VIEWPOINT

WOMEN'S HEALTH

The Swinging Pendulum of Menopausal Hormone Therapy

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Few medications have captured the imagination—and provoked such ire—as menopausal hormone therapy (MHT). For decades, MHT has served as a lightning rod for medical and cultural debate about management of menopause, aging, and women's health. In the mid to late 20th century, MHT was widely touted as an elixir enabling women to stave off the health effects of aging, remain "feminine forever," and prevent such diverse health issues as vasomotor symptoms (VMS), weight gain, skin aging, cardiovascular disease, and dementia.[1] Many regarded MHT as a panacea for all that ailed midlife and older women—a belief that existed in the absence of any large-scale MHT trials for primary disease prevention, particularly trials using clinical disease end points.

In this context, several groundbreaking clinical trials were established. The Women's Health Initiative (WHI) trials were one such undertaking, following up more than 25 000 postmenopausal women for up to 20 years to provide tests of claims about MHT's disease prevention effects. In a now well-known cascade of events, these trials of oral conjugated equine estrogens (CEE) + medroxyprogesterone acetate (MPA) and CEE-alone therapy were terminated early in 2002 to 2004 due to evidence of harm. Despite reducing the risk of osteoporotic fractures, diabetes, and colon cancer, CEE + MPA increased the long-term risk of cardiovascular disease events, and both CEE + MPA and CEE alone increased the risk of stroke, thromboembolic events, and dementia, particularly among older women.[2] Based on these findings that surprised many, women discontinued MHT in record numbers. The unfavorable risk to benefit ratio of MHT for prevention of disease led many to avoid MHT for management of symptoms such as VMS, for which it was an effective treatment. Symptomatic midlife women were left with few treatment options, and many—if not most—simply endured. In short, the pendulum swung from MHT being touted as a panacea to being vilified as a poison.

Recent years have seen the pendulum swinging back, with a resurgence of interest in MHT. In addition to concern about undertreatment of women with menopausal symptoms, there has been a resurrection of old claims about MHT for prevention of chronic diseases including cardiovascular disease and dementia. These claims often rest on studies with weaker designs (eg, observational and/or biased designs, dependence on surrogate end points)[3] or the assertion that WHI findings do not apply to newer MHT formulations. Viewpoints have polarized, with some rejecting MHT for any purpose, while others advocating its use in almost all patients.

Heated debate has ensued. The WHI has been critiqued for key design elements, including enrolling women who were a mean age (63 years) that is older than the typical age at which MHT is used for symptom treatment (but required to allow assessment of disease end points that typically impact older women) and use of CEE + MPA (the MHT formulation most commonly used at the time). The WHI investigators have sought to provide clarity and guidance, including summarizing key findings from the WHI[2] and pointing to the important distinction between MHT for chronic disease prevention—for which it is generally not recommended—and VMS management, for which it remains an important strategy. WHI investigators have also recently reported subgroup analyses of the age-specific impact of MHT on atherosclerotic cardiovascular outcomes among women with moderate to severe VMS[4] who may have a higher underlying risk of cardiovascular disease but also the strongest clinical indication for MHT. These analyses indicated that MHT was associated with greatest cardiovascular disease risk in women with VMS in their 70s but did not detect increased risk for cardiovascular events with MHT use in younger women with VMS. They provide reassuring evidence that symptomatic younger postmenopausal women are at low risk of cardiovascular complications with MHT.

Debate about MHT is unlikely to disappear soon. What is the path forward? One step is liberating MHT from the unrealistic cultural expectations weighing it down. Menopause—and more importantly, midlife aging in women—is not a simple estrogen deficiency state but a multisystem biological and psychological transition, driven by far more than change in any one hormone. Its manifestations can vary widely, transcending VMS alone to include sleep problems, cognitive changes, sexual concerns, urogenital symptoms, and/or mood changes in many women,[5] but minimal symptoms in others. The biological systems impacted by menopause are multiple. No one medication or treatment, including MHT, can dictate, eliminate, or prevent all menopausal manifestations or rleated health changes. Menopause management ideally leverages a multidisciplinary care approach tailored to each woman's symptom constellation and health concerns. Decisions about MHT can be approached as any other medication—not as a silver bullet for all of women's health problems but instead considering each woman's specific needs, discussing MHT's potential benefits in relation to a woman's priorities, and thoughtfully weighing short-term adverse effects and longer-term risks.

MHT is only one tool in the toolbox of menopause care. Other treatment options, including US Food and Drug Administration–approved and other evidence-based pharmacologic agents, as well as behavioral strategies, are available to manage menopausal symptoms.[6] However, these approaches are not widely disseminated, in part due to the dearth of clinicians well-trained in menopause care. In recent surveys, fewer than 1 in 10 residency graduates in internal medicine, family medicine, and obstetrics and gynecology report confidence in their ability to manage menopausal health.[7] Navigating this complex landscape alone, many women have turned to the burgeoning marketplace of non–Food and

Drug Administration–approved MHT formulations or supplements (ie, "lotions and potions") advertised for menopause management, although many of these treatments exist in a near vacuum of evidence of their efficacy and safety. Moreover, patients and even clinicians are increasingly guided by the recommendations of a chorus of online voices, many of whose advice rests on minimal empirical evidence. Dissemination of evidence-based menopause information, as well as training and availability of menopause clinicians, is of paramount importance. Women may seek care for the diversity of menopausal symptoms from multiple medical specialties, allied health professionals, and behavioral health care professionals, all of whom need relevant menopause information.

Too often menopause care is equated with MHT. The field can and should continue to engage in active investigation and innovation in menopause care. Consideration and empirical evaluation are needed of newer MHT formulations, new nonhormonal therapies, and behavioral options for menopause management, to name a few. Key populations, such as symptomatic women older than 60 years, warrant attention. Basic science investigating the physiology of menopausal symptoms—and why they often persist beyond the menopause transition—is critical to informing new treatment development. Expanding the scope of menopause care to include less well-recognized but highly burdensome syndromes reported by menopausal women (eg, cognitive symptoms) is important. Further, given the limited availability of menopause specialists, menopause care models that enable widespread reach and dissemination are required. Finally, the evidence base upon which menopause care rests remains too limited. Investment in menopause science, its symptoms, and its implications for aging women's health is urgently needed.

Women comprise over half of the world's population and will spend almost half of their lives in their peri- or postmenopausal years. Most women will have menopausal symptoms, with a varying degree of impact on quality of life, and many may benefit from menopause care. The field must evolve beyond its polarized positions about MHT—or other products marketed as the next magic bullet. Women deserve more than panaceas or poisons, or lotions or potions. They deserve a comprehensive suite of tools to navigate this critical phase of life.

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