gabapentin, and clonidine for vasomotor symptoms on the grounds that they offer better long-term health outcomes, whereas a more accurate statement would be that they have undergone much less robust or long-term scrutiny for potential adverse effects. These alternate medications have their own immediate adverse effects as well as potential pathways for worsening long-term adverse health outcomes; however, unlike MHT, none have been the subject of controlled trials like the WHI in which many thousands of women have been followed up for more than a decade to evaluate the extended, multisystem consequences.

New and expensive medications are under review by the US Food and Drug Administration (FDA) and will likely be marketed to symptomatic menopausal persons concerned about the dangers of using MHT. Efficacy and safety of these drugs are often based on studies with only 12 weeks of FDA-mandated follow-up. For symptomatic patients in the early postmenopausal years, it is arguably problematic to avoid MHT and favor potentially less effective treatments, when the longer-term implications of those treatments for health have not been evaluated. Alternately, growing numbers of menopausal people are using over-the-counter herbal products, vitamins, and supplements for symptom management and general menopausal “wellness,” although many of these offer unclear benefit for even short-term symptom control and exist in a near-complete evidence void for either long-term benefits or long-term harms for health.14

With this most recent update of the USPSTF guidelines, the scientific and medical community should let go of the past. Instead of investing additional resources into trying to parse out subsets of menopausal patients who may derive some preventive benefit from MHT for a limited amount of time, research should focus on developing more thoughtful guidance for individual decision-making about MHT for menopausal symptoms and conducting more rigorous and extended follow-up of other medications used to treat menopausal symptoms. Strategies are also needed for starting MHT for symptom management in early menopause but then weaning down therapy when the absolute risks of other chronic diseases affected by therapy are known to increase.

For the fifth time, the USPSTF confirms that postmenopausal persons should not be encouraged to use MHT on the grounds that it will preserve their long-term health and functioning. No longer should patients use hormones to stave off the multidimensional consequences of natural menopause or aging.15 But neither should they be frightened away from considering using MHT for distressing symptoms that emerge in midlife or exist in a near-complete evidence void for either long-term benefits or long-term harms for health. Thus, this is an opportunity to clear the field of other medications used to treat menopausal symptoms, vitamins, and supplements for symptom management, and focus on developing more thoughtful guidance for in-clinic referral when MHT is needed. The USPSTF guidelines acknowledge that, despite medical risks,16 menopausal hormone therapy drives prolonged use of other medications used to treat menopausal symptoms, vitamins, and supplements for symptom management. As such, this takes on particular urgency in our current climate.

REFERENCES

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