Night sweats, sleep disturbance, and depression associated with diminished libido in late menopausal transition and early postmenopause: baseline data from the Herbal Alternatives for Menopause Trial (HALT)

Susan D. Reed, MD, MPH; Katherine M. Newton, PhD; Andrea Z. LaCroix, PhD; Lou C. Grothaus, MS; Kelly Ehrlich, MS

OBJECTIVE: The objective of the study was to evaluate the association of depression, sleep disturbance, and menopausal symptoms with diminished libido.

STUDY DESIGN: Data from a 2001-2002 baseline survey of 341 peri- and postmenopausal women, aged 45-55 years, participating in a randomized trial, was analyzed. Eligibility included at least 2 hot flashes and/or night sweats per day and no hormone therapy for at least the prior 3 months. The survey evaluated sexual function, depression, sleep, and vasomotor symptoms. We examined the association between these factors, using multivariate regression models.

RESULTS: Of 341 women, 64% had diminished libido, 18% had moderate to severe depression, and 43% had poor sleep quality. Women averaged 4.6 hot flashes and 1.9 night sweats per day. Depressive symptoms ($P = .003$), poor sleep ($P = .02$), and night sweats ($P = .04$) were significantly associated with diminished libido.

CONCLUSION: Factors associated with diminished libido in midlife are complex but include depression, disturbed sleep, and night sweats, all common symptoms of the menopausal transition and early menopause.

Key words: depression, libido, menopause, sleep, vasomotor symptoms

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The prevalence of diminished sexual desire or libido, in perimenopausal and early postmenopausal women, is estimated to be at least 40%, somewhat greater than that observed in the premenopausal years.[1-6] Diminished libido, or diminished desire, includes both hypoactive sexual desire disorder (HSDD) and sexual aversion disorder and is 1 of 4 defined components of female sexual dysfunction.[7] Along with vaginal dryness, diminished libido is the most common sexual function problem reported among postmenopausal women.[4] New classification schemes with validated diagnostic instruments[8-11] provide improved methodologies for the study and description of sexual function in the menopausal transition.

Known factors that may contribute to diminished libido in the menopausal transition and postmenopause appear to be similar to those recognized to impact libido in premenopausal women and include deterioration in social status[12,13]; history of sexual assault[14]; altered relationship or intimacy with partner[4,12,13,15]; duration of relationship with partner[16]; dyspareunia associated with hypoestrogenism[4,15,17]; medications[18]; and illness.[15] The Melbourne Women's Midlife Health Project longitudinally evaluated sexual function in the menopausal transition and postmenopause and has shown that the most important factors influencing sexual function are prior level of sexual function, losing or gaining a partner, feelings toward a partner, and serum estradiol concentration.[16] However, there exists limited information on the specific impact of depression, vasomotor symptoms, and sleep disturbances on libido.

Several studies suggest depression and anxiety may contribute to diminished libido.[19,20] The multiethnic Study of Women's Health Across the Nation (SWAN) did not find an association of night sweats or depression with diminished libido in middle-aged women,[15] and to the authors' knowledge, sleep disturbances have not been independently asso-

From the Center for Health Studies, Group Health Cooperative (all authors), the Departments of Obstetrics and Gynecology (Dr Reed) and Epidemiology (Drs Reed, Newton, and LaCroix), University of Washington School of Medicine, and the Fred Hutchinson Cancer Research Center, Public Health Sciences Division (Drs Reed and LaCroix), Seattle, WA.

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ciated with diminished libido in the menopausal transition or postmenopause.

The strength and independence of associations of vasomotor symptoms, sleep disturbance, and depression with diminished libido warrants further examination. The Herbal Alternatives for Menopause Trial (HALT) was designed to answer questions about menopausal therapies for symptomatic women in the menopausal transition and early postmenopause. We report here the baseline data on sexual desire as it relates to vasomotor symptoms, sleep disturbance, and depression.

Materials and Methods

Peri- and postmenopausal women, aged 45-55 years, were recruited in western Washington state for a randomized, placebo-controlled trial investigating alternative therapies for menopause. Details on study design and methodology have been described elsewhere.[21] Baseline data were used in this cross-sectional analysis.

Briefly, subjects were Group Health (GH) female enrollees identified using automated data and non-GH women identified from purchased mailing lists, all were recruited through direct mailing. Women were eligible if they had at least 2 hot flashes and/or night sweats per day, confirmed by self-report on baseline vasomotor symptom diaries over a 2-week run-in period. In addition, women had to average 6 or more hot flashes or night sweats of at least moderate intensity as reported in daily diaries over the 2-week period. Other entry criteria included a normal thyroid stimulating hormone and a negative mammogram within 2 years prior to randomization. Women were ineligible if they had used hormone therapy (HT) in the previous 3 months or herbal therapies for menopause in the prior month.

At baseline, physical measurements for additional screening and study measures were recorded including the following relevant factors for this study: height, weight, current medications, supplements, vitamins, and herbs. Subjects were given 2 weeks of daily menopause symptom diaries and questionnaires on health history and general symptoms. The health history questionnaire, included questions on sexual function from the Index of Female Sexual Function (IFSF),[22] with the desire domain identical to that of the desire domain from the Female Sexual Function Index (FSFI).[8] In addition, there were questions on depression from the Patient Health Questionnaire (PHQ-9),[23] and 9 items on sleep from the General Sleep Disturbance Scale (GSDS).[24] These materials were completed at home and returned at randomization.

The measurement of sexual function used by our study (IFSF) was originally validated by Kaplan et al.[22] The sexual desire domain was adapted by Rosen et al[8] in the FSFI and was subsequently tested for validity (factorial, discriminate, and divergent) and reliability (internal consistency and test-retest reliability) in 568 women with normal sexual function, female sexual arousal disorder, female orgasmic disorder, hyposexual desire disorder, and sexual pain disorder.[25] In the study by Kaplan et al, [22] women with no intercourse got a score of 0 on 3 items: lubrication, orgasm, and clitoral sensation. We included women with no intercourse in the preceding 4 weeks in our study and women with female partners because we reasoned having desire is not necessarily impact by the lack of a partner or the gender of a current partner.

The primary outcome, libido or sexual desire, was assessed using the 2 questions that comprise the validated sexual desire domain from the FSFI[8]: (1) "over the last 4 weeks, how often did you feel sexual desire?" ("never/almost never" = 0, "a few times [less than half the time]" = 1, "sometimes [about half the time]" = 2, "most times [more than half the time]" = 3, or "almost always/always" = 4); and (2) "over the past 4 weeks, how would you rate your level of sexual desire?" ("none at all/very low" = 0, "low" = 1, "moderate" = 2, "high" = 3, or "very high" = 4). In validation studies of the FSFI,[8,10,25] women with normal libido or sexual desire consistently score above 6.0 on the sexual desire domain, with a mean of 7.7. We therefore conservatively set a score of greater than 6.0 as normal libido. In addition, the frequencies in specific domains of overall satisfaction with sexual function (2 questions), frequency of sexual activity, orgasm, and clitoral sensation (1 question each), and sexual quality or discomfort (2 questions)[22] were collected and described.

Key exposures were decided a priori and included vasomotor symptoms (with the hypothesis that night sweats would be most predictive), depressive symptoms, and sleep disturbances. Menopausal symptoms were assessed with daily diaries[21]; mean number of daytime symptoms and nighttime symptoms were assessed together and separately. Depression was measured as a total score from a 9-item depression module.[23] A total score of 4 or less was classified as not depressed, 5-9 as mild depressive symptoms, 10-14 as moderate, and at least 15 as severe.

We then dichotomized depression as none to mild vs moderate to severe for our analyses. Sleep was measured using a single sleep quality and sleepiness scale on the basis of 9 items selected from the GSDS.[24] The items ask women to rate the number of days in the past week (scale: 0 = never to 7 = every day) that they, for example, "slept poorly" or "felt tired or fatigued during the day." Items that had the strongest correlation with one another were selected for a varimax factor analysis, which indicated that a single factor fit the data best. This scale, equal to the mean of the 9 items, had very high internal consistency (Cronbach's alpha = 0.90). The factor analysis and the high internal consistency (alpha = 0.89) were confirmed using a randomly selected one third of the data, which were set aside as a "confirmatory" data set prior to doing the main factor analysis on a randomly selected "developmental" data set equal to two thirds of the observations.

Several additional factors were tested for association with the outcome (diminished libido) and the exposures (vasomotor symptoms, depression, and sleep disturbance). These potential confounding variables included marital status, education, menopausal status, prior hysterectomy, self-reported health status, nulliparity, prior HT use, body mass index, physical activity score, and alco-

hol consumption. Women were classified as married or living as married vs not, partnered vs nonpartnered, college graduate vs not, postmenopausal (no menses for at least 12 months prior to study entry), and perimenopausal (at least 1 skipped menses in the 12 months prior to study entry). Prior HT use was defined as ever vs never. Body mass index, weight in kilograms per height in meters squared (measured at baseline), was dichotomized as less than 30 kg/m^2 vs 30 kg/m^2 or greater. Physical activity was defined as the number of episodes per week of any recreational physical activity (including walking, mild, moderate, and strenuous) for at least 20 minutes' duration. Significant alcohol consumption was defined as any amount, at least 3 times per week.

Statistical analysis

To determine whether women with diminished libido differed significantly from women with normal libido on factors measured on an ordinal/continuous scale, such as number of night sweats, we used Student *t* tests to conduct unadjusted analyses comparing the means in the 2 groups. For binary variables, such as depression (none to mild vs moderate to severe), we used χ^2 tests to evaluate whether the percentages varied significantly in the 2 groups. We computed Spearman correlation coefficients to assess whether our key exposure variables (depressive symptoms measured on an ordinal scale, the sleep scale, and the number of vasomotor symptoms) were so strongly correlated that they could not be evaluated in the same multivariate model.

A priori, we identified factors expected to be strongly associated with libido (age, nulliparity, presence of partner) and ran logistic regression models that included these factors as covariates. These logistic models had diminished libido as the outcome, 1 of our key exposures as an independent variable (eg, the sleep scale) plus the 3 covariates. We then compared the *P* values from the adjusted and unadjusted models to assess the robustness of our results to confounding. We also fitted a single model including the 3 potential confounding variables and all the key exposures (depression, sleep, and night sweats). Although the overall model was highly significant ($P < .0001$), because of the high correlation among some of the exposure variables (eg, sleep and depression were highly correlated, Spearman correlation coefficient [SCC] = 0.60), the individual regression coefficients were not significant (or interpretable), and we do not report the results of this model. The high correlations mean that it is impossible to use the regression analysis to separate the effects of our 3 key exposures from one anther. Analyses were first performed with all women with and without partners (male or female) and then again including only women with male partners. We also performed analysis excluding women with depression and compared them with the analyses including all women. Bonferroni correction for the statistical significance of the 9 secondary outcomes, sexual function characteristics in the IFSF[22] was applied ($P = 0.05/9 = 0.006$).

Results

The baseline visit was attended by 509 women; 398 (78.2%) of these were eligible, and 351 (88.2%) consented to participate. Of the 351 women who entered the study, 341 completed questions on sexual desire; 328 (96.2%) had information on partner status in the preceding 4 weeks. Fifty women (15%) were unpartnered and 8 women (2%) had a female partner. Diminished libido, defined as diminished frequency of desire and diminished level of desire, was present in 64% of women. Analyses performed with and without the 58 women who had no partner, or a female partner, did not have an impact on our findings.

Characteristics of the women are shown in Table 1. The mean age of participants was 52.2 years. The only significant difference between women with and without diminished libido was a higher rate of nulliparity among women with diminished libido. There were no differences between women with diminished vs normal libido in age, race, marital status, presence of partner, partner gender, years of schooling, household income, menopausal status, prior hysterectomy, self-reported health status, prior use of HT, body mass index, weekly exercise, or alcohol consumption.

Very few women in the menopausal transition and postmenopause had isolated diminished libido (Table 2); a large proportion of women with diminished libido also exhibited some degree of pain or vaginal dryness with sexual activity. Dyspareunia (discomfort more than 50% of the time) was present in 38% of women with diminished libido vs 12.2% of women with normal libido ($P < .0001$). Vaginal dryness (more than 50% of the time) was present in 62.5% of women with diminished libido and 39.4% of women with normal libido ($P = .0008$).

Diminished libido was associated with depressive symptoms, sleep disturbances, and frequent night sweats (Figure 1 and Table 3). Use of tricyclic antidepressants, selective serotonin reuptake inhibitors, or St John's wort was not associated with diminished libido ($P = .98$); neither was the use of sleeping medications (antihistamines, tricyclics, sedatives, Valerian) ($P = .5$). Only 21 women (6.2%) used beta blockers, and no association with diminished libido was observed.

Among the 341 women, 18% had major depression, and 43% experienced poor sleep quality. On subscale analysis, women with diminished libido were more likely to have increased depressive symptoms ($P = .0003$) and to have poor sleep quality ($P = .02$), although the magnitude of differences between the 2 groups was small. This finding persisted after adjusting for age, partner status, and nulliparity. Overall, women experienced an average of 4.6 hot flashes per day and 1.9 episodes of night sweats. The mean number of hot flashes per day did not differ between women with diminished libido and women with normal libido, 4.6 ± 0.2 and 4.5 ± 0.3, respectively ($P = .8$). The mean number of night sweats per day did differ among women with diminished libido (2.0 ± 0.08) and women with normal libido (1.7 ± 0.1) ($P = .04$). This finding per-

TABLE 1
Characteristics of study participants*

	All women n = 341	Normal libido n = 124	Diminished libido n = 217
Age, mean ± SE	52.2 ± 0.13	52.2 ± 0.22	52.2 ± 0.16
Race			
Caucasian	93%	96%	91%
African American	3%	2%	3%
Other	4%	2%	6%
Married/living as married	74%	73%	74%
Report sexual partner	85%	89%	83%
Female partner	2%	2%	2%
College graduate	60%	55%	62%
Household income over $35,000	82%	81%	83%
Postmenopausal	53%	54%	52%
Hysterectomy (± unilateral oophorectomy)	11%	8%	12%
Health status excellent/very good (self-reported)	79%	81%	77%
Nulliparous (no live births)†	28%	21%	31%
Prior use of HT	40%	40%	40%
Body mass index 30 kg/m^2 or greater	33.2%	34.7%	30.7%
Number of exercise episodes per week, 20 min or greater duration, mean ± SE	4.8 ± 0.23	5.3 ± 0.41	4.5 ± 0.28
Alcohol consumed at least 3 times per week	29.0%	34.7%	25.8%

* Except for age and exercise, where *P* values are from *t* test, all *P* values are from χ^2 tests.

† $P < .05$.

TABLE 2
Characteristics of sexual function

	All women n = 341	Normal libido n = 124	Diminished libido n = 217	*P* value
Discomfort (50% or more of time)*	25.7%	12.2%	38.0%	<.0001
Vaginal dryness (50% or more of time)*	51.7%	39.4%	62.5%	0.0008
Frequency of intercourse (less than 3 times/mo)	55.6%	33.1%	68.5%	<.0001
Satisfied with sex life (less than 50% satisfied)	35.6%	22.6%	43.4%	0.0001
Satisfied with sexual relationship with partner (less than 50% satisfied)†	26.4%	13.1%	34.9%	<.0001
Frequency of orgasm (less than 50% of time)	35.5%	18.3%	48.7%	<.0001
Frequency of clitoral stimulation (less than moderate)	27.7%	9.6%	41.6%	<.0001
Frequency of desire (less than 50% of time)‡	66.3%	8.1%	99.5%	<.0001
Level of desire (less than moderate)‡	69.5%	16.1%	100%	<.0001

Bonferroni correction for significance 0.05 per 9 factors, $P = .006$.

* Among women who attempted intercourse in past 4 weeks, n = 218.

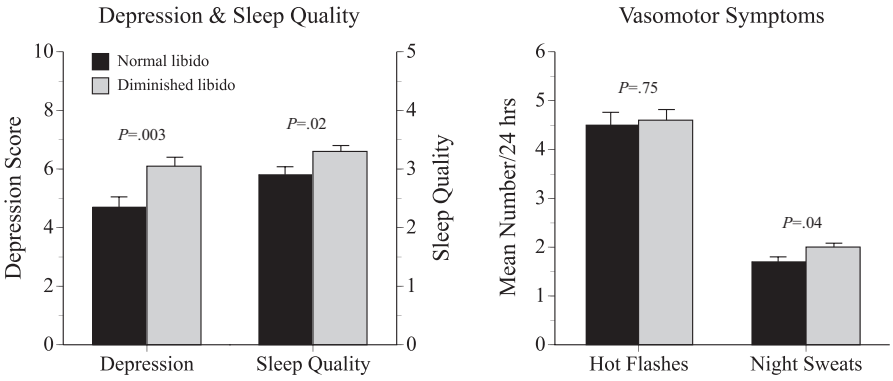
† Among women with a partner, n = 278.

‡ Items that combined created the libido subscale for this study, n = 341.

sisted after adjusting for potential confounding variables.

Poor sleep quality was highly correlated with depression (SCC = 0.6 [$P <$ .0001]) and night sweat rate (SCC = 0.2 [P = .004]). The rate of night sweats also correlated with hot flash rate (SCC = 0.4 [$P <$ .0001]). Because these factors were highly correlated, we were unable to assess their independent associations with libido; however, when women with depression were excluded from the bivariate analyses, the association of diminished libido with night sweats remained significant (P=0.04), and the association of diminished libido and sleep disturbance was no longer significant (P=0.1).

FIGURE
The association of number of vasomotor symptoms, sleep quality, and depression with diminished libido



Depression was assessed using PHQ-9[23] (scale 0 = none, 15 or greater = severe). Poor sleep quality was assessed using 9 items from GSDS[24] (scale 0 = never, 7 = daily).

Comment

Diminished libido was observed in 64% of the women in our study. Observational studies of midlife women have generally found a lower prevalence of diminished libido than observed in our study, including SWAN,[15] the Massachusetts Women's Health Study,[12] and the Melbourne Female Midlife Health Project.[17] The difference in findings may be explained by dissimilarities in age, race, menopausal status, degree of vasomotor symptoms among the women, and recruitment strategies. Women in the HALT study had a minimum of 2 vasomotor symptoms per day. Women from SWAN were multiethnic and younger, half were premenopausal, and only 6% were having daily vasomotor symptoms as compared with 100% of women in HALT. Women in the Massachusetts Women's Health Study and the Melbourne Female Midlife Health Project were similar to our participants in ethnicity and age and were having more vasomotor symptoms than the women described in SWAN, yet the degree of vasomotor symptoms (27%) did not approach those of the HALT participants (100%). Findings of a 30-40% decrease in libido[12,17] from a baseline prev-

TABLE 3
Diminished libido and association with depressive symptoms, sleep quality, and vasomotor symptoms

	All women n = 341	Normal libido n = 124	Diminished libido n = 217	*P* value
Depression*				
None	47%	54%	43%	
Mild	36%	35%	37%	
Moderate/severe	18%	11%	21%	
Depression score (scale of 0-20)	5.6 ± 0.23	4.7 ± 0.35	6.1 ± 0.3	.003†
Sleep				
Slept poorly‡	43%	39%	46%	.22
Sleep quality poor§	3.2 ± 0.17	2.9 ± 0.14	3.3 ± 0.1	.02†
Vasomotor symptoms				
Mean number of hot flashes	4.6 ± 0.17	4.5 ± 0.26	4.6 ± 0.22	.75
Mean number of night sweats	1.9 ± 0.06	1.7 ± 0.1	2.0 ± 0.08	.04†
Total mean number of vasomotor symptoms	6.5 ± 0.20	6.2 ± 0.33	6.6 ± 0.25	.36

* PHQ-9.[23]

† After adjusting for age, partner presence, and nulliparity, *P* value did not change.

‡ From GSDS[24], 4 or greater for "sleep poorly" (scale 0 = never, 7 = every day).

§ From GSDS[24], mean of 9 items (scale 0 = never, 7 = every day).

alence of 30% (as demonstrated by Laumann for predominantly premenopausal women)[5] may indeed be in keeping with our finding of 64% prevalence of diminished libido.

The association of vasomotor symptoms, depression, and sleep disturbances with libido has not been well studied in the postmenopause or menopausal transition. We found that depressive symptoms, sleep disturbances, and night sweats may be important factors associated with diminished libido. The mean differences in the number of night sweats and differences in the sleep subscale scores comparing women with diminished libido and normal libido in our study were small but statistically significant. The clinical significance of 0.3 fewer night sweats per 24 hours in the group with normal libido and a difference of 0.4 on a 7 point scale of sleep between the 2 groups may be debated. In addition, when women with depression were excluded from the analysis, sleep was no longer significantly associated with diminished libido.

To our knowledge, there are no previous studies that have described these associations with the exception of a study by Gracia et al,[19] who found that women with depression had a 3-fold increased risk for diminished libido, and the Melbourne Women's Midlife Health Project, which showed well-being that was influenced by "vasomotor symptoms, insomnia, and stress" had an impact on sexual function.[16] SWAN investigators did not report an association of diminished desire with self-reported depression or night sweats, although their participants had a low prevalence of night sweats overall.[15]

Consistent with the findings by Dennerstein et al[4,17] and in contrast to findings from the SWAN study,[15] we found that women with dyspareunia or vaginal dryness were more apt to have diminished libido. The women in the HALT study were required to be off any hormonal therapies for 3 months as part of the study entry criteria. It was therefore not unexpected that a large percentage of women reported these symptoms. Among women with diminished libido in our study, 38% (vs 12% of women with normal libido, $P \leq .0001$) reported dyspareunia, and 62.5% (vs 39% of women with normal libido, $P = 0.0008$) reported vaginal dryness.

Others have described an association of diminished libido with factors other than depression, poor sleep, and vasomotor symptoms. These factors, including antidepressant use, menopausal status, and chronic illness, were also assessed in our study. In contrast to previous studies, we did not find an association of diminished libido with antidepressant medication use,[18,20] but only 41 women (11.7%) were using antidepressant medications with an additional 13 women (3.8%) reporting use of an over-the-counter medication for depression, like St John's wort. Also, as described by the SWAN investigators[15] but in contrast to studies by Avis et al[12] and Dennerstein et al,[4] we did not find a difference in libido between women in the menopausal transition vs early postmenopause. And because the women in the HALT study were, by definition, relatively healthy, we did not find an association of diminished libido with chronic disease.[12,15]

There are multiple strengths to this study. We had a relatively large sample size with well-defined inclusion and exclusion criteria. The amount of baseline data collected allowed us to evaluate complex associations. None of the women were taking hormonal therapies, and we had the ability to control for all medications that might affect our outcome. The outcomes and exposures were carefully measured and well defined using validated instruments.[8,9,10,23,25] The sleep scale used in this study[24] was validated by factor analysis and had very high internal consistency (Cronbach's alpha = 0.91).

There are several limitations to this study. The data were cross-sectional, and therefore, we were unable to assess changes through the menopausal transition and postmenopausal period. Women were not taking any hormones, so our study does not address the effect of HT on these associations, and the majority of the women in our study were white. All participants were experiencing vasomotor symptoms; were recruited specifically for a randomized, controlled trial; and were willing to be randomized to placebo, herbal therapies plus or minus a soy dietary intervention, or HT; thus, we caution the reader as to the generalizability of our findings.

The importance of the level of distress from any degree of sexual dysfunction was not assessed. We were unable to study the importance of other previously described risk factors for diminished libido, including deterioration in social status, duration of relationship with partner, history of sexual assault, and diminishing hormone levels[16,26] because these data were not collected. Others have shown that relationships with partner, body image, "issues related to midlife" such as children living at home[12,13,16,19] affect sexual desire. Although we did not have information about children living at home, we did find that women who were nulliparous, and therefore unlikely to have children living in the home, were less likely to have normal libido, a finding opposite to that anticipated based on the findings of Gracia et al[19] that diminished libido is associated with children living in the home. We also found that women with diminished libido were less apt "to be satisfied with their partner" ($P < .0001$), a finding that is consistent with that of Basson,[13] who found that "diminished emotional intimacy" with a partner is associated with diminished libido, and findings from the Melbourne Women's Midlife Health Project[16] showing the impact of "feelings toward a partner" on sexual desire.

The complexities of sexual function are well known; these complexities are potentially magnified by changes that occur at menopause. Studies that continue to tease apart the interrelated factors associated with libido and sexual function in the menopausal transition and early postmenopausal period are important as we attempt to prioritize and give clinical weight to various therapeutic interventions. Addressing depression with nonpharmacologic therapies and treating difficulties with sleep and vasomotor symptoms experienced at night may be important steps toward improvement of libido in the midlife. However, it is important to bear in mind that

the significance of these factors for women is most likely overshadowed by the importance of intimate relationships with their partners. ■

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Discussion

Lorna Marshall, MD. This paper describes a cross-sectional study of perimenopausal and early postmenopausal women that examines libido and its association with depression, sleep disturbance, and vasomotor symptoms. It reports baseline information for a clinical trial studying Herbal Alternatives for Menopause (HALT) and does not evaluate any treatment modality. Participants were required to experience at least two hot flushes and/or night sweats per day in order to enter the study. All women discontinued any hormonal therapy including herbal treatments for menopause for three months prior to entering the study.

The number of women studied (n = 341) is large enough to draw significant conclusions but is far smaller than in other studies on perimenopausal women such as the Women's Health Initiative (WHI, n = 161,808 women) or the Study of Women's Health Across the Nation (SWAN, n = 3167 women). Ninety-three percent of enrollees were Caucasian, limiting the applicability of the findings to other ethnic groups.

The primary outcome measured in this study is sexual desire or libido, quantified using a modification of the Index of Female Sexual Function, a tool validated previously in women thought to have normal sexual function as well as a variety of sexual disorders.[1] Sixty-four percent of participants are described as having "diminished libido." Because this is cross-sectional study, libido is not defined as a decrease from the premenopausal years, but a decrease when compared to an expectation of "normal libido." Previous studies suggest a much lower prevalence of decreased sexual desire in perimenopausal and early premenopausal women, in the range of 25-40%.

A significant association between low libido and depressive symptoms, sleep disturbances and frequent night sweats but not hot flashes is reported in this study. Unfortunately, its cross-sectional design does not allow speculation on any causative relationships or any trends over time.

This is an exceedingly difficult topic to study because of the complexity of quantifying libido, confounding factors (like health or sexual function issues in the male partner), lack of a partner, or presence of a female partner. The authors should be congratulated on tackling such a difficult topic, and I look forward to learning the effects of herbal treatments on these parameters that have been so well-studied at baseline.

REFERENCE

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