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Effects of low-dose paroxetine 7.5 mg on weight and sexual function during treatment of vasomotor symptoms associated with menopause

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Abstract

Objective: Two phase 3, randomized, placebo-controlled trials demonstrated that low-dose paroxetine 7.5 mg reduced the frequency and severity of vasomotor symptoms (VMS) associated with menopause and had a favorable tolerability profile. The impact of paroxetine 7.5 mg on body weight and sexual function was evaluated in a pooled analysis.

Methods: Postmenopausal women aged 40 years or older who had moderate to severe VMS were randomly assigned to receive paroxetine 7.5 mg or placebo once daily for 12 or 24 weeks. Assessments included changes in body mass index (BMI) and weight, Arizona Sexual Experiences Scale score, Hot Flash–Related Daily Interference Scale sexuality subscore, and adverse events related to weight or sexual dysfunction.

Results: Pooled efficacy and safety populations comprised 1,174 and 1,175 participants, respectively. Baseline values were similar for median weight (~75 kg), median BMI (~28 kg/m^2), and the proportion of women with sexual dysfunction (~58%). No clinically meaningful or statistically significant changes from baseline in weight or sexual function assessments occurred in the paroxetine 7.5 mg group. Small but statistically significant increases in weight and BMI were observed in the placebo group only on week 4. No significant difference between treatment groups was observed in the proportion of participants who had 7% or higher gain in body weight on week 4, 12, or 24. Rates of adverse events suggestive of sexual dysfunction were low and similar in both treatment groups.

Conclusions: Paroxetine 7.5 mg does not cause weight gain or negative changes in libido when used to treat menopause-associated VMS in postmenopausal women.

Key Words: Hot flashes – Menopause – Paroxetine mesylate – Sexual dysfunction – Vasomotor symptoms – Weight.

Vasomotor symptoms (VMS) associated with menopause, such as hot flashes and night sweats, affect up to 80% of menopausal women,[1] negatively impact quality of life and daily functioning,[2] and cause many women to seek treatment.[3] Although hormone therapy is approved for the treatment of moderate to severe VMS associated with menopause,[4] safe and effective nonhormonal alternatives to hormone therapy are needed.

Since the 1990s, multiple clinical trials have evaluated the efficacy of antidepressants and anticonvulsants in treating VMS associated with menopause[5,6]; yet, until recently, only a few—including some selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)—had suggested efficacy.[5,7] Neurotransmitters such as norepinephrine and serotonin are hypothesized to influence temperature homeostasis,[5,8] and agents such as SSRIs/SNRIs,

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which increase serotonin and norepinephrine transmission, may thereby be able to modulate thermoregulation, although the precise mechanisms remain unclear.[5]

The use of SSRIs and SNRIs at therapeutic doses prescribed for psychiatric disorders is associated with several unwanted adverse effects, including weight gain and sexual dysfunction.[9] Because both weight and libido may already be negatively impacted by menopause,[10,11] any treatment that exacerbates these effects is unlikely to be viewed favorably by women and may result in drug discontinuation, noncompliance, or inappropriate self-management.[9] Despite these tolerability issues, some physicians prescribe antidepressants off-label for the management of menopausal VMS. According to IMS Health estimates, more than 2.4 million SSRI prescriptions were filled in 2012 for the treatment of VMS.[12] For paroxetine prescriptions, 20 and 40 mg were the most commonly prescribed doses.[12]

Findings from previously published clinical studies of paroxetine[13-15] and results of a phase 2 study[16] indicated that doses lower than those prescribed for psychiatric disorders may be efficacious in treating moderate to severe VMS associated with menopause while demonstrating favorable tolerability. Brisdelle (paroxetine 7.5 mg; previously called low-dose mesylate salt of paroxetine) is the first and only US Food and Drug Administration–approved nonhormonal option for the treatment of moderate to severe VMS associated with menopause. Two phase 3 studies (ClinicalTrials.gov identifiers NCT01361308 and NCT01101841) demonstrated that paroxetine 7.5 mg reduced moderate to severe VMS in postmenopausal women and was well tolerated.[17] Using pooled data from the two phase 3 studies, we examined whether treatment with paroxetine 7.5 mg affected weight, sexual function, or both.

METHODS

Participants and study design

Methodologies for the 12-week and 24-week studies, including participant inclusion and exclusion criteria, study designs, primary efficacy endpoints, and statistical analyses, have been previously described in detail.[17] Both studies were conducted in postmenopausal women with moderate to severe VMS associated with menopause. The key eligibility criterion was more than 7 to 8 hot flashes per day (or 50-60 hot flashes per week) in the 30 days before screening. Women with a body mass index (BMI) of 40 kg/m^2 or higher at baseline were excluded from the 24-week study. After a 12-day, single-blind, placebo-controlled run-in period, participants compliant with electronic diary entry who still met hot flash eligibility criteria were randomly assigned 1:1 to receive paroxetine 7.5 mg or an identical capsule of placebo once daily at bedtime for 12 weeks (84 d) or for 24 weeks (168 d; Fig. 1).

Study endpoints and assessments

Secondary objectives included assessments of treatment effects on weight (kg) and BMI (kg/m^2) at each clinic visit and assessment of treatment effects on sexual functioning. Height and weight were recorded at the baseline visit, and weight was recorded at each subsequent clinic visit (Fig. 1). BMI (kg/m^2) was calculated as: weight (kg) / (height [cm] / 100)^2. Analyses of weight change were conducted for both studies to examine the proportion of participants who experienced a body weight gain of 7% or more, which is generally accepted as a clinically significant criterion for weight gain in participants being treated with antidepressants, including SSRIs.[18-20]

The Arizona Sexual Experiences Scale (ASEX; see Figure, Supplemental Digital Content 1, http://links.lww.com/MENO/A90),[21] a rating scale that has been validated in psychiatric patients taking antidepressants, was used in the present studies to quantify and assess participants' sex drive, arousal, vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. ASEX was completed on day 0 (baseline), day 28 (week 4), day 84 (week 12), and day 169 (week 24); women were instructed to skip question 3a. ASEX scores range from 1 (highest sexual function) to 6 (lowest or absent sexual function). The total ASEX score was obtained by adding the five individual domain scores together, resulting in a possible total score range from 5 to 30. Results from this scale were analyzed using two categories (ie, sexual dysfunction and no sexual dysfunction). According to McGahuey et al,[21] participants were considered as having sexual dysfunction if they had a total score of 19 or higher, a score of 5 or higher on any individual questions, or a score of 4 or higher on any three questions. Otherwise, they were considered as having no sexual dysfunction. A decrease in ASEX score indicated an improvement in sexual function.

The Hot Flash–Related Daily Interference Scale (HFRDIS; see Figure, Supplemental Digital Content 2, http://links.lww.com/MENO/A91) is a validated rating scale that measures the degree to which VMS interfere with work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life, and overall quality of life.[22] For each activity, the possible response was a categorical score ranging from 0 to 10. A score of 0 indicated that the participant's hot flashes did not interfere at all with the daily activity (or there were no hot flashes), and a score of 10 indicated that the participant's hot flashes interfered, to the worst possible extent, with the daily activity. Forms were completed on day 1 (baseline), day 28, day 84, and day 169, and change from baseline was calculated. The HFRDIS was a prespecified secondary endpoint in these studies, and sexuality subscore (item 8) was evaluated in the current exploratory analysis. Participants with a score of 3 or less were defined as HFRDIS responders, and participants with a score of 4 or higher were defined as HFRDIS nonresponders.

In addition, spontaneous reports of treatment-emergent adverse events (TEAEs) related to weight gain and sexual dysfunction were recorded throughout the studies and analyzed. Overall safety was assessed by evaluating all adverse events (AEs), clinical laboratory tests, vital signs, physical evaluations, and electrocardiograms.

Statistical analyses

Data from weeks 1 to 12 in the 12-week and 24-week studies were pooled for these analyses. Only the 24-week study had data

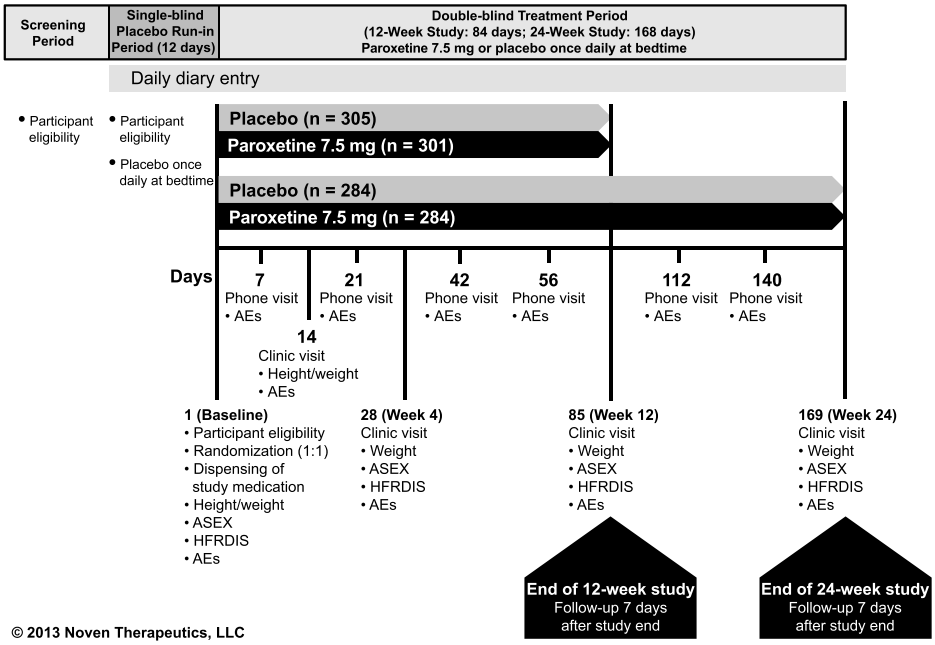

FIG. 1. Study design and timing of evaluations. AE, adverse event; ASEX, Arizona Sexual Experiences Scale; HFRDIS, Hot Flash–Related Daily Interference Scale.

from weeks 13 to 24; therefore, analyses from weeks 13 to 24 were based on data from the 24-week study only. χ^2 test or Fisher's exact test was used to assess results from the HFRDIS and ASEX. Rank-transformed analysis of covariance or a nonparametric method with baseline value as covariate was used to evaluate changes in body weight and BMI from baseline to weeks 4, 12, and 24 and to examine the differences between paroxetine 7.5 mg and placebo. Two post hoc analyses were conducted. The first post hoc analysis determined the proportion of participants in each treatment group who experienced an increase in body weight of 7% or more. Results were summarized categorically, and *P* values for group differences were generated using a logistic model with baseline as covariate. The second post hoc analysis compared sexual function, as expressed by the change from baseline in ASEX scores in relation to relief of VMS (ie, to observe whether women who experienced relief of VMS with paroxetine 7.5 mg and women who continued to have VMS differ in their sexual function wellness over time), in the paroxetine 7.5 mg group on weeks 4, 12, and 24. Relief of VMS was demonstrated by women who achieved a 50% or higher reduction in moderate to severe hot flash frequency from baseline (ie, hot flash responders); hot flash nonresponders referred to women who achieved a less than 50% reduction in moderate to severe hot flash frequency from baseline. *P* values for group differences were generated using Wilcoxon test. In addition, Pearson's correlation analysis was used to examine the correlation between the mean change from baseline in ASEX score and the mean change in weekly hot flash reduction on weeks 4, 12, and 24.

RESULTS

Participant disposition and characteristics

A total of 1,184 participants were enrolled in the two pivotal phase 3 studies: 614 participants were enrolled in the 12-week study and 570 participants were enrolled in the 24-week study. Pooled data for disposition and baseline characteristics are shown in Table 1. At baseline, the median weight was 74.5 kg in the paroxetine 7.5 mg arm and 75.8 kg in the placebo arm, and the median BMI was 27.9 kg/m^2 in the paroxetine 7.5 mg arm and 28.2 kg/m^2 in the placebo arm. The median BMI was similar between the 12-week study (paroxetine 7.5 mg, 28.3 kg/m^2; placebo, 29.0 kg/m^2) and the 24-week study (paroxetine 7.5 mg, 27.4 kg/m^2; placebo, 27.7 kg/m^2). Women with a BMI of 40 kg/m^2 or higher were excluded from the 24-week study. The proportions of participants in the phase 3 studies reporting sexual dysfunction at baseline, using ASEX, were similar between the paroxetine 7.5 mg arm and the placebo treatment arm (59% and 58%, respectively).

Impact of treatment on weight

Body mass index

On week 4 (pooled data), the median change in BMI from baseline was 0.0 kg/m^2 in the paroxetine 7.5 mg arm and +0.07 kg/m^2 in the placebo arm ($P = 0.0003$; Fig. 2). On week 12 (pooled data), the median change in BMI from baseline was +0.06 for the paroxetine 7.5 mg arm and +0.16 for the placebo arm ($P = 0.1383$). On week 24 (24-wk study only), the median change in BMI from baseline was +0.16 for the paroxetine 7.5 mg arm and +0.02 for the placebo arm ($P = 0.3173$).

Body weight

The percent change in median body weight from baseline to week 4 (pooled data) was 0% in the paroxetine 7.5 mg arm and +0.21% in the placebo arm ($P = 0.0002$; Table 2). No significant differences in percent change in median body weight from baseline were observed between treatment arms on week 12 (pooled data; paroxetine 7.5 mg +0.17% vs placebo +0.52%; $P = 0.1124$)

TABLE 1. *Participant disposition and baseline characteristics (pooled phase 3 data)*

	Disposition	
	Paroxetine 7.5 mg	Placebo
Participants, n		
Randomly assigned to treatment	591	593
mITT population	585	589
Safety population	586	589
Completed study, n/N (%)	506/585 (87)	496/589 (84)
Most common reasons for discontinuation, %		
Participant request	3.9	7.8
AE/severe AE	3.8	3.2
Other	4.4	2.9
	Characteristics (mITT population)	
	Paroxetine 7.5 mg (n = 585)	Placebo (n = 589)
Age, median (range), y	54 (40-73)	54 (40-79)
Race, n (%)		
White	395 (67.5)	426 (72.3)
Black	175 (29.9)	146 (24.8)
Asian	4 (0.7)	7 (1.2)
Other	11 (1.8)	10 (1.7)
Weight, kg		
Mean (SD)	77.2 (16.3)	77.7 (16.2)
Median (range)	74.5 (37.6-175.5)	75.8 (45.4-153.8)
Body mass index, kg/m^2		
Mean (SD)	28.6 (5.7)	29.0 (5.5)
Median (range)	27.9 (16.8-60.7)	28.2 (18.7-56.5)
Sexual dysfunction, n (%)		
No	237 (41.3)	238 (42.0)
Yes	337 (58.7)	329 (58.0)

mITT, modified intent-to-treat (received ≥1 dose of study medication and had ≥1 d of on-treatment daily hot flash diary data); AE, adverse event.

or week 24 (24-wk study only; paroxetine 7.5 mg +0.48% vs placebo +0.09%; $P = 0.2941$).

In the pooled analysis, few participants in either treatment arm experienced a weight gain of 7% or more of their baseline body weight on week 4 (<1%; $P = 0.3546$) or week 12 (<2%; $P = 0.5388$; Table 2). In the 24-week study, the proportions of participants with a weight gain of 7% or more of their baseline weight on week 24 were 4% (paroxetine 7.5 mg) and 3% (placebo; $P = 0.4701$).

The incidence of increased body weight spontaneously reported as a TEAE up to week 12 (pooled data) was similar between treatment arms. In the paroxetine 7.5 mg arm, three participants (0.5%) reported increased weight compared with five participants (0.8%) in the placebo arm.

Impact of treatment on sexual functioning

Arizona Sexual Experiences Scale

No statistically significant difference in the proportions of participants reporting sexual dysfunction was observed between the paroxetine 7.5 mg arm and the placebo arm in the pooled analysis on week 4 (56% in both groups), week 12 (55% and 52%, respectively), or week 24 (56% and 57%,

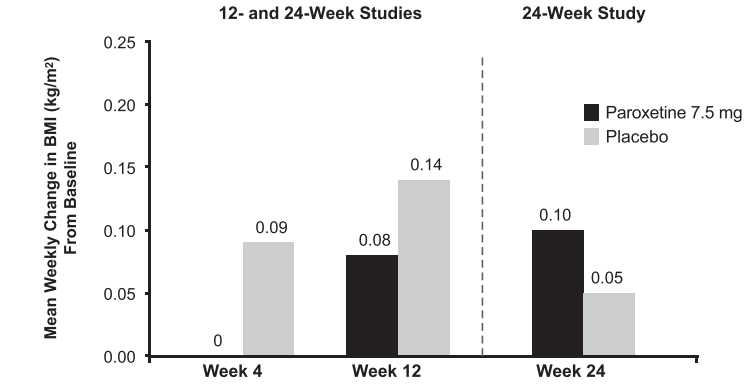

FIG. 2. Impact of treatment on body mass index (BMI). *P* values were calculated from rank-transformed analysis of covariance.

TABLE 2. *Impact of treatment on weight (pooled phase 3 data; mITT population)*

	Paroxetine 7.5 mg (n = 585)	Placebo (n = 589)	*P*
Change in weight from baseline, median (minimum, maximum), %			
Week 4[a]	0.00 (−8.13, 11.11)	+0.21 (−11.04, 37.31)	0.0002
Week 12[a]	+0.17 (−9.56, 9.21)	+0.52 (−19.59, 39.55)	0.1124
Week 24[b]	+0.48 (−18.06, 14.89)	+0.09 (−25.93, 35.82)	0.2941
Participants with weight gain ≥7% from baseline, n (%)			
Week 4[a]	3 (0.54)	1 (0.18)	0.3546
Week 12[a]	6 (1.11)	8 (1.52)	0.5388
Week 24[b]	11 (4.07)	8 (2.99)	0.4701

mITT, modified intent-to-treat (received ≥1 dose of study medication and had ≥1 d of on-treatment daily hot flash diary data).
[a]Pooled data from the 12-week and 24-week studies.
[b]Data from the 24-week study only.

respectively) in the 24-week study (Fig. 3). Furthermore, no shift from "no sexual dysfunction" to "sexual dysfunction" was observed over time from week 4 to week 12 to week 24.

At baseline, the mean ASEX total score was 17.94 in the paroxetine 7.5 mg arm and 17.60 in the placebo arm. On week 4, the mean change in total scores was −0.23 and −0.25, respectively ($P = 0.8523$). No significant changes were observed on week 12 (paroxetine 7.5 mg, −0.29; placebo, −0.41; $P = 0.4742$) or week 24 (paroxetine 7.5 mg, −0.38; placebo, −0.48; $P = 0.8553$), nor were significant differences detected in any of the ASEX symptoms (sex drive, arousal, vaginal lubrication, orgasm, or satisfaction) between the paroxetine 7.5 mg group and the placebo group at any time point during the studies (Table 3).

ASEX in hot flash responders

In the paroxetine 7.5 mg group, women who were hot flash responders (ie, had a ≥50% reduction in moderate to severe hot flash frequency from baseline) showed greater improvement in ASEX scores than women who were nonresponders (ie, had a <50% reduction in moderate to severe hot flash frequency from baseline) on weeks 4, 12, and 24; however, the magnitude of improvement did not reach statistical significance at any time point (Fig. 4). Results of a correlation analysis of mean change from baseline in ASEX scores and mean change from baseline in weekly hot flash reduction in the paroxetine 7.5 mg group were not statistically significant at any time point.

Hot Flash–Related Daily Interference Scale

According to the sexuality subscore of the HFRDIS, participants in both treatment arms reported less interference with sexuality on weeks 4, 12, and 24 compared with baseline (Table 4). No significant differences were noted between treatment arms.

The incidence of sexual dysfunction spontaneously reported as a TEAE up to week 12 (pooled data) was similar between treatment arms. No AE suggestive of sexual dysfunction occurred in 1% or more of participants treated with paroxetine 7.5 mg. Reported sexual function TEAEs (n [%]) included the following: anorgasmia (1 [0.2] in each treatment arm); decreased libido (paroxetine 7.5 mg, 0 [0]; placebo, 2 [0.3]); loss of libido (paroxetine 7.5 mg, 0 [0]; placebo, 1 [0.2]); sexual dysfunction (paroxetine 7.5 mg, 1 [0.2]; placebo, 0 [0]); vulvovaginal discomfort (paroxetine 7.5 mg, 0 [0]; placebo, 1 [0.2]); and vulvovaginal dryness (paroxetine 7.5 mg, 0 [0]; placebo, 1 [0.2]).

DISCUSSION

Use of antidepressants at therapeutic doses prescribed for psychiatric disorders is associated with several unwanted adverse effects,[9] including weight gain and sexual dysfunction. SSRIs may interact with central mechanisms that regulate

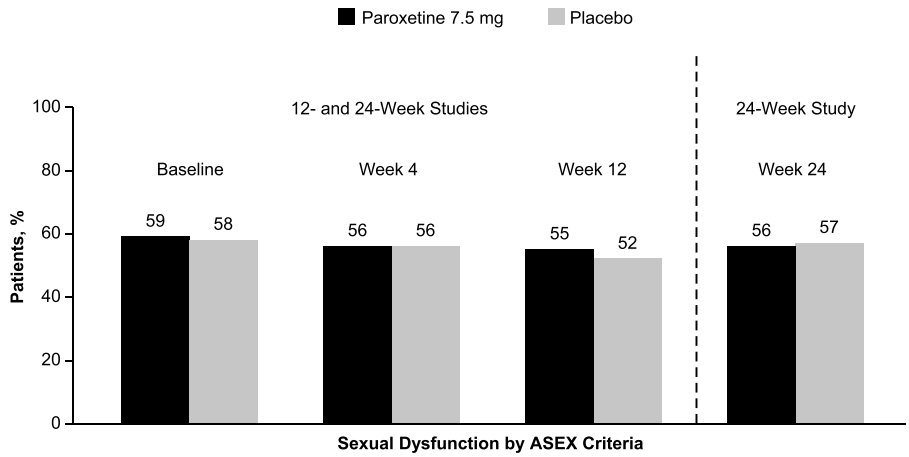

FIG. 3. Impact of treatment on sexual dysfunction. *P* values were not significant versus placebo for all comparisons. ASEX, Arizona Sexual Experiences Scale.

TABLE 3. *Impact of treatment on ASEX scores (pooled phase 3 data; mITT population)*

	Paroxetine 7.5 mg (n = 585)	Placebo (n = 589)	*P*
Sex drive score, mean (SD)			
Baseline	3.98 (1.30)	4.00 (1.35)	
Change on week 4[a]	−0.04 (0.88)	−0.07 (0.89)	0.8179
Change on week 12[a]	−0.12 (0.97)	−0.14 (0.93)	0.9721
Change on week 24[b]	−0.08 (0.93)	−0.18 (0.96)	0.3412
Sexual arousal score, mean (SD)			
Baseline	3.61 (1.21)	3.60 (1.19)	
Change on week 4[a]	−0.05 (0.87)	−0.08 (0.86)	0.4838
Change on week 12[a]	−0.06 (1.02)	−0.15 (0.89)	0.0899
Change on week 24[b]	−0.08 (1.01)	−0.10 (0.95)	0.8224
Vaginal lubrication score, mean (SD)			
Baseline	3.76 (1.22)	3.58 (1.29)	
Change on week 4[a]	−0.11 (0.91)	−0.07 (0.92)	0.7975
Change on week 12[a]	−0.06 (0.98)	−0.05 (0.92)	0.6517
Change on week 24[b]	−0.15 (0.93)	−0.04 (0.97)	0.1664
Orgasm score, mean (SD)			
Baseline	3.71 (1.21)	3.63 (1.22)	
Change on week 4[a]	−0.07 (0.93)	−0.08 (0.81)	0.4022
Change on week 12[a]	−0.11 (0.99)	−0.10 (0.89)	0.9966
Change on week 24[b]	−0.12 (1.09)	−0.15 (0.93)	0.8341
Orgasm satisfaction score, mean (SD)			
Baseline	2.87 (1.37)	2.78 (1.36)	
Change on week 4[a]	0.04 (1.08)	0.06 (0.94)	0.9832
Change on week 12[a]	0.05 (1.04)	0.03 (0.97)	0.9055
Change on week 24[b]	0.05 (1.15)	0.00 (1.10)	0.3022

ASEX, Arizona Sexual Experiences Scale; mITT, modified intent-to-treat.
[a]Pooled data from the 12-week and 24-week studies.
[b]Data from the 24-week study only.

appetite and food intake, and increases in body weight during the treatment of psychiatric disorders are common.[23,24] Many psychiatric medications, including SSRIs and SNRIs, can also adversely affect normal sexual response,[25-27] probably by diminishing the function of the excitatory neurotransmitters dopamine and norepinephrine and by inducing central sexual satiety signaling, with subsequent inhibition of desire, arousal, and/or orgasm.[24] Clinically, this may undermine treatment compliance.[28] Moreover, weight gain and sexual dysfunction are adverse effects that are of special concern to postmenopausal women because menopause itself is associated with changes in body weight, body self-image, and libido.[10,11,29,30] Menopausal symptoms are often associated with loss of libido, dyspareunia, and orgasmic dysfunction.[31] Ideally, therapeutic agents for VMS associated with menopause should not negatively impact sexual function or weight in this vulnerable population.

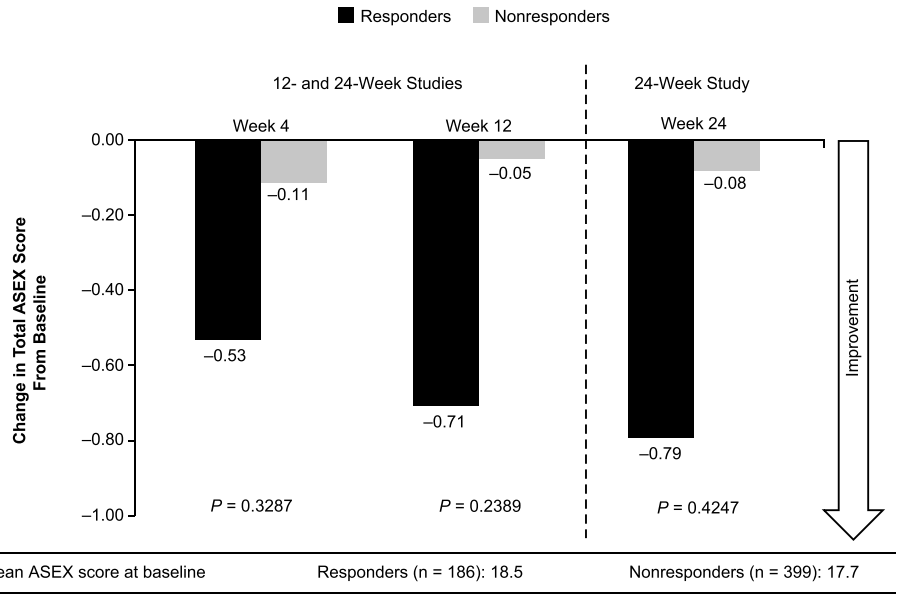

FIG. 4. Arizona Sexual Experiences Scale (ASEX) score reductions in hot flash responders and hot flash nonresponders in the paroxetine 7.5 mg group. Responders were defined as women who achieved a 50% or higher reduction in moderate to severe hot flash frequency from baseline. *P* values are the results of Wilcoxon test.

TABLE 4. *Impact of treatment on HFRDIS sexuality score (pooled phase 3 data; mITT population)*

	Paroxetine 7.5 mg (n = 585)	Placebo (n = 589)	*P*
Responders, n/N (%)			
Baseline	273/573 (47.64)	268/565 (47.43)	0.9434
Week 4[a]	308/527 (58.44)	300/530 (56.60)	0.5451
Week 12[a]	301/487 (61.81)	304/482 (63.07)	0.6847
Week 24[b]	131/216 (60.65)	124/196 (63.27)	0.5849

HFRDIS responders refer to participants with an HFRDIS score of 3 for the activity (indicating that there was little or no interference with the activity attributable to hot flashes). *P* values were defined from the Logit model with baseline as covariate.
HFRDIS, Hot Flash–Related Daily Interference Scale; mITT, modified intent-to-treat (received ≥1 dose of study medication and had ≥1 d of on-treatment daily hot flash diary data).
[a]Pooled data from the 12-week and 24-week phase 3 studies.
[b]Data from the 24-week study only.

In studies of SSRIs and SNRIs used to treat psychiatric disorders, increases in weight and sexual dysfunction were well documented,[24] although the frequency of such increases varied among drugs.[27,32] In a long-term comparison study of SSRIs for the treatment of panic disorder, 12 months of monotherapy with paroxetine, citalopram, or fluoxetine was associated with greater weight gain than was seen with fluvoxamine.[33] Furthermore, citalopram and paroxetine were associated with higher levels of sexual AEs (eg, anorgasmia, loss of libido) when compared with fluoxetine or fluvoxamine.[33] In a sample of adult outpatients receiving antidepressant monotherapy without other risk factors for sexual dysfunction, treatment with the SSRI citalopram and with the SNRI venlafaxine XR was associated with sixfold greater rates of sexual dysfunction than were seen with bupropion.[34]

To date, few clinical trials of SSRIs and SNRIs for the treatment of VMS associated with menopause have reported the impact of treatment on weight gain or libido, and most did not include prospective measures by which these parameters could be assessed. In a 6-week study of 254 postmenopausal women who were treated with the SSRI citalopram or placebo, citalopram-treated women reported worsening scores for sexual relations and difficulty with orgasm and vaginal lubrication compared with baseline.[35] Effects may have been dose-related; scores were worse in women receiving citalopram 30 mg/day than in those given citalopram 10 mg/day.[35] In a 12-week study of 707 postmenopausal women who were treated with the SNRI desvenlafaxine or placebo, weight gain was reported as an AE by up to 7.6% of women who were treated with desvenlafaxine compared with 3.9% of women who were given placebo.[36] Decreased libido was also reported as an AE in up to 5.3% of desvenlafaxine-treated women compared with 1.3% of women given placebo.[36] One recent trial, which included assessment of sexual function, randomly assigned 200 women experiencing bothersome VMS associated with menopause to treatment with the SSRI escitalopram 10 mg/day or placebo for 8 weeks.[37] Using the total female sexual function index score, investigators found that escitalopram did not significantly alter overall sexual function; however, female sexual function index responses revealed that women randomly assigned to this SSRI experienced greater declines in the subdomains of orgasmic function and lubrication compared with those randomly assigned to placebo.[37]

Results of the present analysis based on data from two pivotal phase 3 studies indicate that treatment with paroxetine 7.5 mg up to 24 weeks was not associated with weight gain or change in sexual function in women with moderate to severe VMS associated with menopause. Compared with baseline, no clinically relevant differences in body weight and BMI, or in reports of decreased libido or altered sexual functioning, were observed between treatment arms over time. Participants treated with paroxetine 7.5 mg up to 24 weeks did not experience increases in weight or BMI compared with baseline that differed significantly from placebo; overall, few participants in either treatment arm experienced a clinically significant body weight gain (≥7%).

Among women who received paroxetine 7.5 mg, those who were hot flash responders had a greater magnitude of ASEX score improvement than hot flash nonresponders, but the difference did not reach statistical significance at any time point; results of a correlation analysis between hot flash reduction and change in ASEX score also were not significant. It should be noted that these studies were not powered to conduct these analyses. In small randomized trials of venlafaxine and fluoxetine for the treatment of hot flashes, libido scores improved from baseline during the 4-week study periods.[38,39] Improvement in sexual desire in this treatment population might be postulated as resulting from decreased hot flashes and improved sleep habits and mood symptoms. These preliminary observations may provide an interesting topic for future research, particularly because almost 46% of women who report hot flashes also report reduced libido.[40]

Almost 60% of participants in this study reported sexual dysfunction at baseline according to ASEX, underscoring that a high prevalence of sexual dysfunction seems to be common, particularly surrounding the time of menopause.[41,42] Results of a survey of 1,749 women aged 18 to 59 years in the United States indicated that 43% of women of all ages reported sexual dysfunction.[43] A larger survey of more than 31,000 women aged 18 to 102 years in the United States indicated that 44.2% of women had at least one sexual problem (desire, arousal, or orgasm), with the highest prevalence (80.1%) observed in women 65 years or older.[44] In another study of 1,550 older (aged 57-85 y) US women, approximately half of sexually active women reported at least one bothersome sexual problem.[45] Similar levels of sexual dysfunction are reported in countries worldwide; a study of adults older than 40 years in 29 nations reported that 39% of women were affected by at least one sexual problem, including lack of sexual interest, inability to

reach orgasm, and lubrication difficulties.[46] In Australia, a longitudinal evaluation of 438 women across a period of 9 years, as part of the Melbourne Women's Midlife Health Project, demonstrated that the transition from early to late menopause was associated with a marked increase in questionnaire scores indicating sexual dysfunction (from 42% in the early stages of menopause to 88% at later stages).[47]

In the present study, treatment with paroxetine 7.5 mg for up to 24 weeks did not worsen sexual functioning. No shift from "no sexual dysfunction" to "sexual dysfunction" was observed over time from week 4 to week 12 to week 24, and no meaningful differences in ASEX scores were detected between treatment arms. ASEX score data are particularly noteworthy given that this scale has been validated in psychiatric patients using antidepressants.[21] In addition, no significant differences in HFRDIS sexuality subscore were observed between treatment arms. Participants in both arms demonstrated little or no interference with sexual function on this HFRDIS subscale on weeks 4, 12, and 24 compared with baseline, although it should be noted that this single component of the HFRDIS is not a validated measure for sexual function. Furthermore, the incidence of spontaneously reported AEs suggestive of sexual dysfunction was low and similar in the paroxetine 7.5 mg and placebo arms.

Limitations of the present study should be considered. First, study participants were not specifically recruited from a population of women presenting with VMS and concomitant complaints of sexual dysfunction. Although this observation might seem to reduce the ability of this trial to assess the impact of paroxetine 7.5 mg on women with sexual dysfunction, the high baseline prevalence of this condition among trial participants reduces this concern. Second, the present study had a relatively short duration of treatment and follow-up. Several studies of SSRIs and SNRIs have reported stable weight or even small weight losses during short-term treatment (4-6 mo) and increases in weight across a longer trial duration (eg, ≥12 mo).[23,48-50] The impact of paroxetine 7.5 mg on body weight and sexual function for a treatment duration longer than 24 weeks is unknown.

CONCLUSIONS

Pooled results of two phase 3, randomized, placebo-controlled trials show that paroxetine 7.5 mg is an effective nonhormonal treatment option for moderate to severe VMS associated with menopause and is not associated with meaningful changes in body weight or sexual function for up to 24 weeks of treatment.

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