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Vasomotor and depression symptoms may be associated with different sleep disturbance patterns in postmenopausal women

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Abstract

Objective: This study aims to explore the association of vasomotor symptoms (VMS) and depression symptoms with different symptoms of subjective sleep disturbance in postmenopausal women.

Methods: This is a cross-sectional study of 163 postmenopausal women (not taking hormone therapy) attending a university menopause clinic. Measures included the Athens Insomnia Scale, Greene Climacteric Scale, and Symptom Checklist-90—Revised depression subscale. Covariate-adjusted ordinal logistic regression was used to investigate the association of VMS and depression with each item of the Athens Insomnia Scale.

Results: Controlling for confounding factors, we found VMS to be significantly associated with awakenings during the night (odds ratio [OR], 1.85; $P < 0.001$), overall quality of sleep (OR, 2.00; $P < 0.001$), well-being during the day (OR, 1.63; $P = 0.008$), functioning capacity during the day (OR, 1.72; $P = 0.01$), and sleepiness during the day (OR, 1.66; $P = 0.03$); whereas we found Symptom Checklist-90—Revised depression subscale scores to be associated with sleep induction (OR, 2.09; $P < 0.001$), final awakening earlier than desired (OR, 2.21; $P < 0.001$), total sleep duration (OR, 1.62; $P = 0.01$), overall quality of sleep (OR, 1.64; $P = 0.009$), well-being during the day (OR, 1.67; $P = 0.006$), functioning capacity during the day (OR, 1.68; $P = 0.01$), and sleepiness during the day (OR, 1.57; $P = 0.04$).

Conclusions: VMS and depression symptoms are associated with different patterns of sleep disturbance. Although both symptoms are related to sleep quality, daytime functioning, and daytime well-being, depression is uniquely associated with difficulty falling asleep and waking up earlier than desired, whereas VMS are related to frequent awakenings during sleep. The findings are limited by the cross-sectional design and relatively small sample size of the study. Recommendations for future research are discussed to guide this line of inquiry and to gain a better understanding of the complex relationship between climacteric and mood symptoms and their contribution to the development of sleep disturbances during menopause.

Key Words: Menopause – Insomnia – Vasomotor symptoms – Depression – Sleep disturbance.

Sleep disturbances are highly prevalent during women's transition to menopause[1] and can lead to significant physical discomfort and functional disability.[2] Menopause is often accompanied by a variety of physiological and psychological symptoms. Hot flashes and night sweats—known as vasomotor symptoms (VMS)—are the most commonly reported problems during the perimenopausal and postmenopausal years, affecting as many as 90% of women.[2-5] In addition, menopause is a period of increased vulnerability to mood disorders.[6]

The exact mechanism for the higher prevalence of menopause-related sleep problems and their comorbidity with mood symptoms is not well understood. One of the widely held theories assumes that a domino effect takes place, whereby an increase in body temperature during hot flashes and night sweats disrupts sleep and causes women to wake, which in turn leads to daytime mood symptoms.[7]

However, accumulating evidence shows that the hypothesized domino effect may not fully encompass the nature of menopause-related sleep disturbances. Not all women with VMS develop depression, and many midlife women experience depression symptoms in the absence of VMS.[8] A reverse relationship has also

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been documented, with depression sometimes preceding the occurrence of VMS.[6]

In our previous study of a clinical sample of postmenopausal women, we found an additive effect of VMS and depression on subjective sleep disturbance, suggesting that depression symptoms were significantly associated with sleep disturbance above and beyond the effect of VMS.[9] The aim of this study was to expand on these findings by investigating the association of VMS and depression symptoms with different symptoms of subjective sleep disturbance in a postmenopausal clinical sample.

METHODS

Sample characteristics, study procedures, and measures are described in detail elsewhere.[9,10] Briefly, participants were recruited during their routine visit at the Menopause Clinic of the Second Department of Obstetrics and Gynecology at the University of Athens (Athens, Greece). Of note, women on hormone therapy or psychotropic medications were excluded from the study. From 176 eligible women who fulfilled the study inclusion criteria, 163 women (participation rate, 93%) agreed to participate in the study and provided a written informed consent form.

Participants were at least 1 year postmenopausal at the time of data collection. Besides women's detailed medical records and demographic information, measures included the following: the eight-item self-report Athens Insomnia Scale (AIS),[11] which assesses sleep induction, awakenings during the night, final awakening earlier than desired, total sleep duration, and overall quality of sleep (total score of 0-24, with higher scores indicating greater severity of sleep difficulties); the Greene Climacteric Scale vasomotor subscale (GCS-VMS),[12] which assesses hot flashes and night sweats on a scale from 0 to 3 (0, *not at all*; 3, *extremely*); and the Symptom Checklist-90—Revised (SCL-90-R) depression subscale,[13] which rates distress on a five-point scale (0, *not at all* ; 4, *extremely*) and has been validated for the Greek population.[14]

Statistical analysis

Variables were tested for normality via visual inspection of histograms and *Q-Q* plots, skewness and kurtosis values, and the Kolmogorov-Smirnov test (n > 50). Normal variables are expressed as mean (SD), variables with skewed distribution are expressed as median (interquartile range), and categorical variables are displayed as frequency (percentage). To examine the relationships between VMS, depression symptoms, and sleep disturbance on the AIS, we calculated nonparametric Spearman's ρ correlations because AIS items were ordinal variables.

To explore the association of VMS and depression symptoms with different symptoms of sleep disturbance, we performed ordinal logistic regression models for each of the AIS items. We chose ordinal logistic regression analysis because the dependent variable (ie, each of the eight AIS items) was measured on a four-point Likert scale, with higher scores indicating greater severity (0, *nonproblematic*; 3, *severe*). Ordinal regression analysis was also preferred because it is less sensitive to outlying data and deviations from normality.[15] Because the GCS-VMS and the SCL-90-R depression subscale were measured on different scales (0-3 vs 0-4, respectively), we converted raw scores into *z* scores to ensure comparability of the magnitudes of associations.

We tested eight separate ordinal logistic regression models (ie, proportional odds models) using the SPSS Polytomous Universal Model procedure, with the GCS-VMS and the SCL-90-R depression subscale as independent variables entered as continuous variables. All models controlled for age, education, employment, family status, number of children, time since menopause, and somatic illness. Odds ratio (OR) estimates and corresponding 95% CIs were computed from the results of ordinal regression analyses using the Output Management System (OMS). All reported *P* values are two-tailed. Statistical significance was set at $P < 0.05$, and analyses were conducted using SPSS statistical software (version 21.0).

RESULTS

Fifty-one (31.3%) women had a total score of 6 or higher, a cutoff score validated in the general Greek population to predict insomnia.[16] Overall, 89 (54.6%) women presented with no sleep disturbances (minimum-maximum, 0-3; mean [SD], 0.85 [1.03]), whereas 54 (33.1%) women experienced mild symptoms (minimum-maximum, 4-8; mean [SD], 5.87 [1.32]) and 20 (12.3%) women scored in the moderate to severe range (minimum-maximum, 9-15; mean [SD], 10.83 [1.43]). Item-specific scores for each of the eight items on the AIS are shown in Table 1. Table 2 presents the descriptive statistics for VMS and depression symptoms.

The correlations between the GCS-VMS, the SCL-90-R depression subscale, and each AIS item are shown in Table 3. Overall, depression was found to be a stronger bivariate correlate of sleep disturbances than VMS. VMS correlated positively with all but one item on the AIS—final awakening earlier than desired ($P > 0.05$). The association was strongest with awakenings during the night ($P < 0.001$), followed by overall quality of sleep ($P = 0.001$), functioning capacity during the day ($P = 0.001$), well-being during the day ($P = 0.003$), sleepiness during the day ($P = 0.01$),

TABLE 1. *Frequencies of Athens Insomnia Scale items*

Athens Insomnia Scale items	None	Mild	Moderate	Severe
Sleep induction	100 (61.3)	43 (26.4)	17 (10.4)	3 (1.8)
Awakenings during the night	62 (38.0)	52 (31.9)	33 (20.2)	16 (9.8)
Final awakening earlier than desired	106 (65.0)	39 (23.9)	18 (11.0)	0 (0.0)
Total sleep duration	118 (72.4)	35 (21.5)	10 (6.1)	0 (0.0)
Overall quality of sleep	108 (66.3)	35 (21.5)	19 (11.7)	1 (0.6)
Well-being during the day	99 (60.7)	56 (34.4)	6 (3.7)	2 (1.2)
Functioning capacity during the day	122 (74.8)	33 (20.2)	8 (4.9)	0 (0.0)
Sleepiness during the day	130 (79.8)	28 (17.2)	4 (2.5)	1 (0.6)

Data are presented as n (%).

TABLE 2. *Descriptive statistics for vasomotor symptom and depression symptom scores*

Variables	Mean (SD)	Median (interquartile range)
GCS-VMS	2.15 (2.06)	2.00 (4.00)
SCL-90-R depression subscale	0.98 (0.64)	0.92 (0.98)

GCS-VMS, Greene Climacteric Scale vasomotor subscale; SCL-90-R, Symptom Checklist-90—Revised.

total sleep duration ($P = 0.04$), and sleep induction ($P = 0.04$). Depression scores, on the other hand, correlated positively with all items on the AIS: sleep induction ($P < 0.001$), awakenings during the night ($P < 0.001$), final awakening earlier than desired ($P < 0.001$), total sleep duration ($P = 0.006$), overall quality of sleep ($P = 0.001$), well-being during the day ($P < 0.001$), functioning capacity during the day ($P < 0.001$), and sleepiness during the day ($P = 0.007$).

Results from the multivariate ordinal logistic regression analysis of VMS and SCL-90-R depression subscale scores are shown in Table 4. All models presented a good fit ($P < 0.001$); the test of parallel lines did not reject the null hypothesis ($P > 0.05$), ensuring that there was no violation of the assumption of proportional odds; and the Pearson χ^2 goodness-of-fit measure was nonsignificant. Controlling for confounding factors, we found VMS to be significantly associated with awakenings during the night (OR, 1.85; 95% CI, 1.32-2.60; $P < 0.0001$), overall quality of sleep (OR, 2.00; 95% CI, 1.34-2.97; $P < 0.001$), well-being during the day (OR, 1.63; 95% CI,1.12-2.36; $P = 0.01$), functioning capacity during the day (OR, 1.72; 95% CI, 1.12-2.64; $P = 0.01$), and sleepiness during the day (OR, 1.66; 95% CI, 1.04-2.65; $P = 0.03$). VMS were not significantly associated with either sleep induction (OR, 1.34; 95% CI, 0.92-1.95; $P > 0.05$) or final awakening earlier than desired (OR, 1.16; 95% CI, 0.79-1.70; $P > 0.05$). SCL-90-R depression subscale scores were associated with sleep induction (OR, 2.09; 95% CI, 1.44-3.02; $P < 0.0001$), final awakening earlier than desired (OR, 2.21; 95% CI, 1.52-3.23; $P < 0.0001$), total sleep duration (OR, 1.62; 95% CI, 1.11-2.36; $P = 0.01$), overall quality of sleep (OR, 1.64; 95% CI, 1.13-2.38; $P = 0.009$), well-being during the day (OR, 1.67; 95% CI, 1.16-2.40; $P = 0.006$), functioning capacity during the day (OR, 1.68; 95% CI, 1.12-2.53; $P = 0.01$), and sleepiness during the day (OR, 1.57; 95% CI, 1.01-2.43; $P = 0.04$). No significant relationship was found between SCL-90-R depression subscale scores and awakenings during the night (OR, 1.40; 95% CI, 1.01-1.92; $P > 0.05$).

DISCUSSION

The purpose of this preliminary study was to explore the relationship of VMS and depression symptoms with subjective sleep disturbances among hormone therapy–free postmenopausal women. We found that VMS and depression symptoms were associated with different symptoms of sleep disturbance. Although both symptoms were—independently of each other—associated with sleep quality, daytime well-being, functioning capacity, and sleepiness, some differences emerged depending on the timing of sleep disturbance. VMS—not depression symptoms—were associated with frequent awakenings during the night. Depression symptoms, on the other hand, were uniquely related to delayed sleep induction and final awakening earlier than desired.

VMS were associated with increased frequency of nighttime awakenings and poorer sleep quality, resulting in sleepiness, poor functioning capacity during the day, and poor well-being during the day, consistent with previous self-report findings.[2,17] The multiethnic and multisite Study of Women's Health Across the Nation, one of the largest community-based studies with more than 12,000 midlife women, found a significant relationship between self-reports of VMS and subjective dissatisfaction with sleep quality.[5] Results from objective measures of sleep quality, on the other hand, are much less consistent, with studies showing no relationship between hot flashes and polysomnographic indicators of impaired sleep quality.[18-20] However, a recent polysomnographic study found that nighttime hot flashes did precede arousals and waking episodes, but that held true only during the first half of the night, which contains less rapid-eye-movement sleep.[21] Our results suggest that VMS may be implicated in sleep disturbance through a distinct pathway, wherein night sweats cause women to wake up at nighttime, resulting in poor sleep quality and daytime functional impairment.

Conversely, depression symptoms were uniquely associated with earlier morning awakenings, as opposed to nocturnal awakenings. This finding is consistent with recent evidence by Joffe et al[22] showing that depressed women with hot flashes were more likely to spend less time in bed and had shorter total sleep duration but did not awaken more often than nondepressed controls who also experienced VMS. In addition, depression symptoms were significantly associated with difficulty inducing sleep. Our finding that depressed women had difficulty falling asleep is in agreement with the finding of Terauchi et al[23] suggesting that depressed or anxious perimenopausal and postmenopausal women were more likely to experience difficulty initiating sleep. Similar findings have been reported in the general population, where depression has been linked to subjective sleep disorders (difficulty initiating sleep in particular).[24,25]

TABLE 3. *Spearman's ρ correlations among VMS, depression, and AIS item scores (N = 163)*

AIS items	GCS-VMS	SCL-90-R depression subscale
Sleep induction	0.16[a]	0.35[b]
Awakenings during the night	0.30[b]	0.29[b]
Final awakening earlier than desired	0.10	0.36[b]
Total sleep duration	0.16[a]	0.23[c]
Overall quality of sleep	0.26[c]	0.27[b]
Well-being during the day	0.24[c]	0.32[b]
Functioning capacity during the day (physical and mental)	0.25[c]	0.28[b]
Sleepiness during the day	0.20[a]	0.23[c]

VMS, vasomotor symptoms; AIS, Athens Insomnia Scale; GCS-VMS, Greene Climacteric Scale vasomotor subscale; SCL-90-R, Symptom Checklist-90—Revised.
[a] $P < 0.05$.
[b] $P < 0.001$.
[c] $P < 0.01$.

TABLE 4. *Results from multiple ordinal logistic regression models, with each of the AIS items as dependent variable and with GCS-VMS and SCL-90-R depression subscale scores as independent variables (N = 163)*

	GCS-VMS[a]				SCL-90-R depression subscale[a]			
Regression models	Estimate	SE	Wald	OR (95% CI)	Estimate	SE	Wald	OR (95% CI)
(1) Sleep induction	0.29	0.19	2.32	1.34 (0.92-1.95)	0.737	0.19	15.24	2.09 (1.44-3.02)[b]
(2) Awakenings during the night	0.62	0.17	12.65	1.85 (1.32-2.60)[b]	0.333	0.16	4.13	1.40 (1.01-1.92)
(3) Final awakening earlier than desired	0.15	0.19	0.59	1.16 (0.79-1.70)	0.795	0.19	16.96	2.21 (1.52-3.23)[b]
(4) Total sleep duration	0.29	0.20	2.12	1.34 (0.90-1.98)	0.481	0.19	6.23	1.62 (1.11-2.36)[c]
(5) Overall quality of sleep	0.69	0.20	11.72	2.00 (1.34-2.97)[b]	0.494	0.19	6.73	1.64 (1.13-2.38)[d]
(6) Well-being during the day	0.49	0.19	6.59	1.63 (1.12-2.36)[c]	0.513	0.18	7.65	1.67 (1.16-2.40)[d]
(7) Functioning capacity during the day	0.54	0.22	6.03	1.72 (1.12-2.64)[c]	0.521	0.21	6.37	1.68 (1.12-2.53)[c]
(8) Sleepiness during the day	0.51	0.24	4.52	1.66 (1.04-2.65)[c]	0.450	0.22	4.01	1.57 (1.01-2.43)[c]

ORs were adjusted for age, education level, employment status, marital status, number of children, time since menopause, and somatic illness (hypertension, cardiac disease, diabetes mellitus, or thyroid disease).

AIS, Athens Insomnia Scale; GCS-VMS, Greene Climacteric Scale vasomotor subscale; SCL-90-R, Symptom Checklist-90—Revised; OR, odds ratio.

[a]Raw scores were converted into *z* scores.

[b]$P < 0.001$.

[c]$P < 0.05$.

[d]$P < 0.01$.

Furthermore, our study findings revealed a strong relationship between sleep disturbance and mood symptoms, above and beyond VMS. These findings do not come as a surprise given the high comorbidity between insomnia and depression during the menopausal transition.[26-30] Terauchi et al[31] found that as many as one third of perimenopausal and postmenopausal women with insomnia were severely depressed.

Taken together, these preliminary findings suggest that VMS are associated with poor subjective sleep quality and nighttime awakenings, which may probably be caused by sweats and hot flashes during the night. However, women with depression presented with a distinct profile of sleep difficulties, different from that of VMS: they had difficulty initiating sleep and were more likely to experience early awakenings. These problems seem to be different from VMS-related sleep disturbances that occur during sleep at nighttime and are attributable to hot flashes and night sweats, as proposed by the domino hypothesis. These findings suggest that menopause is a period of increased vulnerability to sleep problems; however, the exact pathogenic pathway of menopausal insomnia is likely to be multifactorial rather than linear, as proposed in the domino hypothesis. These findings echo previous studies advocating for the need to conduct a comprehensive assessment of menopausal insomnia.[22]

This preliminary study has several limitations that are worth mentioning. The most important limitation is the cross-sectional nature of our study design, which does not allow us to determine the temporal relationship between sleep disturbance and VMS and mood symptoms and to make claims about causality. Accumulating evidence suggests that the relationship between sleep disturbance and mood symptoms is complex and interrelated in a bidirectional fashion. Not only does depression place midlife women at risk for developing sleep disturbances but sleep disturbances also precede and often constitute a negative prognostic factor for depression.[32,33] In addition, the sample size of this study was relatively small, which lowered the power of the analyses and increased the chances of Type I error.

Second, the study sample was recruited from a specialty clinic and may not be generalizable to the entire menopausal population. That being said, the clinic treats a highly representative and socioeconomically diverse sample of women from both rural and urban areas in central and south Greece. It is of note, however, that the sample consisted of postmenopausal women only. Given significant heterogeneity in the prevalence of both climacteric and mood symptoms depending on women's menopause status (premenopause, perimenopause, and postmenopause), it is possible that our findings may not be applicable to premenopausal women or women in the menopausal transition. Future studies should extend this line of inquiry to women of different menopause statuses, with a particular emphasis on the menopausal transition because it is a period of increased vulnerability to developing mood pathology.[27]

Another limitation is that sleep disturbance, menopausal symptoms, and depression were all measured using self-report questionnaires. As mentioned earlier, subjective impairment in sleep quality does not always translate into objective abnormalities in polysomnographic sleep recordings,[18,19] and some evidence suggests that mood symptoms in climacteric women way negatively impact the accuracy of self-reported hot flashes.[27] To avoid any potential drug effect and to ensure the accuracy of subjective reports, we excluded women who were receiving hormone therapy or any psychotropic medications; however, we were unable to control for commonly used stimulants such as caffeine. In addition, the study focused on subjective sleep disturbances as measured by the AIS and did not assess for underlying primary sleep disorders such as sleep apnea or restless leg syndrome, which are very common in peri- and postmenopausal women.[34] In light of these important limitations, our findings should be regarded as preliminary and must be interpreted with caution.

The study, albeit exploratory in nature rather than hypothesis testing, provides some preliminary support for the notion that VMS and depression may be associated with different patterns of sleep disturbance in postmenopausal women. These findings should stimulate future research to identify distinct pathways for the development of menopausal insomnia and, more specifically, to investigate whether the timing

of sleep disturbance (eg, difficulty initiating vs maintaining sleep) is likely to reveal an underlying mood pathology versus somatic climacteric symptoms.

This line of research is of great public health significance, as it would aid clinicians in the assessment and management of menopausal insomnia—a highly prevalent and debilitating condition. Although hormone therapy is the gold standard in the treatment of climacteric symptoms, alternative treatment options could be explored for women with comorbid mood symptoms. Antidepressant medications have been shown to be efficacious in treating depression symptoms and in significantly improving sleep quality, sleep efficiency, and quality of life in postmenopausal women.[35] Antianxiety medications and sleep agents have also been found to be effective in treating menopausal symptoms.[36] Preliminary evidence also supports the efficacy of nonpharmacological interventions, such as yoga, in reducing sleep and climacteric symptoms.[37]

CONCLUSIONS

This exploratory study provides preliminary evidence for the notion that VMS and depression may be associated with different patterns of sleep disturbance in postmenopausal women. VMS seem to be uniquely related to difficulty maintaining sleep caused by frequent nighttime awakenings, whereas depression is related to difficulty falling asleep and waking up too early. Because of the cross-sectional design and small sample size of the study, future studies need to shed light on whether the focus on the timing of sleep disturbances could be an accurate and reliable approach to ruling out comorbid mood symptoms. Although our results highlight the importance of a multifactorial comprehensive assessment of insomnia during menopause, more research is needed to decipher the complex relationship between climacteric, mood, and sleep symptoms to improve the assessment and management of sleep-related difficulties during menopause.

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