

EDITORIAL

Persistent concerns over the use of compounded hormone therapies

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Although nonhormonal alternatives and lifestyle changes offer options for alleviating postmenopausal conditions such as osteoporosis, vasomotor symptoms, genitourinary symptoms, among others, therapies that involve female sex steroid hormone supplementation are perhaps the most effective and broadly used, particularly when vasomotor symptoms are evident.^{1,2} Over the past several decades, the use of such hormone therapy (HT) has fluctuated greatly from extensive in 2000, when about 22% of women aged 50 years and older used HT for menopausal symptoms and purported prevention of some chronic age-dependent conditions,³ to 2002 when use dramatically declined due to negative results from the estrogen (E₂) + progesterone (P₄) arm of the Women's Health Initiative (WHI). The WHI established an increased risk of developing one or more cardiovascular conditions or breast cancer with the combined use of conjugated equine estrogens and progestins.^{4,5} In addition to decreased use of HT in general following the WHI findings, a significant push has been made to move away from conventional US Food and Drug Administration (FDA)-approved HT toward alternative therapies that include nonprescription supplements and compounded hormones. Many of these products have been promoted as being bioidentical or natural HT and perceived by women as being safer than FDA-approved HT. However, the misguided term "bioidentical" is a marketing ploy that is not always supported scientifically or clinically in that some bioidentical hormones do not actually elicit biological responses consistent with ovarian-derived E₂ and P₄. Likewise, the term "natural" used to describe some hormones is also misleading. By example, phytoestrogens are marketed as "natural" hormones because they are derived from plants. However, while many phytoestrogens have been shown to molecularly bind the estrogen receptor, their ability to recruit coactivators, corepressors, and other components of the estrogen receptor transcriptional apparatus, can result in distinct biological outcomes compared with ovarian-derived E₂. This is not to say that phytoestrogens are not useful as HT

alternatives; they are merely being misrepresented and misunderstood as natural E₂ produced by the human ovary.

Beyond the general consensus that the use of compounded HT has been on the rise in the United States since the WHI study, a recent North American Menopause Society survey reported that approximately 31% of HT users aged 40 to 84 years use compounded HT.⁶ Furthermore, among women aged 40 to 49 years, 41% of HT users prefer compounded HT. These figures are striking given that more women in The North American Menopause Society survey actually reported greater benefit from using FDA-approved HT for vasomotor symptoms, vaginal dryness, and bone health than from compounded HT.⁶ The negative results of the WHI study, in which FDA-approved HT was used, may be largely responsible for the negative perception by women toward FDA-approved HT. Although The North American Menopause Society survey does have limitations, it nevertheless supports the concept that compounded HT used to treat postmenopausal symptoms is pervasive. Unlike FDA-approved HT, compounded HT in capsules, cream, or other applications are not subject to tight federal regulatory oversight making it difficult to track or survey their use. Importantly, this also makes it difficult to assess risk and to ensure compounded hormone product consistency. In this issue of *Menopause*, Stanczyk et al⁷ offer new information on compounded product consistency. In their study, prescriptions for E₂ + P₄ capsules (2 doses) and creams (2 doses) were filled in at least duplicate by 13 different pharmacies. Radioimmunoassays were then used to quantify compounded E₂ and P₄ content for comparison between and within pharmacies. The investigators observed that capsules from 11 of the 13 pharmacies contained E₂ within 10% of the prescribed dose and 2 pharmacies had mean capsular E₂ measurements at 20% and 26% below the labeled content. Interpharmacy variability was also observed in E₂ content in cream with most being within 10% of the labeled content. Interestingly, intrapharmacy E₂ measurements differed by as much as 13%. Progesterone measurements in capsules showed even greater variability with differences between labeled and actual content being as high as 31%. The variation in compounded E₂ and P₄ capsules and cream highlights concerns over the use of nonfederally regulated compounded HT. This new study supports the need to develop further FDA-approved, truly bioidentical HT for postmenopausal women where such therapy has the greatest impact.

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