Original Research

Sexual Function in Women on Estradiol or Venlafaxine for Hot Flushes

A Randomized Controlled Trial

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OBJECTIVE: To evaluate sexual function in midlife women taking low-dose oral estradiol or venlafaxine for hot flushes.

METHODS: In an 8-week randomized controlled trial among women aged 40–62 years, sexual function was compared between 0.5 mg oral estradiol per day or 75 mg venlafaxine per day (both compared with a placebo). Measures included composite and six domain scores from the Female Sexual Function Index and sexually related personal distress.

RESULTS: Participants were aged 54.6 years (standard deviation [SD] 3.8) years, 59% white, with 8.1 (SD 5.3) daily hot flushes. Median composite baseline Female Sexual Function Index score was 16.3 (SD 11.9, n=256) for all women and 21.7 (SD 9.3, n=198) among sexually active women. Composite mean Female Sexual Function Index change from baseline to week 8 was 1.4 (95% confidence interval [CI] −0.4 to 3.2) for estradiol, 1.1 (95% CI −0.5 to 2.7) for venlafaxine, and −0.3 (95% CI −1.6 to 1.0) for placebo. Composite Female Sexual Function Index and sexually related distress change from baseline did not differ between estradiol and placebo (P=.38, P=.30) or venlafaxine and placebo (P=.79, P=.48). Among sexually active women, Female Sexual Function Index domain score change from baseline differences (active compared with placebo) in desire was 0.3 (95% CI 0.0–0.6) for estradiol, −0.6 (95% CI −1.2 to 0.0) in orgasm for venlafaxine, and 0.9 (95% CI 0.2–1.6) in penetration pain for venlafaxine. No women reported adverse events related to sexual dysfunction.

CONCLUSION: Overall sexual function among nondepressed midlife women experiencing hot flushes did not change over 8 weeks with low-dose oral estradiol or venlafaxine (compared with placebo), although a subtle increase in desire (estradiol) and decreases in orgasm and pain (venlafaxine) may exist.

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Clinicians strive to individualize menopausal therapies. Commonly, shared decision-making takes into account a woman's concerns for quality-of-life

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outcomes such as sexual function when choosing treatment. Libido, lubrication, orgasm, and penetration pain may be adversely altered during menopause[1–5] and medications to treat other menopausal symptoms can potentially worsen or improve sexual function.

Although postmenopausal estrogen therapy is approved by the U.S. Food and Drug Administration for treatment of moderate to severe hot flushes and genital atrophy, only ospemifene is U.S. Food and Drug Administration-approved for improving menopausal dyspareunia. Relatively few postmenopausal hormone therapy trials have examined sexual function[6]; the majority evaluated transdermal estrogen.[7–10] Oral estrogen can increase sex hormone-binding globulin and decrease circulating free testosterone,[11] theoretically diminishing desire and arousal. Women continue to choose oral hormone formulations to manage menopausal symptoms[12]; further study of sexual function is warranted.

Although many women manage hot flushes with hormone therapy, increasing numbers are considering nonhormonal options,[13] including selective norepinephrine reuptake inhibitors, like venlafaxine. However, decreased sexual function with serotonergic medications used in depressed populations has been observed,[14] specifically diminished libido,[14–18] arousal,[14,17,18] and orgasm[14,16–18] with venlafaxine. Sexual dysfunction with selective norepinephrine reuptake inhibitors appears dose-related[19]; doses recommended for depression are higher than those recommended for hot flushes. Few venlafaxine studies in nondepressed populations exist,[20–22] but limited menopausal trial data suggest no sexual function changes.[20–22]

We prospectively evaluated self-reported sexual function among nondepressed midlife women with bothersome hot flushes in a double-blind randomized trial of oral low-dose estradiol or venlafaxine (compared with a placebo).

MATERIALS AND METHODS

Details regarding study design and methodology are published[23] as well as the primary study results on hot flushes.[23,24] The study was a multisite, randomized, placebo-controlled, double-blind clinical trial and was approved by the institutional review boards at participating sites. Participants provided written informed consent.

The trial was conducted at Menopause Strategies: Finding Lasting Answers for Symptoms and Health network sites in Boston, Philadelphia, and Seattle. Participants were recruited by mail (November 2011 to October 2012). Eligible midlife women were perimenopausal or postmenopausal aged 40–62 years. Women had at least 14 hot flushes or night sweats per week for 2 weeks (4 or more days or nights each week rated bothersome or severe). Hot flush diaries over a third week ensured that hot flush frequency did not decline more than 50% from the 2-week baseline. Women were excluded if they used psychotropic, hot flush therapies, or hormonally mediated therapies (low-dose vaginal estrogen three times or less per week allowed). Women were excluded for a major

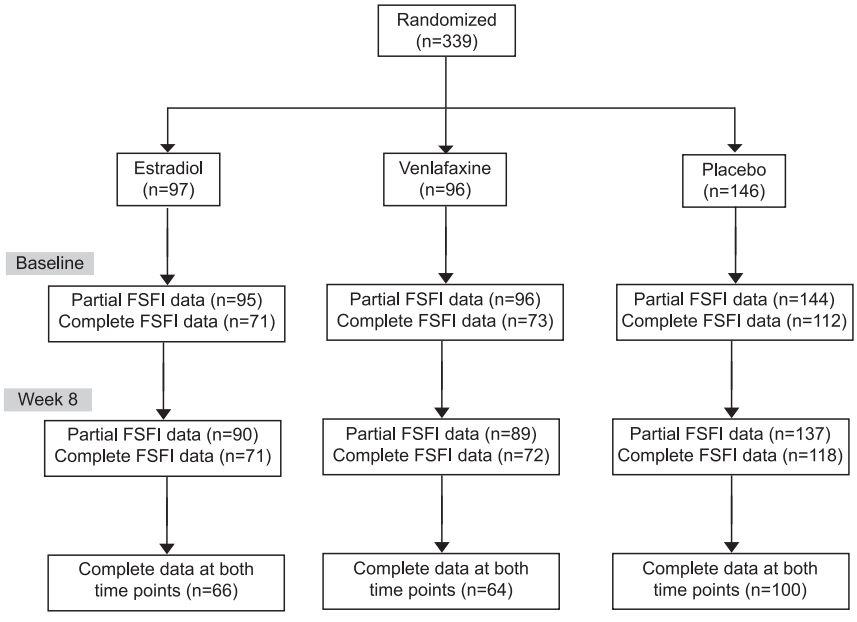

Fig. 1. Randomization and data collection. FSFI, Female Sexual Function Index.

Reed. Estradiol, Venlafaxine, and Sexual Function. Obstet Gynecol 2014.

depression episode or addiction problems (past year), suicide attempt (past 3 years), bipolar disorder or psychosis, or any major preexisting health problem, including contraindication to study medications. There were no eligibility criteria specifically related to sexual function and both sexually active and inactive women were enrolled.

Eligible participants were screened by phone and had at least three in-person visits. Stratified randomization of eligible women to 0.5 mg oral estradiol per day, 75 mg venlafaxine per day, or a matching placebo pill occurred at the second visit using a dynamic randomization algorithm (2:2:3) to ensure comparability between treatment groups with respect to site and to increase power to detect differences. Women randomized to venlafaxine started on 37.5 mg and increased to 75 mg on day 8.

Women received a phone call 1 and 4 weeks after randomization to assess adverse events and adherence. They were mailed questionnaires to complete during week 4.

Sexual function was measured at baseline and 4 and 8 weeks using the Female Sexual Function Index (see Appendices 1 and 2, available online at http://links.lww.com/AOG/A538).[25] The composite score is a sum of the six domain scores (desire, arousal, lubrication, orgasm, satisfaction, pain) and ranges from 2 (not sexually active and no desire) to 36. Women were classified as sexually inactive at baseline if they reported "no sexual activity" over the past 4 weeks with a partner or self (not restricted to vaginal penetration).

To determine how bothered or distressed women were by their levels of sexual function, we adapted two questions (nos. 1 and 13) from the Female Sexual Distress Scale, "In the past 4 weeks, how often did you feel distressed or bothered about your sex life?"[26] Scoring was: 0=never, 1=rarely, 2=occasionally, 3=frequently, or 4=always and was analyzed as a binary outcome with 0, 1, and 2 defined as "not or minimally" and 3 and 4 defined as "frequently or always" distressed.

All analyses were based on the intention-to-treat principle and included all randomized participants with follow-up Female Sexual Function Index measurements irrespective of study medication adherence. Baseline characteristics and possible correlates of sexual function (eg, urinary incontinence, vaginal dryness) were compared pairwise across two treatment groups (active, placebo) using t tests or χ^2 tests. Our primary aims were to compare the change in sexual function from baseline to 8 weeks among 1) all randomized women; and 2) participants who were sexually active at baseline. The primary analysis consisted of the treatment group-estimated contrast from

Table 1. Baseline Characteristics by Treatment Arm

Characteristic	Estradiol (n=95)	Venlafaxine (n=96)	Placebo (n=144)
Age (y)	54.9±4.1	54.8±3.7	54.3±3.7
42–49	9 (9.5)	8 (8.3)	12 (8.3)
50–54	37 (38.9)	41 (42.7)	66 (45.8)
55–59	34 (35.8)	36 (37.5)	53 (36.8)
60–62	15 (15.8)	11 (11.5)	13 (9.0)
Race			
White	58 (61.1)	53 (55.2)	88 (61.1)
African American	32 (33.7)	38 (39.6)	46 (31.9)
Other or unknown	5 (5.3)	5 (5.2)	10 (6.9)
Site			
Boston	27 (28.4)	28 (29.2)	43 (29.9)
Philadelphia	35 (36.8)	35 (36.5)	50 (34.7)
Seattle	33 (34.7)	33 (34.4)	51 (35.4)
College graduate	47 (49.5)	48 (50.0)	74 (51.4)
Married, living with partner	56 (58.9)	56 (58.3)	96 (66.7)
Current smoker	17 (17.9)	14 (14.6)	24 (16.7)
7 or more alcoholic drinks/wk	20 (21.1)	13 (13.5)	27 (18.8)
BMI (kg/m^2)	28.5±6.5	29.3±6.9	27.5±6.9
Less than 25	30 (31.6)	27 (28.1)	60 (41.7)
25 to less than 30	35 (36.8)	32 (33.3)	39 (27.1)
Greater than 30	29 (30.5)	34 (35.4)	42 (29.2)
Postmenopausal	73 (76.8)	72 (75.0)	109 (75.7)
Hysterectomy	24 (25.3)	20 (20.8)	22 (15.3)
Oophorectomy	15 (15.8)	6 (6.3)	11 (7.6)
Self-reported excellent or very good health	56 (58.9)	51 (53.1)	86 (59.7)
Moderate depressive symptoms (Patient Health Questionnaire 9 score of 10 or greater)	11 (11.6)	3 (3.1)	14 (9.7)
Moderate sleep disturbance (Pittsburgh Sleep Quality Index score of 8 or greater)	45 (47.4)	40 (41.7)	64 (44.4)
Moderate anxiety (General Anxiety Disorder-7 score of 5 or greater)	23 (24.2)	20 (20.8)	30 (20.8)
Stress (Perceived Stress Scale)	12.5±6.5	12.2±6.8	12.2±7.2
Hot flush frequency/d	8.6±5.8	8.2±5.5	7.7±4.9
Urinary incontinence	59 (62.1)	62 (64.6)	79 (54.9)
Vaginal dryness during sexual activity	36 (37.9)	36 (37.5)	60 (41.7)
Vaginal estrogen past 2 mo	1 (1.1)	1 (1.0)	6 (4.2)

BMI, body mass index.
Data are mean±standard deviation or n (%).
There were no differences in demographic factors between active and placebo groups ($P>.05$), with the exception of differences between venlafaxine and placebo in alcohol use ($P=.03$).

Table 2. Composite Female Sexual Function Index* at Baseline and Weeks 4 and 8 by Treatment Arm Among Women Sexually Active† at Baseline

	Estradiol		Venlafaxine		Placebo	
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Baseline	53	23.6 (21.5–25.7)	50	23.2 (20.7–25.7)	95	23.7 (22.3–25.1)
Week 4–Baseline	46	−0.5 (−2.5 to 1.5)	41	0.1 (−1.2 to 1.5)	85	−0.7 (−1.9 to 0.5)
Week 8–Baseline	50	0.2 (−1.6 to 2.1)	44	−0.6 (−2.0 to 0.9)	86	−1.1 (−2.4 to 0.2)

CI, confidence interval.
* Female Sexual Function Index composite score range 2 (not sexually active and no desire) to 36 (Appendices 1 and 2, http://links.lww.com/AOG/A538).[25]
† Sexually active defined as sexual activity either with a partner or alone with our without vaginal penetration.
‡ *P* values from active treatment compared with placebo contrasts in a repeated measures linear model of outcome as a function of treatment arm, clinical site, visit week (4 or 8), and baseline sexual function score.

a linear regression model summarizing composite Female Sexual Function Index score at 4 and 8 weeks as a function of group, clinical site, time point, and baseline Female Sexual Function Index. Subgroup analyses were performed to assess effect modification among women who were postmenopausal, had anxiety, or poor sleep.

Our secondary aims were to compare, across treatment group, the changes from baseline to week 8 in: 1) the frequency of all women reporting distress or bother in sexual function; and 2) Female Sexual Function Index sexual domain scores among sexually active women. The first of these aims was analyzed using logistic regression models summarizing the prevalence of distress at week 8 as a function of treatment assignment and baseline distress, and the second was analyzed using methods described as in aim 1. Among sexual domains that showed significant differences in change from baseline (active compared with placebo), we compared the proportions of women (active compared with placebo) with at least 2-point decreases or increases in any given domain through χ^2 tests. A priori, 2-point change differences were considered clinically significant.[26] We also assessed differences in the proportions of women with change from baseline in anorgasmia (orgasm never or almost never), urinary incontinence (3-Incontinence Question Index),[27] and vaginal dryness (single item, Menopause Quality of Life questionnaire)[28] using logistic regression models summarizing the prevalence of the outcome at week 8 as a function of treatment assignment and baseline prevalence.

Adverse sexual experiences were not specified in a symptom checklist recorded at baseline and 8 weeks; rather, newly emergent events related to sexual function were captured in a write-in "other" category.

The sample size of the trial was determined by the primary trial endpoint (hot flush frequency).[29] Post hoc analysis showed 88% power to detect an effect size of 0.5 standard deviation between each active group and placebo with two-sided $P<.05$ or a 3-point difference between groups in change from baseline to week 8 in composite Female Sexual Function Index. No adjustments in sexual function analyses were made for multiple comparisons. Analyses were conducted using SAS 9.3 with two-sided $P<.05$ considered statistically significant.

RESULTS

The study included 335 women (Fig. 1) after excluding four women without any sexual function question responses at baseline. Treatment adherence was 94–95% for all groups. One hundred seventy-five women reported sexual activity with male partners; five with female partners; and 105 reported self-stimulation (not mutually exclusive). Sexual preference did not vary by group. Among women who reported being married or in an intimate relationship, the average relationship duration was 24 years (range 0.5–45 years). There were no statistically significant differences in baseline characteristics between treatment groups with the exception of decreased alcohol use in the venlafaxine group as compared with placebo (Table 1).

Median composite baseline Female Sexual Function Index score was 16.3 (SD 11.9, n=256) for all women and 21.7 (SD 9.3, n=198) among sexually active women. At baseline, 67% of women on estradiol, 63% on venlafaxine, and 72% on placebo were sexually active (n=228). The distribution of baseline composite sexual function scores was bimodal for all women but displayed a single mode among those who

Difference			
Estradiol-Placebo		Venlafaxine-Placebo	
Mean (95% CI)	$P^{\ddagger}$	Mean (95% CI)	$P^{\ddagger}$
	.34		.35
−0.1 (−2.5 to 2.3)		−0.5 (−3.3 to 2.4)	
0.2 (−2.0 to 2.3)		0.8 (−1.1 to 2.7)	
1.3 (−0.9 to 3.5)		0.5 (−1.5 to 2.6)	

were sexually active at baseline. Baseline scores did not vary by group (Table 2).

A total of 230 participants were available for analysis of composite Female Sexual Function Index change from baseline to week 8. Composite mean Female Sexual Function Index score change from baseline to week 8 was 1.4 (95% confidence interval [CI] −0.4 to 3.2) for estradiol, 1.1 (95% CI −0.5 to 2.7) for venlafaxine, and −0.3 (95% CI −1.6 to 1.0) for placebo. In an adjusted linear regression model, 8-week treatment with either estradiol or venlafaxine (compared with placebo) did not affect composite Female Sexual Function Index (P=.38, P=.79, respectively; Fig. 2). The same analysis was repeated among the women who were sexually active at baseline with similar results (Table 2). The same analysis repeated in three subgroups of women–postmenopausal, moderately anxious, or with moderate sleep disturbances–revealed no differences (data not shown).

Sixty-five of 335 participants (estradiol n=22, venlafaxine n=21, placebo, n=22) reported sexually related personal distress at baseline (distress score=3 or 4). Treatment with either estradiol or venlafaxine (both compared with placebo) for 8 weeks did not significantly alter the prevalence of sexually related distress among all women (P=.30, P=.48, respectively) or the sexually active women (P=.51, P=.19, respectively).

Changes in specific Female Sexual Function Index domain scores (week 8 minus baseline) were compared by treatment group among women sexually active at baseline (Table 3). Among women randomized to estradiol compared with placebo, there was improvement in the desire score (P=.04). Women randomized to venlafaxine, as compared with placebo, had worsened orgasm (P=.04) but improvement in penetration pain scores (P=.04). All differences from placebo were small; the greatest difference observed was score improvement of 0.9 out of 6 for penetration pain with venlafaxine.

There were 209 sexually active women (62%) who answered questions about orgasm at baseline and follow-up. The proportion of women randomized to estradiol and placebo who reported anorgasmia at baseline was 9.4% and 12.5%, respectively, and decreased to 8.3% and 11.2%, respectively, at 8 weeks

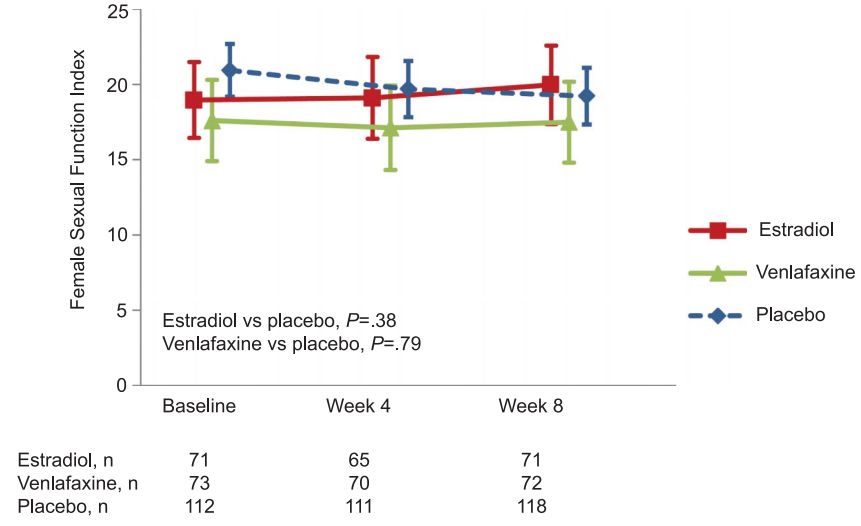

Fig. 2. Change in composite female sexual function index scores among all women from baseline to 4 and 8 weeks: estradiol, venlafaxine, and placebo. Y axis: mean composite Female Sexual Function Index score with standard deviation ranges from 2 (not sexually active and no desire) to 36. Analysis consisted of the treatment group-estimated contrast from a linear regression model summarizing composite female sexual function index score at 4 and 8 weeks as a function of group, clinical site, time point, and baseline sexual function score.

Reed. Estradiol, Venlafaxine, and Sexual Function. Obstet Gynecol 2014.

Table 3. Change in Female Sexual Function Index Domains* (Week 8 Minus Baseline Score) by Treatment Arm Among Women Sexually Active† at Baseline

	Estradiol		Venlafaxine		Placebo	
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Desire	62	0.3 (0.0–0.5)	54	0.0 (−0.2 to 0.3)	99	−0.1 (−0.2 to 0.1)
Arousal	61	−0.1 (−0.6 to 0.4)	54	−0.5 (−0.9 to 0.0)	98	−0.2 (−0.5 to 0.0)
Lubrication	61	0.1 (−0.4 to 0.6)	55	−0.2 (−0.6 to 0.2)	99	−0.3 (−0.6 to 0.1)
Orgasm	60	−0.4 (−0.9 to 0.2)	54	−0.8 (−1.3 to −0.2)	95	−0.2 (−0.5 to 0.1)
Satisfaction	52	0.0 (−0.3 to 0.3)	47	0.1 (−0.2 to 0.4)	89	0.0 (−0.3 to 0.3)
Pain	58	0.2 (−0.3 to 0.8)	50	0.5 (−0.1 to 1.0)	96	−0.4 (−0.8 to 0.0)

CI, confidence interval.
* Domain score range 0–6 (Appendices 1 and 2, http://links.lww.com/AOG/A538).[25]
† Sexually active is defined as sexual activity either with a partner or alone with or without vaginal penetration.
‡ *P* values from active treatment compared with placebo, linear model of wk 8 outcome as a function of treatment arm, clinical site, and baseline domain score.

(change from baseline, estradiol compared with placebo, *P*=.10). In contrast, the proportion of women randomized to venlafaxine who reported anorgasmia at baseline was 11.9% but increased to 20.8% at 8 weeks, although this change in proportions was not statistically different from the change observed in the placebo group (*P*=.07). A greater proportion of women in the venlafaxine (61%) as compared with the placebo-assigned (39%) groups reported at least a 2-point decrease on the orgasm domain over the 8-week intervention (*P*=.03).

No statistically significant differences (active compared with placebo) in the change in proportions of women reporting at least a 2-point change over the 8-week intervention were observed in the other Female Sexual Function Index domains that showed statistically significant change from baseline, ie, for desire (estradiol compared with placebo) and for penetration pain (venlafaxine compared with placebo).

Proportions of women reporting either stress or urge incontinence at baseline were high among all groups (62.1% estradiol, 64.6% venlafaxine, 54.9% placebo). Although proportions were diminished in all groups by 8 weeks, the change in the proportions did not statistically vary between groups (46.2% estradiol, 40.7% venlafaxine, 41.6% placebo).

Women randomized to venlafaxine reported the greatest improvement in vaginal dryness during intercourse. At baseline, 37.9%, 37.5%, and 41.7% of women in the estradiol, venlafaxine, and placebo groups, respectively, reported vaginal dryness. At 8 weeks, this decreased to 26.4%, 18.2%, and 35.6%, respectively. Only the venlafaxine group had statistically significant improvement in the proportion of women reporting vaginal dryness compared with the placebo (*P*=.006).

There were no newly emergent adverse events related to sexual function reported in any group and no women discontinued the study as a result of sexual adverse events.

DISCUSSION

Among nondepressed midlife women with bothersome hot flushes, neither low-dose oral estradiol nor low-dose venlafaxine (75 mg per day) over 8 weeks significantly altered sexual function as measured with a validated composite sexual function questionnaire, the Female Sexual Function Index.[25] Results did not vary when only those women who were sexually active at baseline were included in the analysis. However, subtle domain differences were observed among sexually active women. Desire domain scores improved in women randomized to estradiol (compared with placebo); no differences in arousal, orgasm, lubrication, or penetration pain were observed. Orgasm domain scores slightly worsened but pain improved in women randomized to venlafaxine (compared with placebo); no differences in other sexual function domains were found. Compared with baseline, the proportion of women randomized to venlafaxine who reported never having orgasms, or almost never, doubled at 8 weeks but was not significantly different from placebo.

A plethora of trials have examined low-dose oral estradiol effects on bone, endometrium, and hot flushes, but little data on sexual function exist. One 16-week study found no improvement in sexual function with oral conjugated estrogen.[30] Similarly, an open-label study of low-dose oral estrogen found sexual function was not statistically different from baseline at 12 weeks.[31] Studies of longer duration

Difference			
Estradiol-Placebo		Venlafaxine-Placebo	
Mean (95% CI)	$P^{\ddagger}$	Mean (95% CI)	$P^{\ddagger}$
0.3 (0.0–0.6)	.04	0.1 (−0.2 to 0.4)	.32
0.1 (−0.4 to 0.7)	.59	−0.3 (−0.7 to 0.2)	.30
0.3 (−0.2 to 0.9)	.14	0.1 (−0.4 to 0.6)	.82
−0.2 (−0.8 to 0.5)	.93	−0.6 (−1.2 to 0.0)	.04
0.0 (−0.5 to 0.5)	.76	0.1 (−0.4 to 0.5)	.72
0.6 (0.0–1.3)	.08	0.9 (0.2–1.6)	.04

have found improvement,[4] including preliminary analyses from the 4-year Kronos Early Estrogen Prevention Study (KEEPS). Both oral conjugated estrogens and transdermal estradiol improved lubrication and reduced pain; transdermal, but not oral, estradiol improved desire, arousal, and orgasm.[32]

Diminished orgasm with venlafaxine observed in our study was anticipated as similar findings have been observed in depressed populations evaluating venlafaxine,[14,16–18] sertraline, paroxetine,[14,16–18] and escitalopram.[26] Selective norepinephrine reuptake inhibitors act by increasing availability of serotonin and norepinephrine at synapses, which can then inhibit dopamine centrally, potentially decreasing arousal and orgasm. However, in a review of 16 studies of selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors for hot flushes, sexual function side effects were not increased above placebo.[33] Other studies concur with these findings,[20–22,34–39] but validated sexual function measures were not used consistently and many were small studies.

Our findings of diminished pain and dryness with venlafaxine were not anticipated, although there is evidence of biologic plausibility for both. Venlafaxine is not uncommonly prescribed for treatment of pain syndromes[40,41] and increased serotonin may up- or downregulate serotonin receptors, over 90% of which are present peripherally, thus modulating pain, arteriole vasodilation, vasoconstriction, or a combination of these mechanisms are likely important for improved dryness. All of these affects appear variable woman to woman, as supported by our findings.[42]

Female sexual physiology is complex and although sexual desire, orgasmic response, and sexual activity frequency decrease with age in women,[3,4] sexual distress also decreases. Clearly, the changes that occur in midlife women are poorly understood. "Normal" Female Sexual Function Index scores in midlife women from the Penn Ovarian Aging cohort (ages 40–54 years)[5] and from the first Menopause Strategies: Finding Lasting Answers for Symptoms and Health trial (ages 40–62 years)[26] suggest assigning a "new normal" cut point of sexual function at a composite score of 20 may be most appropriate for midlife women based on observed bimodal distributions.[26] The Female Sexual Function Index scores and distributions in this trial were comparable to those prior studies.[5,26] This is in contradistinction to scores observed among younger women, mean age 36.2 years (range 18–74 years), in which a cut point of 26.5 or greater was used to assign normal female sexual function based on a bimodal distribution.[43]

Strengths of this study include detailed sexual function information obtained with validated questionnaires, including an assessment of sexually related distress, 25% nonwhite participants, high adherence to therapy, and a low dropout rate. This study has limitations. Although this was a community-based sample, the volunteer participants may be a select group who were motivated to seek treatment. An 8-week treatment interval may have been too brief. There were missing data, but data completeness did not vary by group and at week 8, 89% of women provided data on approximately 90% of sexual function questions. Detecting differences between groups in our primary outcome smaller than 3 points would have required a greater sample size; the clinical relevance of this magnitude is unknown. Finally, secondary analyses were considered exploratory and should be interpreted with caution.

These findings are important because the use of serotoninergic agents for hot flushes is likely to increase, because a low-dose formulation of paroxetine was recently approved by the U.S. Food and Drug Administration, representing the first nonhormonal agent indicated for the treatment of vasomotor symptoms.[44] A full understanding of the differences in sexual function among women taking oral estradiol or

a serotoninergic agent for menopausal symptoms is important for clinical discussions between patients and their health care providers.

REFERENCES

1. Avis NE, Brockwell S, Randolph JF Jr, Shen S, Cain VS, Ory M, et al. Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. Menopause 2009;16: 442–52.
2. Avis NE, Colvin A, Bromberger JT, Hess R, Matthews KA, Ory M, et al. Change in health-related quality of life over the menopausal transition in a multiethnic cohort of middle-aged women: Study of Women's Health Across the Nation. Menopause 2009;16:860–9.
3. Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? Fertil Steril 2001;76:456–60.
4. Dennerstein L, Guthrie JR, Hayes RD, Derogatis LR, Lehert P. Sexual function, dysfunction, and sexual distress in a prospective, population-based sample of mid-aged, Australian-born women. J Sex Med 2008;5:2291–9.
5. Gracia CR, Freeman EW, Sammel MD, Lin H, Mogul M. Hormones and sexuality during transition to menopause. Obstet Gynecol 2007;109:831–40.
6. Nastri CO, Lara LA, Ferriani RA, Rosa-E-Silva AC, Figueiredo JB, Martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. The Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD009672. DOI: 10.1002/14651858.CD009672.pub2.
7. Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. Obstet Gynecol 2003; 102:823–34.
8. Haines C, Yu SL, Hiemeyer F, Schaefers M. Micro-dose transdermal estradiol for relief of hot flushes in postmenopausal Asian women: a randomized controlled trial. Climacteric 2009;12:419–26.
9. Nathorst-Böös J, Wiklund I, Mattsson LA, Sandin K, von SB. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. Acta Obstet Gynecol Scand 1993;72:656–60.
10. Nielsen TF, Ravn P, Pitkin J, Christiansen C. Pulsed estrogen therapy improves postmenopausal quality of life: a 2-year placebo-controlled study. Maturitas 2006;53:184–90.
11. Shifren JL, Desindes S, McIlwain M, Doros G, Mazer NA. A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. Menopause 2007;14:985–94.
12. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999-2010. Obstet Gynecol 2012;120:595–603.
13. Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006;295:2057–71.
14. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 2009;29:259–66.
15. Clayton A, Keller A, McGarvey EL. Burden of phase-specific sexual dysfunction with SSRIs. J Affect Disord 2006;91:27–32.
16. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clin Psychopharmacol 2008;28:329–33.
17. Vanderkooy JD, Kennedy SH, Bagby RM. Antidepressant side effects in depression patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. Can J Psychiatry 2002;47:174–80.
18. Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J Clin Psychopharmacol 2006;26:482–8.
19. Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002;63:357–66.
20. Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB. Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. Obstet Gynecol 2005;105:161–6.
21. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059–63.
22. Carpenter JS, Storniolo AM, Johns S, Monahan PO, Azzouz F, Elam JL, et al. Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. Oncologist 2007;12:124–35.
23. Newton KM, Carpenter JS, Guthrie KA, Anderson GL, Caan B, Cohen LS, et al. Methods for the design of vasomotor symptom trials: the menopausal strategies: finding lasting answers to symptoms and health network. Menopause 2013;21: 45–58.
24. Joffe H, Guthrie KA, LaCroix AZ, Reed SD, Ensrud KE, Manson JE, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. JAMA Intern Med 2014 [epub ahead of print].
25. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26: 191–208.
26. Reed SD, Guthrie KA, Joffe H, Shifren JL, Seguin RA, Freeman EW. Sexual function in nondepressed women using escitalopram for vasomotor symptoms: a randomized controlled trial. Obstet Gynecol 2012;119:527–38.
27. Brown JS, Bradley CS, Subak LL, Richter HE, Kraus SR, Brubaker L, et al; Diagnostic Aspects of Incontinence Study (DAISy) Research Group. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med 2006;144:715–23.
28. Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. Maturitas 1996;24: 161–75.
29. Freeman EW, Guthrie KA, Caan B, Sternfeld B, Cohen LS, Joffe H, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. JAMA 2011;305:267–74.
30. Maki PM, Gast MJ, Vieweg AJ, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. Neurology 2007;69:1322–30.

31. Rebar RW, Trabal J, Mortola J. Low-dose esterified estrogens (0.3 mg/day): long-term and short-term effects on menopausal symptoms and quality of life in postmenopausal women. Climacteric 2000;3:176–82.

32. Manson JE. The Kronos Early Estrogen Prevention Study by Charlotte Barker. Womens Health (Lond Engl) 2013;9:9–11.

33. Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. Am J Obstet Gynecol 2007;196:97–106.

34. Archer DF, Seidman L, Constantine GD, Pickar JH, Olivier S. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. Am J Obstet Gynecol 2009;200:172.e1–10.

35. Barton DL, LaVasseur BI, Sloan JA, Stawis AN, Flynn KA, Dyar M, et al. Phase III, placebo-controlled trial of three doses of citalopram for the treatment of hot flashes; NCCTG trial N05C9. J Clin Oncol 2010;28:3278–83.

36. Gordon PR, Kerwin JP, Boesen KG, Senf J. Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population. Menopause 2006;13:568–75.

37. Kalay AE, Demir B, Haberal A, Kalay M, Kandemir O. Efficacy of citalopram on climacteric symptoms. Menopause 2007; 14:223–9.

38. Soares CN, Arsenio H, Joffe H, Bankier B, Cassano P, Petrillo LF, et al. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. Menopause 2006;13:780–6.

39. Speroff L, Gass M, Constantine G, Olivier S; Study 315 Investigators. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstet Gynecol 2008;111:77–87.

40. Nguyen TM, Eslick GD. Systematic review: the treatment of noncardiac chest pain with antidepressants. Aliment Pharmacol Ther 2012;35:493–500.

41. Spallone V, Lacerenza M, Rossi A, Sicuteri R, Marchettini P. Painful diabetic polyneuropathy: approach to diagnosis and management. Clin J Pain 2012;28:726–43.

42. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. Annu Rev Med 2009;60:355–66.

43. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1–20.

44. Simon JA, Portman DJ, Kaunitz AM, Mekonnen H, Kazempour K, Bhaskar S, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause 2013;20:1027–35.