Menopause: The Journal of The Menopause Society
Vol. 31, No. 1, pp. 1-2
DOI: 10.1097/GME.0000000000002295

EDITORIAL

Sleep and hot flashes: COMMA endpoints applied to the MsFLASH studies

Andrea Ries Thurman, MD

This issue of *Menopause* includes an important article by Carpenter et al.[1] They note that the United States Food and Drug Administration (US FDA) 2003 Guidance on the coprimary endpoints to test the efficacy of hormone therapy on the treatment of vasomotor symptoms (VMS) includes the change from baseline in the frequency and severity of VMS.[2] Because this guidance document was issued more than 20 years ago, several studies have examined the impact of VMS on sleep and other health outcomes.[3] As with the known consequences of sleep apnea, the fractured and disrupted sleep that many menopausal women experience as a result of VMS is likely related to larger health consequences such as cardiovascular disease and mood disorders. To better standardize VMS treatment endpoints and select measures, which are most relevant to the experience of symptomatic women, the Core Outcomes in Menopause (COMMA) group recommended and published in this journal[4] a core outcome set (COS) of six endpoints for use in clinical trials of VMS treatments. The COS endpoints include the two US FDA recommended endpoints, (1) frequency of VMS and (2) severity of VMS, and recommend the addition of (3) distress, bother, or interference caused by VMS; (4) impact of VMS on sleep; (5) satisfaction with VMS treatment; and (6) adverse effects associated with VMS treatment.

The authors identified a gap in understanding how to best measure the COMMA COS endpoint of the impact of VMS on sleep, which is a major quality of life issue for symptomatic women. Unfortunately, validated sleep scales, such as the Insomnia Severity Index (ISI)[5,6] and the Pittsburgh Sleep Quality Index (PSQI),[7,8] are not specific to the impact of VMS on sleep.

The authors used data from the Menopause Strategies Finding Lasting Answers to Symptoms and Health (MsFLASH)[9] trials 01,[10] 02,[11-13] and 03[14] to (1) to examine correlations reported by MsFLASH participants on VMS frequency per day, severity, bother (none to a lot), and VMS interference (measured on an 11-point Likert scale) with the participant's sleep interference. Sleep interference was measured in the MsFLASH trials by the 3-item Hot Flash Interference (HFI) derivative scale, which is a subset of the Hot Flash Related Disturbance Interference Scale (HFRDIS) developed by the authors for breast cancer survivors,[15] the ISI,[5,6] and the PSQI.[7,8] At all time points measured (baseline and posttreatment with active or placebo), participant's reports of VMS frequency, an FDA required endpoint, were not significantly correlated with results of the ISI or PSQI surveys (R = 0.06-0.19, all P values >0.05). This makes sense because many women in the clinic or in research studies are not able to quantify how many VMS episodes kept them up all night. Studies using electronic VMS skin monitors support that many women are having VMS events that may not fully wake them but are occurring nonetheless. VMS severity, the second US FDA required endpoint, was more strongly correlated with the ISI and PSQI surveys (R = 0.16-0.30, all P values <0.001) except the correlation of VMS severity with the PSQI posttreatment with placebo study product. Again, this makes sense because women who have disrupted sleep, insomnia, and mood disorders possibly related to chronic sleep deprivation may report more severe VMS symptoms. The endpoints that were most highly correlated with validated sleep assessments were not US FDA–required endpoints but, instead, included the sleep question in the HFRDIS and the calculated sleep interference score from its subset, the HFI. These two scores had R values of 0.40 to 0.54, respectively (all P values <0.001). These data support a potential scale and assessment to be used in future VMS treatment trials to meet a COMMA COS endpoint.

The HFRDIS is a widely used, 10-item, self-report, psychometrically sound questionnaire, which assesses the impact of VMS on a woman's life. The scale asks women to describe how much during the past week hot flashes have interfered with 10 aspects of their life, with a score of 0 indicating no interference and a score of 10 indicating complete interference.[15] The questionnaire asks about the impact of hot flashes on sleep, work, social and leisure activities, mood concentration, relations with others, sexuality, enjoyment of life, and overall quality of life.[15]

The second aim of this study was to examine relationships between VMS satisfaction with treatment, another COMMA COS, and baseline to posttreatment changes in VMS frequency, severity, bother, interference (including impact on sleep), and

Received October 16, 2023; revised and accepted October 19, 2023.
From the Dare Bioscience, San Diego, CA.
Funding/support: None reported.
Financial disclosure/conflicts of interest: None reported.
Address correspondence to: Andrea Ries Thurman, MD, Dare Bioscience, 3655 Nobel Drive, Suite 260, San Diego, CA 92122, CA. E-mail: AThurman@DareBioscience.com

standardized sleep scales (insomnia severity, sleep quality/disturbance). Satisfaction with VMS treatment measured at the end of active treatment was most highly correlated with insomnia severity (ISI) (R = −5.1 [5.0]), VMS frequency (R = −4.9 [3.8]), and measures of VMS interference on sleep (HFRDIS and HFI) and sleep quality (PSQI) (R = −2.3 to −3.0). Similarly, the impression of study benefit was most highly correlated with sleep quality (PSQI) (R = −5.1 [5.1]). Finally, the desire to continue study treatment was most highly correlated with sleep quality (PSQI) (R = −4.4 [5.0]) and VMS frequency (R = −4.4 [4.0]).

These data support that one of the best ways to determine if hormone therapy is working for patients is to ask them about their sleep, in addition to VMS frequency and severity. As clinical researchers, these data support the addition of the impact of VMS on sleep, a COMMA COS endpoint, into future VMS treatment trials.

REFERENCES

1. Carpenter JS, Larson JC, Hunter MS, et al. Correlations among COMMA-recommended VMS outcomes in MsFLASH trials. *Menopause* 2024;31:3-9. doi: 10.1097/GME.0000000000002280
2. FDA. FDA Guidance Document Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation. 2003. Available at: https://wwwfdagov/regulatory-information/search-fda-guidance-documents/estrogen-and-estrogenprogestin-drug-products-treat-vasomotor-symptoms-and-vulvar-and-vaginal-atrophy. 2003. Accessed October 1, 2023.
3. Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. *Climacteric* 2018;21:96-100. doi: 10.1080/13697137.2018.1430131
4. Lensen S, Archer D, Bell RJ, et al. A core outcome set for vasomotor symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative. *Menopause* 2021;28:852-858. doi: 10.1097/GME.0000000000001787
5. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297-307. doi: 10.1016/s1389-9457(00)00065-4
6. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601-608. doi: 10.1093/sleep/34.5.601
7. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213. doi: 10.1016/0165-1781(89)90047-4
8. Otte JL, Rand KL, Landis CA, et al. Confirmatory factor analysis of the Pittsburgh Sleep Quality Index in women with hot flashes. *Menopause* 2015;22:1190-1196. doi: 10.1097/GME.0000000000000459
9. Newton KM, Carpenter JS, Guthrie KA, et al. Methods for the design of vasomotor symptom trials: the menopausal strategies: finding lasting answers to symptoms and health network. *Menopause* 2014;21:45-58. doi: 10.1097/GME.0b013e31829337a4
10. Freeman EW, Guthrie KA, Caan B, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA* 2011;305:267-274. doi: 10.1001/jama.2010.2016
11. Cohen LS, Joffe H, Guthrie KA, et al. Efficacy of omega-3 for vasomotor symptoms treatment: a randomized controlled trial. *Menopause* 2014;21:347-354. doi: 10.1097/GME.0b013e31829e40b8
12. Newton KM, Reed SD, Guthrie KA, et al. Efficacy of yoga for vasomotor symptoms: a randomized controlled trial. *Menopause* 2014;21:339-346. doi: 10.1097/GME.0b013e31829e4baa
13. Sternfeld B, Guthrie KA, Ensrud KE, et al. Efficacy of exercise for menopausal symptoms: a randomized controlled trial. *Menopause* 2014;21:330-338. doi: 10.1097/GME.0b013e31829e4089
14. Joffe H, Guthrie KA, LaCroix AZ, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. *JAMA Intern Med* 2014;174:1058-1066. doi: 10.1001/jamainternmed.2014.1891
15. Carpenter JS. The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manage* 2001;22:979-989. doi: 10.1016/s0885-3924(01)00353-0