A review of menopausal hormone therapy: recalibrating the balance of benefit and risk

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ABSTRACT

While menopausal hormone therapy (MHT) was initially marketed to women of menopausal age to prolong youth, it has endured a tumultuous history evaluating the risk-to-benefit ratio. In response to evidence that MHT may confer cardioprotective effects, 2 landmark randomized controlled trials tested this hypothesis, and both were stopped prematurely due to increased incident cancers and cardiovascular events, creating much controversy and confusion. As women and physicians grew reticent to use MHT, most symptomatic menopausal women remained untreated. Further evaluation of available data has since lent support for the "timing hypothesis," which posits that younger women may not be at risk of adverse events following the use of MHT and may instead experience a survival advantage. Most recently, the 18-year follow-up data of postmenopausal women in the Women's Health Institute trial did not show any change in long-term survival associated with the use of MHT at any age. More recent studies have evaluated alternative treatments for high-risk women, including lower doses and newer formulations of MHT, along with combined new therapies such as selective estrogen receptor modulators, antidepressants, and exercise therapies, which are effective in reducing vasomotor symptoms and improving menopause-specific quality of life. These alternatives provide new options to symptomatic women who are unable or unwilling to take conventional MHT and allow for more person-centered decision making strategies to support women through the menopause.

Introduction **A brief history of hormone therapy**
There is a tumultuous history of prescribing women of menopausal age exogenous hormones to prolong health, youth, and as Dr. Wilson famously wrote in his 1966 book *Feminine Forever*, "avert the death of their own womanhood."[1] However, the captivation with this hypothesis can be traced back to the 1930s when the first synthetic estrogen, diethyl-sitosterol, and the first nonsynthetic estrogen, Premarin (manufactured from the urine of pregnant mares) demonstrated promising results,[2] and consequently in 1941 the Food and Drug Administration of the United States approved estrogen as a hormone replacement. As Dr. Wilson's book sold 100 000 copies in the first 7 months of its release alone, sales of Premarin tripled between 1967 and 1975.[3] While the popularity of hormone therapy use was rising, so too were cases from uterine and endometrial cancers,

and a series of retrospective studies identified up to an 8-fold increased risk of uterine and endometrial cancers among women on estrogen therapy.[3-6] In 1979, the National Institutes on Aging held a conference on postmenopausal estrogen use and concluded that estrogen replacement therapy was only effective for vasomotor management such as hot flashes and vaginal dryness[7,8] and recommended that "women using estrogens should take them only for the shortest possible time, in the lowest possible dose," and not surprisingly, sales of Premarin subsequently plummeted for the following few years.[3]

However, despite the devastating findings, the clinical community was reluctant to abandon hormone replacement, and soon discovered that adding progesterone (Provera, ie, medroxyprogesterone acetate, commonly referred to as MPA) to estrogen therapy could mitigate the risks

of uterine and endometrial cancers in women with intact uteruses,[3] and while hormone therapy was no longer marketed as a means of "prolonging femininity," a biomedical model of hormone therapy emerged, framing menopause and postmenopause as a biological state of "deficiency"[9] or "endocrinopathy,"[10] which needed to be corrected. As a result, the new modern concept of hormone replacement therapy (HRT) included estrogen and progesterone therapy (usually a combination of Premarin + Provera) and was targeted to treat vasomotor symptoms (VMSs) and protect against osteoporosis[11] whilst correcting this endocrinopathy.

At the same time, it is important to note that cardiovascular disease (CVD) was and continues to be the leading cause of death among women and men in the United States. However, in the mid-1980s cardiovascular deaths among women were surpassing those among men[12] despite common perception that "CVD is a man's disease." Epidemiologic studies revealed an age–sex interaction, where the prevalence and incidence of CVD among women increased dramatically in the postmenopausal age, renewing support for the hypothesis that women "enjoy immunity" in the premenopausal years due to "estrogen protection." During this time, observational studies suggesting protective effects of HRT were accumulating, and in 1991 a landmark nonsystematic review reported "strong evidence" for the protective cardiovascular effects of HRT.[13] These findings encouraged 2 things to occur. First, a shift in the focus of hormone therapy from symptom management to disease prevention of CVD, so much so that the United States Preventive Services Task Force recommended in 1996 that all postmenopausal women should be counselled and consider using preventative hormone therapy.[13] Correspondingly, the annual number of HRT prescriptions increased from 58 million in 1995 to 90 million in 1999,[14] making estrogen the biggest selling prescription drug. Second, it inspired 2 large randomized controlled trials to "definitively" determine the cardioprotective effects of estrogen, 1) the Heart Estrogen/Progesterone Replacement Study (HERS), which recruited 2763 postmenopausal women with established CVD between 1993 and 1994 to be randomized to estrogen-progesterone versus placebo therapy, and 2) the Women's Health Initiative (WHI), which enrolled 27 347 postmenopausal women from 1993 till 1998 and randomized those with prior hysterectomy to estrogen versus placebo and those with intact uteruses to estrogen plus progesterone versus placebo. Despite such hope and promise in the hormone replacement theory, an elevated risk of breast cancer, coronary heart disease, stroke, and venous thromboembolic disease was reported.[15] This prompted the United States Preventive Services Task Force to denounce support for HRT as prevention therapy, inciting a lasting and widespread fear among women and clinicians, and not surprisingly, estrogen therapy sales plummeted.[16]

Also of note, soon after the WHI study findings were published, a transition in terminology followed, replacing the commonly used HRT with the newer term "menopausal hormone therapy" (MHT). This shift served to distinguish the use of hormone therapies during menopause from their alternative indications, including oral contraceptive use. It also harnessed the ideology that these treatments were developed to alleviate menopausal symptoms, rather than to provide a biological correction of a harmful underlying defect.

The impact of the treatment of menopausal symptoms immediately after the Women's Health Initiative study

Besides the unexpected results and safety concerns surrounding menopausal hormone therapy (MHT), much controversy ensued over the validity of the WHI findings. Whilst the WHI, HERS, and their substudies were all designed to evaluate the cardioprotective effect of MHT, they all failed to address its fundamental role in treating women for menopausal symptoms. Approximately 360 million women worldwide over the age of 45 experience VMS.[17] Many others suffer from genitourinary symptoms as well as psychological and cognitive dysfunction during menopause,[18,19] all of which contribute to increased work absenteeism and health care costs.[20-22] Further, untreated VMS can impede quality of life (QOL), particularly in marginalized women with chronic health problems.[18,23,24] Trapped in a conflict between the ongoing controversy surrounding MHT and their debilitating symptoms, nearly 60% of menopausal women sought treatment for menopausal symptoms in the post-WHI era, but less than 30% received hormone therapies.[25] This resultant treatment gap has created a burden that cannot be underestimated.

The treatment gap in menopausal symptoms after the Women's Health Initiative study

In the United Kingdom, more than half of women turned instead to complementary and alternative medicines.[18] These treatments were poorly evidenced, expensive, unregulated, and potentially unsafe when administered in combination with prescribed medications.[26] Nevertheless, despite the fall in favor of MHT across a number of medical specialties, many women's health specialists continued to recommend the use of MHT to women for symptom relief. The treatment options available to women are in part determined by the institutional framework of their respective health care system. Women in the United Kingdom and increasingly in Canada and Poland are typically cared for by primary care physicians (in the absence of complex symptoms). On the contrary, American women are more likely to consult gynecologists, who are in turn 2.6-fold more likely to prescribe MHT.[27] The reticence among

primary care physicians to prescribe MHT may in part be due to insufficient specialty training but one cannot negate the effect of conflicting guidance from the cardiovascular and women's health communities over the last decade. With such a gap in an unmet need affecting a significant proportion of the population, the hormone replacement hypothesis has resurfaced in 2 ways: 1) reinvestigating the methodologic challenges in WHI and HERS randomized trials, and 2) ensuring the safety profile of lower doses and newer formulations of MHT to alleviate symptoms and improve QOL while providing cardiovascular protection or mitigating cardiovascular risk among young menopausal women.

Revisiting the challenges in the findings of the Women's Health Initiative study Publication of the WHI results caused initial consternation among women and their health care providers and raised critical questions regarding study design and clinical applicability.[28] The study itself suffered from high rates of attrition and crossover and generated findings based upon numerous subgroup analyses (with some papers performing up to 23 tests for interaction).[29] In an effort to provide some clarity, in 2004, Salpeter et al[30] published a controversial meta-analysis of 30 randomized trials involving 26 708 menopausal women. They revealed an unexpected 39% reduction in total mortality in younger but not older women using MHT,[30] and this finding was later supported by age-specific mortality data from the WHI.[31] In a similar analysis of coronary heart disease published in 2006, the same investigators reported a 32% reduction in coronary heart disease, which again was restricted to younger women under the age of 60.[32] These findings paved the way for the so-called timing hypothesis, which posits that the adverse effects of MHT are limited to older women in the later stages of menopause, who are likely to be in poorer vascular health and supports a reduction in mortality among younger women. In a subsequent meta-analysis of randomized controlled trials of women under 60, Salpeter et al[33] employed nuanced Bayesian methods (to enable quantification of the effects of incorrectly made assumptions) and yet again identified 27% reduced mortality associated with the early use of MHT. Most recently, the cumulative 18-year follow-up results from both arms of the WHI trial did not support the proposition that MHT shortens or prolongs lives[34] in postmenopausal women at any age.

Endogenous estrogens A concurrent interest in the safety profile of lower doses and newer formulations of MHT inspired the Estrogen in the Prevention of Atherosclerosis Trial (EPAT),[35] which showed a reduction in the progression of atherosclerosis among younger healthy women randomized to 1-mg micronized 17β-estradiol compared with placebo. However, when the same formulation was used in a sister trial of older women with preexisting coronary artery disease, there was no change in the progression of atherosclerosis.[36] Most recently, the Early versus Late Intervention Trial with Estradiol (ELITE)[37] compared the effects of the same formulation of estrogen on atherosclerosis progression in early compared to late menopause. The authors reported a similar reduction in the progression of atherosclerosis in women who were within 6 years of menopausal onset but not later in menopause.

Lower doses and newer formulations Other studies have documented the benefits of synthetic low dose oral and transdermal MHT. In the Kronos Early Estrogen Prevention Study (KEEPS),[38] women aged between 42 and 59 who were at low risk of CVD were randomized to either progestin therapy plus low dose conjugated estrogens, transdermal 17β-estradiol patches or placebo. After 4 years of follow-up, women randomized to the treatment arms experienced improved menopausal symptoms, lipid profiles, mood, and bone density without any progression of atherosclerosis.[38] While this study did not detect the same slowing down of atherosclerosis as the EPAT trial, the results support the hypothesis that in younger symptomatic menopausal women, the benefits of low dose oral and transdermal formulations outweigh the risks.

Symptom relief trials More than half of menopausal women cite VMS as their highest priority symptom.[39] Yet, the determination of the scientific community to disentangle the potential cardioprotective effects of MHT has left many untreated women with disabling symptoms in a quandary. A recent Cochrane systematic review described 24 placebo-controlled randomized trials designed to examine the management of VMS and showed clear beneficial effects of estrogen replacement therapies.[40] Subsequently, a network meta-analysis performed by the National Institute of Clinical Excellence (NICE) in the UK reiterated these findings and further supported the cost-effectiveness of transdermal treatments compared with oral therapies.[41] However, for a number of women for whom MHT is contraindicated due to comorbidities such as hormone receptive breast cancers, alternative options are required. The NICE also summarized a total of 32 randomized controlled trials of MHT in addition to alternative treatments including herbal remedies, other complementary (alternative) therapies and antidepressants and concluded in favor of overall benefits for MHT to treat the frequency of VMS.[41]

Quality of life Growing populations of older women with greater caregiver burdens are now presenting new challenges to policy-makers. Health care is less dominated by mortality outcomes than by domains outside of the examination room, such as QOL. The WHI study reported no improvement in any of the components

of health-related quality of life (HRQOL) among women randomized to estrogen plus progesterone when compared with placebo over 3 years of follow-up.[42] Nevertheless, the WHI population reflects older women (the mean age was 63 years) without severe symptoms and the measures of QOL were not specific to menopause. A number of tools have since been developed including the menopause-specific quality of life (MENQOL) measure, which explicitly captures perceptions of menopausal women, particularly relating to interference with daily living. Whereas HRQOL may not be sensitive or specific enough to detect any improvement when using MHT, benefits to QOL have been reported using the MENQOL in a review of trials of MHT published between 2002 and 2012.[43] These include the Selective Estrogens, Menopause, and Response to Therapy (SMART) trial,[44] which reported benefits to vasomotor-specific MENQOL scores at 3 and 12 months following the combined use of selective estrogen receptor modulators and bazedoxifene (a tissue selective estrogen complex). Subsequent evidence from the Menopause Strategies: Finding Lasting Answers to Symptoms and Health (MS-FLASH) trials demonstrated comparable, albeit minor, VMS relief following use of escitalopram, oral low-dose estrogen therapy, ga, aerobic exercise and omega 3 supplements compared with placebo.[45] Estrogen therapies were superior to venlaflaxine for relieving bothersome hot flushes and improving all but the psychosocial domains within MENQOL, but were equally effective at reducing hot flush frequency compared with placebo.[46,47] MS-FLASH also revealed that whilst yoga and exercise treatments do not directly benefit VMS symptoms, yoga can alleviate their impact on daily functioning and exercise can independently improve MENQOL.[48,49] These studies provide new options for women who are symptomatic but unwilling or unable to take MHT. They represent a pivotal change in the scientific literature by enabling more person-centered care and shared decision-making aimed at helping women alleviate their most problematic symptoms.

New directions   Recent years have witnessed a shift away from specialist and inconsistent consensus statements towards toolkits[50] and decision trees.[51] In their recently published and radical guidance, the NICE proposed that women over 50 who use MHT are only at an increased risk of breast cancer for the duration of treatment and this risk is actually only increased by 0.5%.[41] In addition, a recent Cochrane systematic review concluded that early initiation of MHT is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality; moreover, they suggest that late initiation, 10 years after menopausal onset is not associated with an overall increased risk in CVD events, cardiovascular death, or all-cause mortality but there was an increased risk of stroke (RR = 1.21, 95% CI [1.06, 1.38]).[52] The NICE opposes any arbitrary limits on the duration of usage of MHT, citing that up to 10% of women experience menopausal symptoms for up to 12 years and have been underserved by previous guidance that discouraged prolonged treatment. To support this, they recommend an initial risk assessment and subsequent annual review of risks and benefits of MHT to enable ongoing safe and holistic care that empowers women.[41] During late menopause and in women with risk factors, lower dose formulations are suggested, with a preference for transdermal estradiol preparations, which are unlikely to increase the risks of venous thromboembolism or stroke. In the United Kingdom, a system of National Health Service health checks has been implemented to all adults between 40 and 74 years of age, who are entitled to free assessment of their cardiovascular risk factors. Some professional groups have now suggested a similar model, in which women are invited for a health and lifestyle consultation at the age of 50 to discuss menopausal symptoms and the possible long-term consequences of estrogen depletion. In parallel, there has been unbridled development of credible resources for women, which include websites and apps. These help women map their journey through menopause to promote living and aging in good health. A number of professional societies, which are listed below also offer recommendations on the use of MHT, each from their own perspective.

Conclusion   The HRT hypothesis is a powerful hypothesis that has persevered for close to a century. While there has been a sea change in the perception of the safety profile of MHT, there is no doubt that the MHT landscape remains difficult to evaluate in the context of unresolved controversies and competing perspectives from the cardiovascular and women's health community. New evidence from the WHI and other novel trials suggest that previously reported adverse effects are small and nonsignificant in young healthy women, and that new formulations and doses of MHT are safe and effective in the treatment of VMS. As a result, new guidance now advocates for individualizing MHT for symptom relief in appropriately risk-assessed women for as long as the burden of symptoms outweigh the risks. Furthermore, lower doses, newer formulations and nonpharmacological therapies are now known to be efficacious at safely improving VMS and menopause specific QOL. Further research is still required to examine the potential preventative effect of lower doses and new formulations of MHT using larger samples with substantial power to detect changes in event rates.

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