Sexual Function in Nondepressed Women Using Escitalopram for Vasomotor Symptoms

A Randomized Controlled Trial

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OBJECTIVE: To evaluate sexual function in midlife women using selective serotonin reuptake inhibitors for vasomotor symptoms. Selective serotonin reuptake inhibitors effectively treat vasomotor symptoms but adversely affect sexual function in depressed populations. Information on sexual function in nondepressed midlife women using selective serotonin reuptake inhibitors for vasomotor symptoms is lacking; any treatments that might impair function are of concern.

METHODS: This was a randomized controlled trial comparing 8 weeks of escitalopram with placebo in women ages 40–62 years with 28 or more bothersome vasomotor symptoms per week. Change in Female Sexual Function Index composite score (ranges from 2 [not sexually active, no desire] to 36) and six sexual domains (desire, arousal, lubrication, orgasm, satisfaction, pain) and the Female Sexual Distress Scale, and a single-question of sexually-related personal distress from the Female Sexual Distress Scale, were compared between groups.

RESULTS: Among all women, median composite baseline Female Sexual Function Index score was 18.1 (interquartile range 2.4–26.5, n=200) and among sexually active women was 22.8 (interquartile range 17.4–27.0, n=75) in the escitalopram group and 23.6 (interquartile range 14.9–31.0, n=70) in the placebo group. Treatment with escitalopram did not affect composite Female Sexual Function Index score at follow-up compared with placebo (P=.18 all women; P=.47 sexually active at baseline). Composite mean Female Sexual Function Index change from baseline to week 8 was 0.1 (95% confidence interval [CI] −1.5 to 1.7) for escitalopram and 2.0 (95% CI 0.2–3.8) for placebo. The Female Sexual Distress Scale results did not differ between groups (P=.73) nor did adverse reports of sexual function. At week 8, among those women sexually active at baseline, there was a small difference between groups in Female Sexual Function Index domain mean score change in lubrication (P=.02) and a marginal nonsignificant difference in orgasm (P=.07).

CONCLUSION: Escitalopram, when used in the treatment of vasomotor symptoms, did not worsen overall sexual function among nondepressed midlife women.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00894543.

(Obstet Gynecol 2012;119:527–38)
DOI: 10.1097/AOG.0b013e3182475fa4

LEVEL OF EVIDENCE: I

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Supported by a cooperative agreement issued by the National Institute of Aging (NIA) in collaboration with the Eunice Kennedy Shriver *National Institute of Child Health and Development (NICHD), the National Center for Complementary and Alternative Medicine (NCCAM), and the Office of Research and Women's Health (ORWH) and grants U01 AG032656, U01AG032659, U01AG032669, U01AG032682, U01AG032699, and U01AG032700 from the NIA. At the Indiana University site, the project was funded in part with support from the Indiana Clinical and Translational Sciences Institute, funded in part by grant UL1 RR025761 from the National Institutes of Health, National Center for Research Resources, Clinical and Translational Sciences Award. Escitalopram and matching placebo were supplied by Forest Research Institute.*

The authors thank Joseph Larson for statistical support.

Presented at the International Menopause Society Meeting, June 8–11, 2011, Rome, Italy, and at the North American Menopause Society Meeting, September 21–24, 2011, Washington, DC.

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Financial Disclosure

Dr. Joffe received research support from Bayer Healthcare Pharmaceuticals and has performed advisory or consulting work for Sanofi-Aventis/Sunovion, Pfizer, and Noven. Dr Shifren has been a research consultant to the New England Research Institutes and received research support from Boehringer Ingelheim Pharmaceuticals. Dr Freeman has received research support from Forest Research, Inc, Wyeth, and Anodyne Pharmaceuticals. The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/12

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors are used to treat vasomotor symptoms in women and men, the majority of whom are not depressed. Selective serotonin reuptake inhibitor therapy for menopause is particularly common because the Women's Health Initiative showed increased risk of breast cancer, stroke, myocardial infarction, and venous thromboembolism with conventional hormonal therapies.[1–3] We previously reported a modest benefit of the SSRI, escitalopram, for nondepressed midlife women with vasomotor symptoms.[4] Escitalopram was well-tolerated and promoted vasomotor symptom improvement for the majority of study participants randomly assigned to the SSRI.

Notably, however, sexual dysfunction is a commonly reported adverse effect of SSRIs among men and women with depression.[5,6] Sexual dysfunction is also reported among premenopausal women taking SSRIs for premenstrual dysphoric disorder.[7] Chief complaints most common among depressed men receiving SSRI or selective norepinephrine reuptake inhibitor therapy are erectile dysfunction, decreased libido, anorgasmia, and premature ejaculation.[6,8] Among depressed women taking SSRIs, reported problems include diminished sexual desire and arousal as well as orgasm difficulties[5,6,9] with a 10–20% report of SSRI treatment-emergent sexual dysfunction.[8]

Little is known about sexual side effects experienced by nondepressed midlife women taking SSRIs for vasomotor symptoms. Most trials to date evaluated libido and or pain as a single item in a checklist or as a component of a menopause quality-of-life scale.[2,10–16] Possible sexual dysfunction as an adverse effect of SSRI therapy is a major consideration for peri- and postmenopausal women with vasomotor symptoms and may influence choices and acceptability of therapies. Sexual function (libido, lubrication, orgasm, and pain) may already be altered during the menopause transition[17–20] and any medications that could potentially worsen already diminished sexual function may not be acceptable to women.

We hypothesized that, if sexual function is diminished among nondepressed menopausal women taking SSRIs for vasomotor symptoms, desire, arousal, and orgasm domains most likely would be affected. Alternatively, it also seemed plausible that overall sexual function may improve in women with effective treatment of bothersome vasomotor symptoms, mood, and sleep. Our study provided a unique opportunity to prospectively evaluate sexual function among nondepressed midlife women in a double-blind randomized trial comparing the use of escitalopram compared with placebo among peri- and postmenopausal women with bothersome vasomotor symptoms. We also compared the effect of escitalopram compared with placebo on six female sexual domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) and sexually related personal distress.

MATERIALS AND METHODS

Details regarding study design and methodology are published.[4] The study was a multisite, randomized, placebo-controlled, double-blind clinical trial and was approved by the institutional review board at each participating site. Participants provided written informed consent.

The trial was conducted at Menopause strategies–Finding Lasting Answers for Symptoms and Health network sites in Philadelphia, Boston, Oakland, and Indianapolis. Participants were recruited by mail (July 2009–June 2010). Eligible women were ages 40–62 years, perimenopausal or postmenopausal, including those who had a hysterectomy with or without oophorectomy. Women were required to have 28 or more hot flushes or night sweats per week as well as bothersome, severe vasomotor symptoms, or both vasomotor symptoms on 4 or more days per week. Women were excluded if they used psychotropic medications, prescription or over-the-counter hot flush therapies, hormonal therapies, selective estrogen receptor modulators, or aromatase inhibitors. In addition, women were excluded if they had a major depression episode or major alcohol or drug addiction problems in the past year, suicide attempt in the past 3 years, lifetime diagnosis of bipolar disorder or psychosis, or any major pre-existing health problems that precluded participation.

Eligible participants were screened initially by phone and then had two in-person visits. Stratified randomization of eligible women in equal proportions to 10 mg escitalopram per day or a matching placebo pill occurred at the second visit using a dynamic randomization algorithm to ensure comparability between treatment groups with respect to race and clinical site.[21] For women whose vasomotor symptoms had not improved by week 4, their daily dose was increased from one to two pills until 8 weeks. Women received a phone call 1 week after randomization to assess adverse events and adherence. Additional clinic visits occurred at weeks 4 and 8.

Primary outcomes for the trial are published.[4] In these analyses, sexual function was measured using the Female Sexual Function Index (Appendices 1 and 2).[22] Female Sexual Function Index questions are

coded from 0 to 5 in six sexual domains (desire, arousal, lubrication, orgasm, satisfaction, pain). The maximum score for each domain is 6 obtained by summing scores for all questions and multiplying by a correction factor. The final composite score is a sum of the six domain scores and ranges from 2 (not sexually active and no desire) to 36. A single question, "Over the past 4 weeks, how satisfied have you been with your overall sex life?" was inadvertently omitted from the questionnaire; a value for this question was imputed for each woman as an average of their answers to the two other questions in the Female Sexual Function Index satisfaction domain.

To determine how bothered or distressed women were by their levels of sexual function, we adapted a single question from the Female Sexual Distress Scale, "In the past 4 weeks, how often did you feel distressed or bothered about your sex life?" 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.

Possible correlates of sexual function were assessed using self-reported questionnaires completed at baseline and follow-up. These included: 1) vasomotor symptom frequency, severity, bother, and interference; 2) sleep; 3) stress; 4) depressed mood and anxiety; 5) menopausal status (transition, postmenopause); 6) self-reported health on a 5-point scale; and 7) other variables, including smoking, alcohol use, body mass index, and demographic information.

Adverse events, including sexual dysfunction, were obtained at each visit using a self-administered questionnaire listing 12 commonly reported SSRI-related adverse events. Newly emergent adverse events were identified by comparing adverse event reports during treatment with the patients' baseline reports.

All analyses were based on the intention-to-treat principle and included all randomized participants with follow-up Female Sexual Function Index measurements, which were collected irrespective of study medication adherence. Baseline characteristics were compared across groups using t tests or χ^2 tests. Our primary aims were to compare the change in sexual function from baseline to 4 and 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 a linear regression model summarizing total Female Sexual Function Index score at 4 and 8 weeks as a function of group and baseline Female Sexual Function Index. Generalized estimating equations were applied to account for correlation between participants' repeated measures.

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; and 2) various Female Sexual Function Index sexual domains among sexually active women; and also 3) to evaluate the association of baseline to week 8 changes in total Female Sexual Function Index with those in vasomotor symptom frequency, sleep quality (Pittsburgh Sleep Quality Index), stress (Perceived Stress Scale), and anxiety (Hopkins Symptoms Checklist).[4] The first of these aims was analyzed by a logistic regression model summarizing the prevalence of distress at week 8 as a function of treatment assignment and baseline distress. The changes in sexual domain scores were analyzed through linear regression models of the week 8 scores as functions of treatment assignment and the corresponding baseline domain score followed by comparing the proportions of women in the two treatment arms with at least 1- and 2-point decreases in any given domain by χ^2 tests (a priori, 2-point change differences were considered clinically significant).

All models were adjusted for race and site because the trial randomization was stratified by these factors. Factors considered as potential confounders included baseline age, education, menopausal status, body mass index, sleep, mood (Patient Health Questionnaire-9), vasomotor symptom frequency, stress, and self-reported health. A factor was included as a confounder if the estimated coefficient of interest differed by 10% or more between the multivariable models with and without the factor.

The planned sample size of the trial (90 women per treatment group) was determined by the primary trial end points (hot flush frequency and severity),[4] although the sample sizes provided 80% power to detect a 10% difference between groups in the composite Female Sexual Function Index. Reported P values are based on the Wald statistic. No adjustments were made for multiple comparisons. Analyses were conducted using SAS 9.1 with two-sided $P<.05$ considered statistically significant. Secondary analyses are considered exploratory and should be interpreted with caution.

RESULTS

The study population consisted of 200 participants (Fig. 1) after excluding five participants missing responses to the Female Sexual Function Index questions at baseline. Women in our study were well educated, 59% were married or living with a partner,

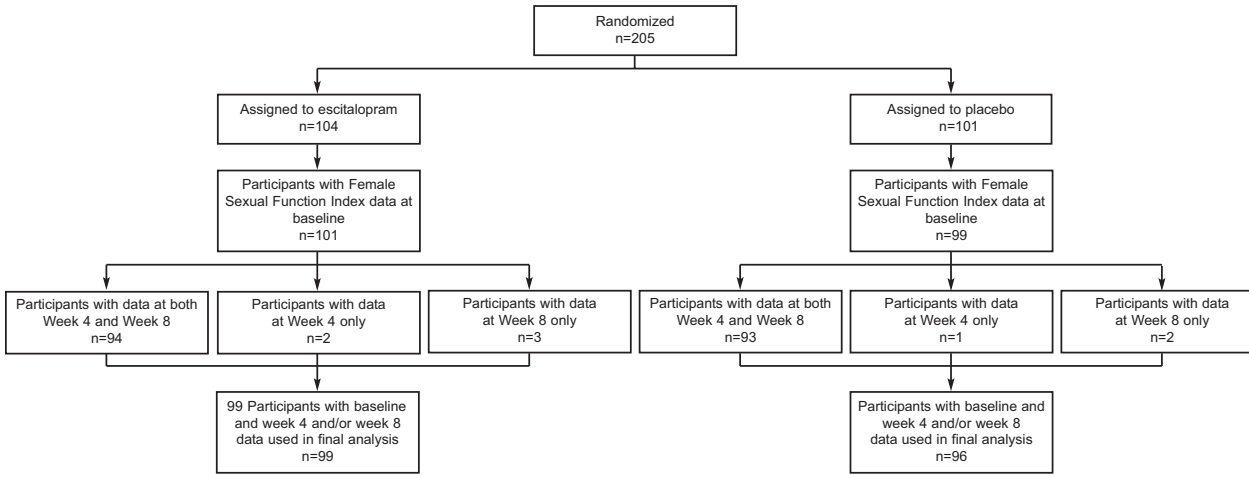

Fig. 1. Study participant sexual function data collection.
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and 39% were obese. Approximately 22% of women had a hysterectomy and 82% were postmenopausal. None had major depressive disorder, only 6% had moderate depressive symptoms, 5% were moderately anxious, and 40% had poor sleep quality. Overall, participants ' stress levels, Perceived Stress Scale score mean of 13.5 (standard deviation 7.4), were similar to the standard norm of 13.7 (standard deviation 6.6)[23]; 14.3% had Perceived Stress Scale scores greater than 20. Women had an average of almost 10 hot flushes per day. There were no statistically significant differences in baseline characteristics between treatment groups (Table 1).

Median composite baseline Female Sexual Function Index score was 18.1 (interquartile range 2.4–26.5). Only 74% of women on escitalopram and 71% on placebo were sexually active at baseline. The distribution of baseline composite sexual function scores was bimodal for all women but displayed a single mode among those who were sexually active at baseline (Fig. 2). In the latter subgroup, median composite baseline Female Sexual Function Index score was 22.8 (interquartile range 17.4–27.0) in the escitalopram group and 23.6 (interquartile range 14.9–31.0) in the placebo group.

A total of 195 participants were available for analysis of sexual function (Female Sexual Function Index score at week 4, week 8, or both), 99 in the escitalopram group and 96 in the placebo group. After adjustment for race, site, and baseline Female Sexual Function Index score in a linear regression model, treatment with escitalopram did not affect composite Female Sexual Function Index score at follow-up as compared with placebo (P=.18 overall treatment effect; Table 2). This same analysis was repeated among the women who were sexually active at baseline with similar results (P=.47 overall treatment effect; Table 2). Analyses were repeated without imputation of the missing question in the satisfaction domain and findings did not change. Fifty-three percent of participants assigned to escitalopram and 72% assigned to placebo received an increased dose at week 4. If anything, scores improved from 4 to 8 weeks; therefore, the increase in dose from 10 to 20 mg at the 4-week visit among some participants did not appear to adversely affect sexual function. Adjustment for other potential confounders did not alter the results of the treatment arm comparisons.

Forty-one of 199 participants (n=24 escitalopram, n=17 placebo) reported sexually related personal distress at baseline (Female Sexual Distress Scale=3 or 4). This decreased to 33 of 195 participants (n=15 escitalopram, n=18 placebo) at 8 weeks. There was no significant increase in sexually related personal distress among women taking escitalopram compared with placebo (P=.73).

Changes in specific Female Sexual Function Index domains from baseline to week 8 were compared by treatment group among those women who were sexually active at baseline (Table 3). There was a small statistically significant difference in mean change between groups in the lubrication domain (P=.02) and a marginal difference that did not reach statistical significance in the orgasm domain (P=.07). The different items in the lubrication and orgasm domains showed minimal mean changes from baseline to week 4 and 8 with overlapping confidence intervals (Fig. 3). Among women who reported being

Table 1. Demographic and Clinical Characteristics at Baseline by Treatment Arm

Baseline Characteristic*	Escitalopram (n=101)	Placebo (n=99)
Age at screening (y)	53.3±4.2	54.3±3.9
42–49	16 (16)	8 (9)
50–54	47 (47)	46 (46)
55–59	29 (29)	35 (35)
60–62	9 (9)	10 (10)
Race		
White	52 (51)	48 (48)
African American	45 (45)	47 (47)
Other	4 (4)	4 (4)
Clinic site		
Boston	24 (24)	19 (19)
Indianapolis	16 (16)	17 (17)
Oakland	30 (30)	25 (25)
Philadelphia	31 (31)	38 (38)
Education		
Less than a high school diploma or high school equivalency degree	15 (15)	21 (21)
School or training after high school	44 (44)	41 (41)
College graduate	42 (42)	37 (37)
Marital status: married or living with partner	63 (62)	55 (56)
Currently smoking	19 (19)	25 (25)
Alcohol use (seven or more drinks/wk)	12 (12)	16 (16)
Body mass index (kg/m^2)	28.7±6.7	29.6±6.2
Lower than 25	31 (31)	21 (21)
25–29	32 (32)	38 (38)
30 or higher	38 (38)	39 (39)
Menopause status		
Postmenopause	81 (80)	82 (83)
Late transition	17 (17)	14 (14)
Early transition	3 (3)	3 (3)
Hysterectomy	23 (23)	20 (20)
Oophorectomy†	14 (14)	10 (10)
Self-reported health		
Excellent	18 (18)	13 (13)
Very good	40 (40)	40 (40)
Good	35 (35)	35 (35)
Fair	7 (7)	11 (11)
Poor	1 (1)	0 (0)
PHQ-9 Depression score	3.2±3.1	2.9±3.2
No depression (0–4)	74 (73)	76 (77)
Mild depression (5–9)	23 (23)	15 (15)
Moderate depression (10–13)	4 (4)	7 (7)
Hot flash frequency per day	9.9±6.3	9.6±4.9
Vaginal estrogen use in past 2 mo	2 (2)	0 (0)

PHQ-9, Patient Health Questionnaire-9; FSFI, Female Sexual Function Index; FSDS, Female Sexual Distress Scale.
Data are mean±standard deviation or n (%).
* $P>.05$ for all comparisons by treatment group as tested by t test or χ^2.
† Three women randomized to escitalopram and two women randomized to placebo also each underwent a hysterectomy.

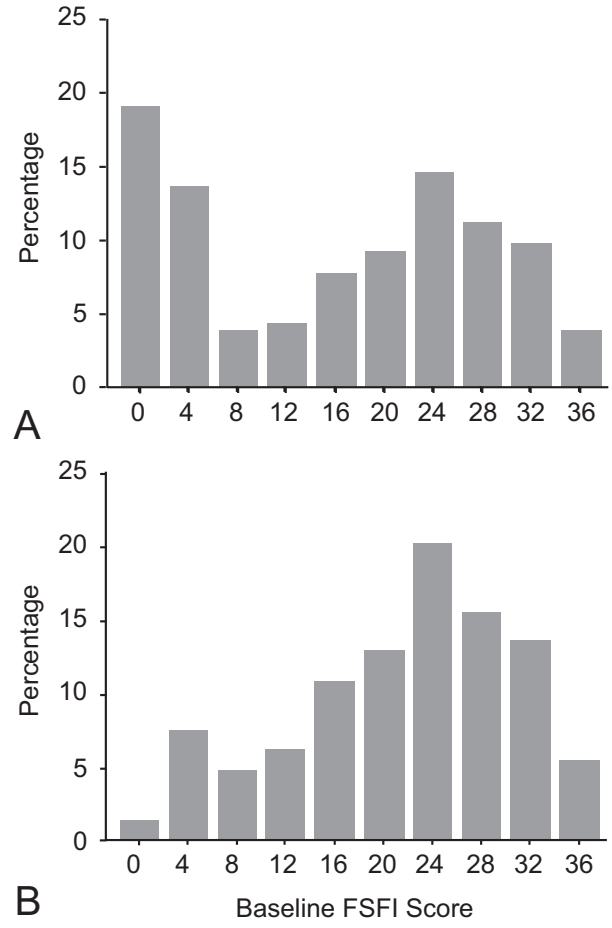

Fig. 2. Distribution of baseline Female Sexual Function Index (FSFI) composite scores among **A.** all women and **B.** women sexually active at baseline.
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sexually active on orgasm-related questions at baseline (126 [65%] of study participants), orgasmic function domain scores were reduced by at least 1 point, out of 6 points, in 33% of escitalopram-treated and 15% of placebo-treated women (P=.02) and by at least 2 points in 15% of escitalopram-treated and 10% of placebo-treated women (P=.39) at week 8. The proportion of sexually active women with anorgasmia did not vary by treatment group. Frequency of anorgasmia in the women taking escitalopram was 13%, 11%, and 14% at baseline, 4 weeks, and 8 weeks, respectively. Frequency of anorgasmia in the women taking placebo was 6%, 10%, and 7% at baseline, 4 weeks, and 8 weeks, respectively. Among the 130 participants who reported being sexually active on lubrication-related questions at baseline, lubrication domain scores were reduced at week 8 by at least 1 point, out of 6 points, in 17% escitalopram-treated and

Table 2. Sexual Function (Female Sexual Function Index) at Weeks 4 and 8 by Treatment Arm*

	Escitalopram		Placebo		Difference
	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)
All women					
Baseline	99	15.9 (13.7 to 18.2)	96	16.3 (13.8 to 18.9)	−0.4 (−3.8 to 2.9)
Change at week 4	96	−0.3 (−1.7 to 1.2)	94	0.8 (−1.1 to 2.7)	−1.1 (−3.4 to 1.3)
Change at week 8	97	0.1 (−1.5 to 1.7)	95	2.0 (0.2 to 3.8)	−1.9 (−4.3 to 0.5)
Sexually active at baseline					
Baseline	73	20.9 (18.9 to 22.9)	68	22.2 (19.8 to 24.6)	−1.3 (−4.4 to 1.8)
Change at week 4	71	−1.0 (−2.8 to 0.8)	67	−0.7 (−2.9 to 1.4)	−0.3 (−3.0 to 2.5)
Change at week 8	72	−0.4 (−2.4 to 1.5)	67	0.9 (−1.1 to 2.8)	−1.3 (−4.1 to 1.5)

CI, confidence interval.

* Comparison of women randomized to escitalopram compared with placebo in a linear model of the outcome as a function of intervention arm and adjusted for race, clinical center, and baseline Female Sexual Function Index; *P*=.18 for comparison of all women and *P*=.47 of women sexually active at baseline. Only those participants with baseline and week 4 and or week 8 data were included in the analyses.

10% of placebo-treated women (*P*=.21) and by at least 2 points in 12% escitalopram-treated and 7% of placebo-treated women (*P*=.32).

We evaluated the characteristics of those women with at least a 1-point decrease in the lubrication or orgasm domain in the escitalopram and placebo groups with regard to anxiety, vasomotor symptom frequency, stress, and sleep at baseline and at 8 weeks and found no significant associations.

Newly emergent adverse events related to sexual function did not differ between groups. Decreased sexual desire or ability was reported in 11% of women in the escitalopram group (n=7) and in 12% of women in the placebo group (n=8).

DISCUSSION

Escitalopram at doses of 10 or 20 mg per day did not significantly alter overall sexual function among nondepressed midlife women as compared with placebo using a validated sexual function questionnaire, the Female Sexual Function Index.[22] We found diminished lubrication and a marginal change in orgasm, which did not reach statistical significance, among women taking escitalopram; the clinical significance of these findings requires additional study in larger populations. A small proportion of women who were sexually active at baseline reported experiencing treatment-related changes in lubrication or orgasm that may be clinically meaningful such that domain response scores decreased at least 2 points from being approximately "equally satisfied/dissatisfied" to "very dissatisfied" for example. These differences (5% more women taking escitalopram reported diminished function as compared with placebo) were not statistically significant between groups. There was no evidence of escitalopram-related anorgasmia in this sexually active subgroup. No differences in other sexual function domains, including desire, arousal, satisfaction, or pain, were observed.

Our findings support observations from biologic and epidemiologic studies of serotonin and SSRI effects on female sexual function. Female sexual physiology is complex and the changes that occur in midlife women are poorly understood, although it is

Table 3. Change in Sexual Function Domains From Baseline to Week 8 by Treatment Arm Among Participants With Sexual Activity at Baseline

	Escitalopram		Placebo		Difference	
FSFI Domain	n	Mean (95% CI)	n	Mean (95% CI)	Mean (95% CI)	*P**
Desire	73	0.3 (0 to 0.5)	68	0.1 (−0.2 to 0.4)	0.2 (−0.2 to 0.6)	.84
Arousal	73	−0.2 (−0.5 to 0.2)	68	−0.1 (−0.5 to 0.3)	−0.1 (−0.6 to 0.4)	.56
Lubrication	73	−0.3 (−0.7 to 0.1)	68	0.3 (−0.1 to 0.7)	− 0.6 (− 1.2 to − 0.1)	.02
Orgasm	73	−0.5 (−0.9 to 0)	68	0 (−0.4 to 0.5)	−0.5 (−1.1 to 0.1)	.07
Satisfaction	72	0.3 (−0.2 to 0.7)	68	0.2 (−0.3 to 0.6)	0.1 (−0.6 to 0.7)	.83
Pain	73	0 (−0.6 to 0.5)	67	0.3 (−0.2 to 0.9)	−0.3 (−1.1 to 0.4)	.65

FSFI, Female Sexual Function Index; CI, confidence interval.

* *P* value from comparison of escitalopram compared with placebo in a linear model of the week 8 Female Sexual Function Index domain score as a function of intervention arm and adjusted for race, clinical center, and baseline Female Sexual Function Index domain score.

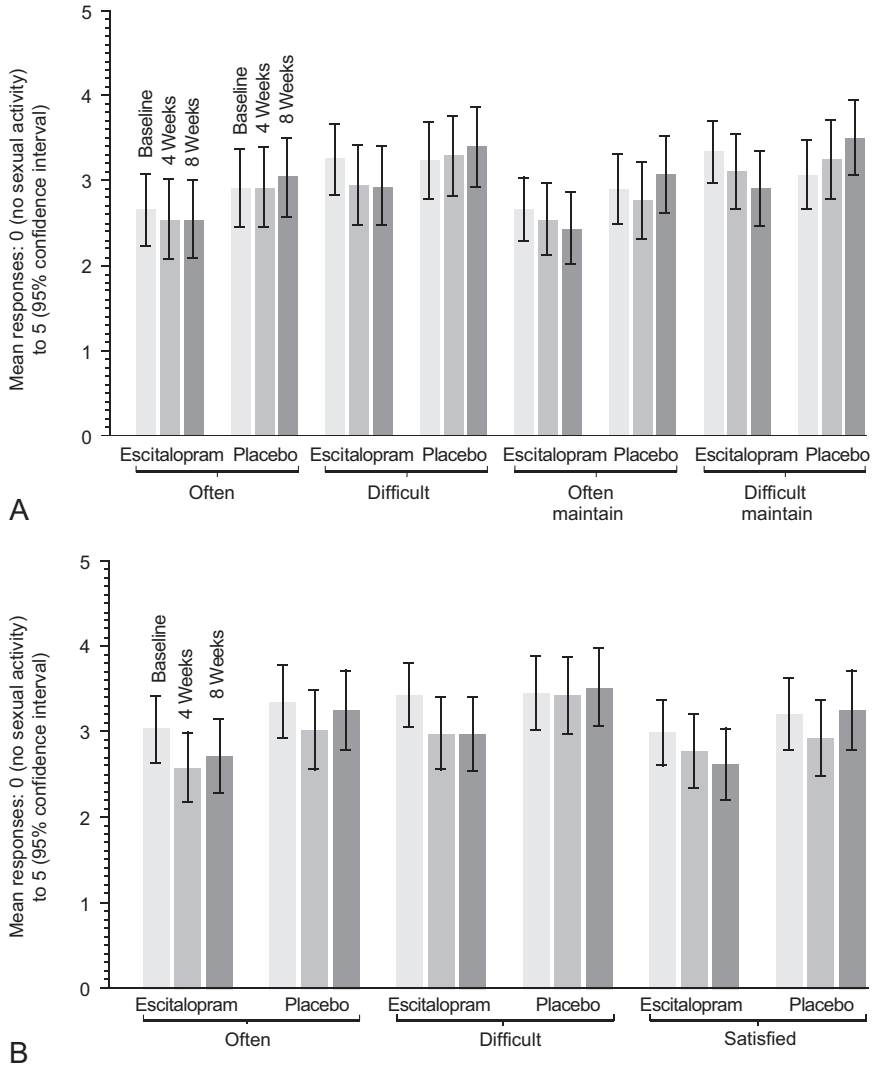

Fig. 3. Mean and 95% confidence intervals of responses to questions in the **A.** Female Sexual Function Index (FSFI) lubrication domain and **B.** FSFI orgasm domain at baseline, 4 weeks, and 8 weeks among women who were sexually active at baseline (n=73 escitalopram, n=68 placebo). Y-axis: possible scores ranged from 0=poor to 5=maximum function. X-axis: Sexual function items. Questions for lubrication included: "Often"=Over the past 4 weeks, how often did you become lubricated (wet) during sexual activity or intercourse?; "Difficult"=How difficult was it to become lubricated (wet) during sexual activity or intercourse?; "Often Maintain"=How often did you maintain your lubrication (wetness) until completion of sexual activity or intercourse?; and "Difficult Maintain"=How difficult was it to maintain your lubrication (wetness) until completion of sexual activity or intercourse? Changes in domain scores (weighted average of all domain item scores) from baseline to 8 weeks, comparing escitalopram with placebo, were significant for lubrication (P=.02) but not orgasm (P=.07).

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clear that sexual function in women decreases with age.[18,19] Selective serotonin reuptake inhibitors act by increasing the availability of serotonin at synapses, which can then inhibit dopamine centrally, affecting arousal and orgasm. Increased serotonin may also up- or downregulate serotonin receptors, over 95% of which are present peripherally, thus modulating arteriole vasodilation and vasoconstriction, mechanisms likely important for lubrication, arousal, and normal orgasmic function.[24] Anorgasmia is a well-described specific side effect of SSRIs among women with clinical depression or premenstrual dysphoric disorder.[7,8] Diminished lubrication, on the other hand, is not commonly described as being associated with SSRI use in either of these populations.[8,25] Peri- and postmenopausal women are more likely to have problems with lubrication before SSRI treatment; therefore, our findings may be explained by an already diminished baseline ability to lubricate, reducing the amount of change needed to achieve a clinically significant effect with the addition of an SSRI.

There is only one other report of SSRI therapy for vasomotor symptoms in nondepressed midlife women with detailed sexual function information.[26] Although women in that trial did not find benefit for vasomotor symptoms with sertraline as compared with placebo, significant worsening in Female Sexual Function Index domains for arousal, lubrication, orgasm, satisfaction, and pain were observed. Others have evaluated SSRIs for vasomotor symptoms, but sexual function was assessed by a simple checklist of side effects or a single sexual function question, usually related to desire, embedded in a quality-of-life

measure. In an extensive review of 16 studies of SSRIs and selective norepinephrine reuptake inhibitors for vasomotor symptoms, sexual function side effects were not reported as increased above placebo.[2] Other studies concur with these findings.[10–13,15,16]

Only a few studies have specifically studied the SSRI we used, escitalopram, for premenstrual dysphoric disorder,[27] major depressive disorder,[8] or vasomotor symptoms[28]; some degree of sexual dysfunction was reported in all three studies, but again, sexual function was not measured with a structured assessment of the various female sexual domains. In a 12-week premenstrual dysphoric disorder trial, escitalopram treatment-emergent effects of diminished libido (10–22%) and decrease in orgasm function (14–22%) were observed beyond the baseline reported for placebo (9% and 7%, respectively).[27] In depressed individuals, escitalopram was associated with 10–20% short-term treatment-emergent sexual dysfunction as compared with placebo; however, after 12 weeks, this was no longer significant.[8]Lastly, in an 8-week pilot study of 25 women taking escitalopram for vasomotor symptoms, four (16%) developed diminished libido and two (8%) developed anorgasmia, although there was no comparison group.

Most studies in depressed populations report sexual function does not vary by SSRI type, including citalopram, venlafaxine, paroxetine, fluoxetine, and sertraline.[8,24,29] Others, however, suggest that female orgasm disorder is most commonly associated with paroxetine and venlafaxine,[6,9,30] and an improvement in SSRI or selective norepinephrine reuptake inhibitor-induced sexual dysfunction may be achieved by switching to escitalopram.[31]

Details reported on sexual function in the Penn Ovarian Aging cohort inform the interpretation of our findings.[21] The majority of women in that study were ages 40–54 years, whereas the mean age of women in our study was 54 years. Gracia et al also noted a bimodal distribution in the composite Female Sexual Function Index score and assigned a cut point of normal sexual function at 20 rather than the cut point of 26.5 used in a large population of women, mean age 36.2 years (range 18–74 years).[32] The Female Sexual Function Index scores among our sexually active, predominantly postmenopausal women were quite comparable to those observed in the Penn Ovarian Aging cohort, both overall and among the six female sexual function domains.

Strengths of this study include detailed sexual function information, similar numbers of African American and white women, the inclusion of peri- and postmenopausal women, high adherence to therapy, and a low dropout rate (95% provided response data at week 8) comparable across arms. We note that although this was a community-based sample, the volunteer participants may be a select group who were motivated to seek treatment. It could be, at recruitment, that after describing sexual dysfunction as a possible side effect, women who already had sexual dysfunction were not concerned regarding a worsening effect and were apt to enroll in the study. On the other hand, women worried about sexual dysfunction may have been apt to decline participation. An 8-week treatment interval may be considered brief, but data indicate that this interval is sufficient time to assess sexual function side effects[33]; others suggest symptoms improve through time.[8] Longer studies, beyond 8 weeks, of sexual function in healthy women have not been done. We examined several potential modulating factors of sexual function and escitalopram but had limited power to assess any interactions, and other factors that we did not measure could have confounded the results.

Our findings are reassuring that among healthy nondepressed midlife women with bothersome vasomotor symptoms, 10–20 mg escitalopram per day did not affect overall sexual function and only minimally affected orgasmic response and lubrication with no effect on sexually related personal distress. Our report is important for women considering the use of escitalopram for management of vasomotor symptoms. A key consideration for all menopausal therapies is medication tolerance and adverse events. Although a majority reported common mild side effects of escitalopram after initiating treatment, there were no serious adverse events and equal numbers of women reported sexual function adverse events in the two groups. Further detailed evaluation of sexual function in midlife women is warranted, particularly among healthy nondepressed women taking SSRIs for vasomotor symptoms, and particularly to further assess any changes in the lubrication and orgasm domains.

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Appendix 1. Female Sexual Function Index Scoring

Question	Response Options
1. Over the past 4 weeks, how often did you feel sexual desire or interest?	5=Almost always or always 4=Most times (more than half the time) 3=Sometimes (approximately half the time) 2=A few times (less than half the time) 1=Almost never or never
2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?	5=Very high 4=High 3=Moderate 2=Low 1=Very low or none at all
3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?	0=No sexual activity 5=Almost always or always 4=Most times (more than half the time) 3=Sometimes (approximately half the time) 2=A few times (less than half the time) 1=Almost never or never
4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?	0=No sexual activity 5=Very high 4=High 3=Moderate 2=Low 1=Very low or none at all
5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?	0=No sexual activity 5=Very high confidence 4=High confidence 3=Moderate confidence 2=Low confidence 1=Very low or no confidence
7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?	0=No sexual activity 5=Almost always or always 4=Most times (more than half the time) 3=Sometimes (approximately half the time) 2=A few times (less than half the time) 1=Almost never or never
8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?	0=No sexual activity 1=Extremely difficult or impossible 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult
9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0=No sexual activity 5=Almost always or always 4=Most times (more than half the time) 3=Sometimes (approximately half the time) 2=A few times (less than half the time) 1=Almost never or never
10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0=No sexual activity 1=Extremely difficult or impossible 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult

(*continued*)

Appendix 1. Female Sexual Function Index Scoring (*continued*)

Question	Response Options
11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?	0=No sexual activity 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (approximately half the time) 4=A few times (less than half the time) 5=Almost never or never
12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?	0=No sexual activity 1=Extremely difficult or impossible 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult
13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	0=No sexual activity 5=Very satisfied 4=Moderately satisfied 3=Approximately equally satisfied and dissatisfied 2=Moderately dissatisfied 1=Very dissatisfied
14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?	0=No sexual activity 5=Very satisfied 4=Moderately satisfied 3=Approximately equally satisfied and dissatisfied 2=Moderately dissatisfied 1=Very dissatisfied
15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?	5=Very satisfied 4=Moderately satisfied 3=Approximately equally satisfied and dissatisfied 2=Moderately dissatisfied 1=Very dissatisfied
16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?	5=Very satisfied 4=Moderately satisfied 3=Approximately equally satisfied and dissatisfied 2=Moderately dissatisfied 1=Very dissatisfied
17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?	0=Did not attempt intercourse 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (approximately half the time) 4=A few times (less than half the time) 5=Almost never or never
18. Over the past 4 weeks, how often did you experience discomfort or pain after vaginal penetration?	0=Did not attempt intercourse 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (approximately half the time) 4=A few times (less than half the time) 5=Almost never or never
19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or after vaginal penetration?	0=Did not attempt intercourse 1=Very high 2=High 3=Moderate 4=Low 5=Very low or none at all

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Appendix 2. Female Sexual Function Index Domain Scores and Full Scale Score*

Domain	Questions	Score Range	Factor	Minimum Score	Maximum Score	Score
Desire	1, 2	1–5	0.6	1.2	6.0	
Arousal	3, 4, 5, 6	0–5	0.3	0	6.0	
Lubrication	7, 8, 9, 10	0–5	0.3	0	6.0	
Orgasm	11, 12, 13	0–5	0.4	0	6.0	
Satisfaction	14, 15, 16	0 (or 1)–5	0.4	0.8	6.0	
Pain	17, 18, 19	0–5	0.4	0	6.0	
Full scale score range				2.0	36.0	

* The individual domain scores and full scale (overall) score of the Female Sexual Function Index can be derived from the computational formula outlined in this table. For individual domain scores, add the scores of the individual items that comprise the domain and multiply the sum by the domain factor. Add the six domain scores to obtain the full scale score. It should be noted that within the individual domains, a domain score of zero indicates that the subject reported having no sexual activity during the past month. Subject scores can be entered in the right hand column.

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