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Looking Ahead: Interesting Developments in Menopause Management

Kristi Tough DeSapri*

Assistant Professor of Obstetrics and Gynecology and Internal Medicine, Feinberg School of Medicine, Center for Sexual Medicine and Menopause, Director, Northwestern Women's Bone Health Program, Northwestern University, USA

*Correspondence should be addressed to Kristi Tough DeSapri; kristi.toughdesapri@nm.org

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There are many exciting developments in the field of midlife women's health which explain how menopause symptoms, particularly hot flashes, may be an important vital sign and predictor of future health status. Additionally, in the therapeutic realm, there is a new class of medications that affect the thermoregulatory channels in the brain that control vasomotor symptoms (VMS). This development may unlock treatment options for women who cannot tolerate or cannot safely take hormone therapy.

For many women experiencing bothersome symptoms of night sweats and hot flashes, there is no finite deadline when symptoms abate. It's a common misconception that women "go through" and are done with menopause after menses cease, However, the Study of Women's Health Across the Nation (SWAN) study, a prospective study characterizing health status across the menopause transition in a multi-racial/ethnic community-based cohort of 3302 women revealed that many women have continued VMS beyond the menopause transition, may continue for 10 years, and for some the symptoms are lifelong [1]. Both typical menopausal symptoms (night sweats, hot flashes, sleep disturbance) and lesser acknowledged symptoms of genito-urinary syndrome of menopause (GSM) are important to recognize and ensure patients make the connection that menopause and post- menopause is where they will spend up to 1/3 of their reproductive lives.

Understanding this importance, researchers in the last decade have studied correlation between VMS and cardiovascular function, sleep, bone density and most recently biologic aging.

To date, studies have demonstrated a correlation of VMS in younger women (age 40-53) with changes in endothelial function based on brachial artery blood flow independent of known cardiac risk factors or estradiol levels [2]. In evaluating bone health, surges of VMS are associated with declining BMD at lumbar spine and total hip BMD. Crandall et al. studied over 2,000 women in the SWAN bone substudy and found BMD was lower among women with VMS compared to without VMS, the effect was more pronounced with lower femoral neck BMD in early perimenopausal women with VMS than without. Alternatively, postmenopausal women with VMS had lower spine and total hip than those not reporting VMS. These effects were not directly affected by serum estradiol level [3]. The most recent association evaluated is VMS and biologic aging. A recent publication examined DNA methylation-based epigenetic indicators in women in the Women's Health Initiative (WHI) sub study. Severe hot flashes were associated with higher levels. Additionally, higher BMI and greater pack years of smoking conferred higher epigenetic indicators [4].

Looking ahead to menopausal treatments on the horizon, a selective neurokinin 3 (NK3) receptor antagonist (fezolinetant) is an effective, oral nonhormonal therapy for moderate to severe hot flashes by effecting KNDy (kisspeptin/NKB/dynorphin) neuron activity, which modulates the temperature regulation in the hypothalamus. Recent phase 2 randomized, placebo-controlled trials including 287 women aged 41-65 years with multiple dosing regimens of daily to BID showed significant VMS reduction by week 4 which continued at week 12 (1.8- 2.6 reductions/day $P<0.05$ vs placebo). Various doses of fezolinetant (60 mg BID, 90 mg BID and 60 mg QD) also significantly reduced severity vs. placebo at week 12. At least 50% reduction in baseline VMS was noted in 81-95% of women on fezolinetant, whereas 59% reported reduction in placebo group [5]. Severity of VMS are also reduced. Longer (52 weeks) and larger phase 3 clinical trials are underway.

Management of menopause includes treating women with bothersome symptoms, however with more research confirming VMS affects health status of midlife women, we must review current evidence-based implications of VMS. Thankfully in addition to hormonal and non- hormonal options, another viable treatment of menopausal symptoms is on the horizon.

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