REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause

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OBJECTIVE: The objective of the study was to assess the efficacy and safety of desvenlafaxine (administered as desvenlafaxine succinate) for menopausal vasomotor symptoms.

STUDY DESIGN: Postmenopausal women (n = 458) experiencing 50 or more moderate to severe hot flushes per week received desvenlafaxine 100 or 150 mg/d, with titration at therapy initiation, or placebo. Hot flush number and severity were assessed at weeks 4 and 12. Safety data were collected throughout the trial.

RESULTS: Desvenlafaxine 100 and 150 mg/d significantly reduced the number of hot flushes compared with placebo at weeks 4 and 12 (all $P \leq .012$), achieving 65.4% and 66.6% reductions from baseline at week 12, respectively (placebo, 50.8%). Hot flush severity and number of nighttime awakenings were significantly reduced at both time points (all $P \leq .048$). Desvenlafaxine groups reported significantly more adverse events compared with placebo during week 1 only. No difference in discontinuations because of adverse events was observed.

CONCLUSION: Desvenlafaxine is an effective nonhormonal treatment for menopausal hot flushes. Dose titration improves initial tolerability.

Key words: desvenlafaxine succinate, hot flushes, menopause, nonhormonal treatment, vasomotor symptoms

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Vasomotor symptoms (VMS), among the most common symptoms of menopause, can interfere with daily activities[1] and have been associated with mood disturbances[2-4] and disrupted sleep.[5,6] Hormone therapy (estrogen with or without progesterone) is the most effective treatment for VMS.[7] However, many women who experience hot flushes either cannot take hormone therapy or choose not to use it. There are no currently approved nonhormonal treatments for hot flushes associated with menopause. Thus, there is a need for a safe and effective nonhormonal treatment for VMS to complement existing therapies.

Serotonin and norepinephrine pathways are thought to play an important role in thermoregulatory function. Estrogen has been shown to modulate serotonin and norepinephrine signaling throughout the brain, including hypothalamic areas associated with temperature homeostasis in preclinical trials.[8-10] During menopause, fluctuating estrogen levels may alter the balance of these neurotransmitters, with the resulting disruption in signaling leading to the onset of hot flushes.[11-15] Several trials[16-21] have recently demonstrated a role for selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the treatment of VMS. However, these studies were small and of short duration (≤ 12 weeks) and their methods and symptom assessment varied.[22] Their patient populations were not restricted to generally healthy, menopausal women with moderate to severe symptoms, who are typically included in hormone therapy trials.

Desvenlafaxine (administered as desvenlafaxine succinate) is a novel SNRI for the treatment of VMS associated with menopause, also shown to effectively treat major depressive disorder at doses ranging from 50 to 400 mg/d.[23-25] Desvenlafaxine alleviated thermoregulatory dysfunction in 2 animal models of thermoregulation[14] and reduced the number and severity of hot flushes compared with placebo in a phase 3 clinical trial.[26] Adverse drug reactions (ADRs) reported with desvenlafaxine are consistent with other SSRIs/SNRIs. Treatment with desvenlafaxine was initiated in the first VMS

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trial at the maintenance dose without titration and discontinued at study end without tapering. As a result, a high incidence of adverse events (AEs) and early withdrawals because of AEs occurred during the first week of treatment, and increased AEs were reported on discontinuation of desvenlafaxine.[26] Dose titration at the onset of treatment and gradual tapering at termination are usual practice with this class of drugs to improve early tolerability and reduce discontinuation symptoms.[27-29] The current trial included titration and tapering protocols to manage AEs at the beginning of therapy and at its conclusion. The primary objective was to assess the efficacy and safety of 2 doses of desvenlafaxine compared with placebo for the treatment of moderate to severe VMS associated with menopause.

MATERIALS AND METHODS

Participants

The study was conducted at 34 sites in the United States, including private and institutional practice and research centers, between June 2006 and February 2007. This multicenter clinical trial was designed to be a registration trial for desvenlafaxine. All methods, including inclusion criteria and primary outcome measures, were based on US Food and Drug Administration guidelines and European Medicines Agency Committee for Medicinal Products for Human Use guidance for VMS trials.[30,31]

Postmenopausal women were eligible for enrollment if they were generally healthy, had a body mass index 40 kg/m^2 or less, and experienced at least 7 moderate to severe hot flushes per day or 50 or more per week for 2 consecutive weeks at baseline. Menopause was defined as at least 12 months of spontaneous amenorrhea; at least 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels greater than 40 mIU/mL; at least 6 weeks postsurgical bilateral oophorectomy (with or without hysterectomy); or hysterectomy without bilateral oophorectomy with serum follicle-stimulating hormone levels greater than 40 mIU/mL.

Exclusion criteria included the use of any hormone-containing drug (including selective estrogen receptor modulators) within 4 weeks to 6 months of screening, depending on the route of administration of the hormone; any psychoactive medications and any medications thought to treat VMS within 4 weeks of screening; or any investigational drug within 30 days of screening. Women were excluded if they had a history of seizure disorder, myocardial infarction (within 6 months), or malignancy or treatment for malignancy (within 2 years) other than basal or squamous cell carcinoma; a history of narrow-angle glaucoma or current raised intraocular pressure; hepatic, renal, or other medical disease; presence of psychiatric disease requiring therapy (major depressive, bipolar, psychotic, or generalized anxiety disorders), untreated malabsorption disorder; persistent elevated blood pressure or other clinically important abnormalities at screening; or a known hypersensitivity to desvenlafaxine.

The institutional review board at each site approved the protocol, and the study was conducted according to the Declaration of Helsinki. Participants provided written informed consent before enrollment, and all participant information was coded for confidentiality.

Design and procedures

Women were randomly assigned to receive a daily dose of desvenlafaxine 100 mg/d, desvenlafaxine 150 mg/d, or placebo using a computerized randomization/enrollment system into which study site personnel entered information and from which participant randomization numbers were issued. Study sites received desvenlafaxine and matched placebo tablets from Wyeth Research in individual packages code labeled with randomization numbers. Participants and all study site and Wyeth personnel were blinded to treatment allocation.

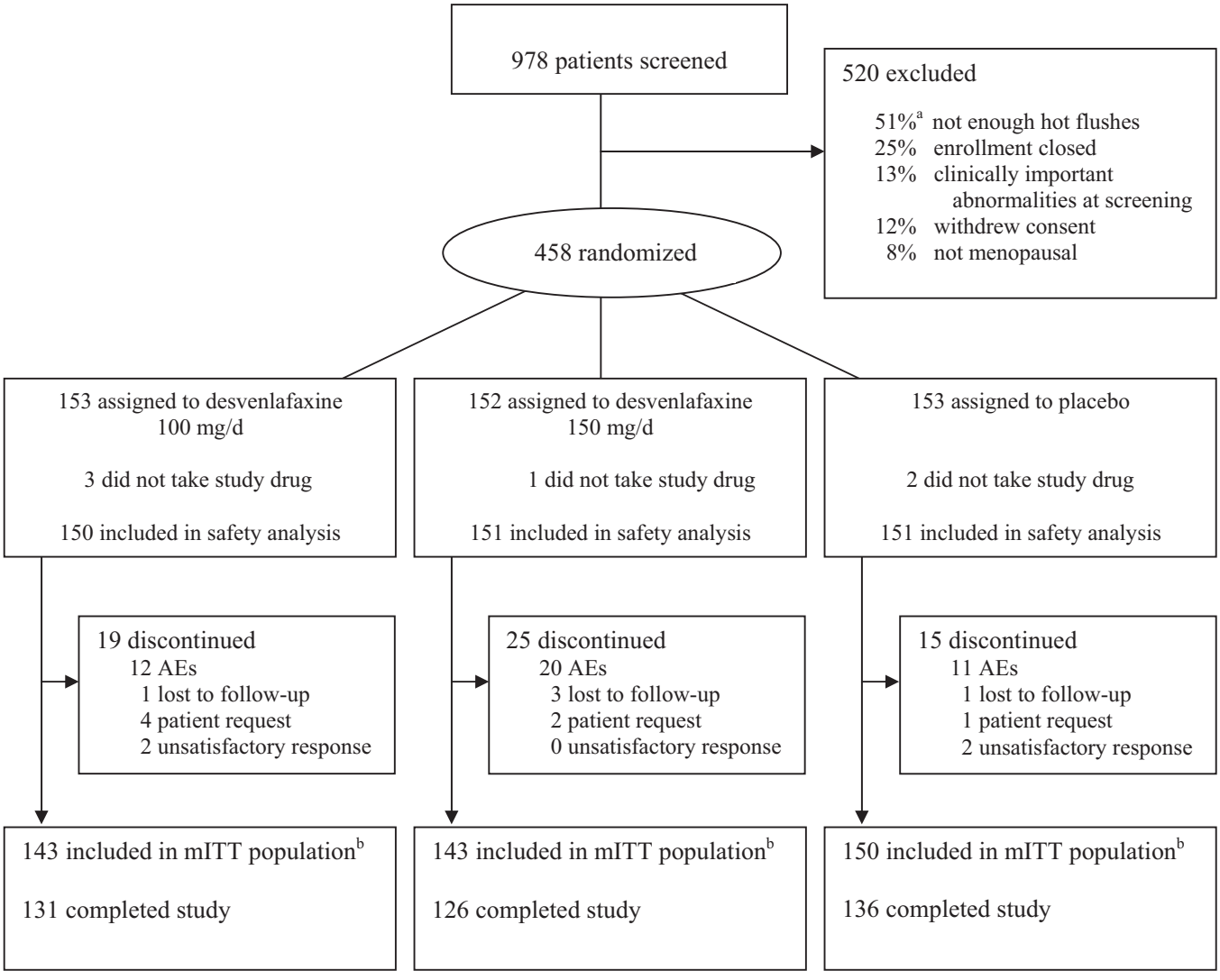
Therapy duration was 12 weeks, with both desvenlafaxine doses titrated starting at 50 mg/d during the first week on therapy. Women assigned to the desvenlafaxine 100-mg/d group received the 50 mg/d dose on days 1-3, and then the 100 mg dose from day 4 through the duration of the treatment phase. The desvenlafaxine 150-mg/d dose group started their assigned maintenance dose on day 8 after 3 days on the 50-mg/d dose, followed by 4 days on the 100-mg/d dose. The 12-week treatment phase was followed by a 2-week dose-tapering period. The dose for the desvenlafaxine 100 mg/d group was reduced to 50 mg/d during the first week of the taper period followed by 1 week on placebo. The desvenlafaxine 150-mg/d group received 100 mg/d during the first week of taper followed by 50 mg/d during the second week. Placebo treatment was continued throughout the taper period. Any unused pills from the previous week were collected at each visit.

Treatment compliance was determined by returned pill counts; women who took at least 80% of study drug tablets per week were considered compliant. Follow-up visits were scheduled 7 days after the end of the taper period.

Participants kept daily records of the number and severity (rated as mild, moderate, or severe) of hot flushes experienced[31] and the number of nighttime awakenings because of hot flushes. Participants completed daily hot flush diaries for at least 2 baseline weeks prior to randomization and throughout the on-therapy period.

The primary endpoints of the study were the change from baseline in daily number of moderate to severe hot flushes and change from baseline in average daily severity score compared with placebo at weeks 4 and 12. Secondary endpoints included: (1) change from baseline in weekly weighted severity score, calculated for each week as: 2 times the number of moderate hot flushes plus 3 times the number of severe hot flushes; (2) change from baseline in the number of mild, moderate, and severe hot flushes; (3) the 50% and 75% responder rates (women who had a reduction in the number of moderate and severe hot flushes of at least 50% and at least 75% from baseline); (4) the time to onset of efficacy (50% reduction in hot flushes for at least 3 consecutive days); and (5) change from baseline in the number of nighttime awakenings because of hot flushes.

FIGURE 1
Participant flow chart



Abbreviations: *AE*, adverse event; *mITT*, modified intent to treat.

[a] The total is > 100%; some women were excluded for multiple reasons; [b] The mITT population included all randomly assigned participants who took at least 1 dose of the study drug and had ≥ 5 days of vasomotor symptom data at baseline and ≥ 5 on-therapy days of vasomotor symptom data during the first 12 weeks.

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Women completed self-administered questionnaires (Profile of Mood States [POMS],[32] Visual Analog Scale–Pain Intensity [VAS-PI],[33] Greene Climacteric Scale [GCS],[34] and Menopause Symptoms Treatment Satisfaction Questionnaire [MS-TSQ][35]) at baseline (except MS-TSQ) and at weeks 4 and 12. Results from the POMS and VAS-PI are presented elsewhere. Safety was assessed based on AE collection, scheduled physical examinations, vital sign measurements, clinical laboratory testing, and electrocardiogram results.

Primary efficacy evaluations were made at weeks 4 and 12, and safety data were collected throughout the trial. The primary objective was to assess the efficacy and safety of desvenlafaxine 100 and 150 mg/d for the treatment of moderate to severe hot flushes associated with menopause, testing the hypothesis that treatment with desvenlafaxine will reduce the number and severity of menopausal hot flushes significantly more compared with placebo.

Statistical analyses

Statistical analyses were carried out by the Biostatistics Department of Wyeth Research. The primary efficacy analysis was carried out on the modified intent-to-treat (mITT) population, defined as women who were randomly assigned to treatment, received at least 1 dose of desvenlafaxine or placebo, recorded at least

TABLE 1
Demographics and baseline clinical characteristics

Characteristic	Desvenlafaxine, 100 mg/d	Desvenlafaxine, 150 mg/d	Placebo
Demographics, safety population	n = 150	n = 151	n = 151
Age (y)			
Mean (SD)	53.29 (4.70)	53.43 (4.64)	53.36 (5.05)
Minimum-maximum	41-69	29-69	39-71
Race, n (%)			
White	127 (85)	120 (79)	127 (84)
African American	20 (13)	28 (19)	22 (15)
Other	3 (2)	3 (2)	2 (1)
Body mass index (kg/m^2)			
Mean (SD)	27.69 (4.90)	27.69 (5.02)	28.21 (4.95)
Minimum-maximum	18.51-38.42	17.17-40.12	17.36-39.55
Type of menopause, n (%)			
Natural menopause	120 (80)	119 (79)	122 (81)
Bilateral oophorectomy	30 (20)	32 (21)	29 (19)
Years since last natural menstrual period[a]			
Mean (SD)	4.39 (3.69)	4.53 (4.25)	4.23 (3.71)
Minimum-maximum	0.59-14.41	0.52-19.87	0.08-15.88
Years since last presurgical menstrual period			
Mean (SD)	12.54 (11.38)	10.20 (6.16)	11.43 (9.21)
Minimum-maximum	0.51-35.82	1.50-24.41	1.43-32.58
Baseline characteristics, mITT population			
Daily number of moderate and severe HFs	n = 143	n = 143	n = 150
Mean (SD)	11.1 (4.5)	10.5 (3.4)	10.9 (4.6)
Daily severity score of HFs	n = 143	n = 143	n = 150
Mean (SD)	2.4 (0.3)	2.4 (0.3)	2.4 (0.3)
Number of awakenings per night because of HFs	n = 144	n = 144	n = 150
Mean (SD)	3.3 (2.0)	3.1 (1.9)	3.2 (1.7)

HF, hot flush; *mITT*, modified intent to treat.

[a] Refers only to women with a uterus.

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5 days of data during the baseline week and had at least 5 days of on-therapy data for at least 1 on-therapy week. Missing data were dealt with using a last-observation-carried-forward approach.

Safety analyses included all randomly assigned participants who received at least 1 dose of desvenlafaxine or placebo. A treatment group size of 125 was targeted to provide approximately 90% power to achieve statistical significance on all primary endpoints. To compensate for women who failed to qualify for the mITT analysis, 150 women were randomly assigned to each group.

The average daily number of moderate to severe hot flushes, average daily severity score, average weekly weighted score of moderate to severe hot flushes, and average daily number of nighttime awakenings because of hot flushes were calculated from daily diary entries and analyzed using analysis of covariance with treatment and study site as factors and baseline value as covariate. Pairwise comparisons between the desvenlafaxine dose groups and placebo were done using *t* tests, with the Hochberg method[36] to control the type I error rate.

Logistic regression was used to analyze the percentage of women having reductions of at least 50% and at least 75% from baseline, using treatment and study site as covariates. The time to onset of efficacy was calculated as the median number of days to reach at least 3 con-

TABLE 2
Summary of efficacy results at week 12 (mITT population)

Variable	Desvenlafaxine, 100 mg/d n	Mean (SE)[a]	*P* value[b]	Desvenlafaxine, 150 mg/d n	Mean (SE)[a]	*P* value[b]	Placebo n	Mean (SE)[a]
Primary efficacy variables[c]								
Number of moderate and severe HFs	143	-7.1 (0.34)	.005	143	-7.0 (0.35)	.012	150	-5.8 (0.34)
Daily severity score	143	-0.65 (0.07)	< .001	143	-0.66 (0.07)	< .001	150	-0.33 (0.07)
Secondary efficacy variables[c]								
Weekly weighted severity score	143	-143.5 (5.4)	.006	143	-139.7 (5.5)	.025	150	-123.3 (5.3)
Number of mild, moderate, and severe HFs	143	-7.7 (0.39)	.003	143	-7.2 (0.39)	.036	150	-6.1 (0.38)
Number of nighttime awakenings per night	144	-2.0 (0.15)	.003	144	-1.8 (0.15)	.048	150	-1.4 (0.15)
GCS total score	143	-7.6 (0.58)	< .001	142	-7.0 (0.59)	< .001	145	-4.1 (0.59)
		Participants (%)			Participants (%)			Participants (%)
50% responder rate[c]	143	74.8	< .001	143	77.6	< .001	150	51.3
75% responder rate[c]	143	49.7	< .001	143	53.2	< .001	150	29.3
MS-TSQ[c] overall "satisfied" or "extremely satisfied"	143	69.9	< .001	143	67.8	.002	149	49.7
		Median (range)			Median (range)			Median (range)
Time to 50% reduction in number of HFs, d[d]		7.0 (5-9)	< .001		8.0 (6-11)	< .001		25.0 (19-31)

GCS, Greene Climacteric Scale; *HF*, hot flush; *mITT*, modified intent to treat; *MS-TSQ*, Menopause Symptoms Treatment Satisfaction Questionnaire.

[a] Adjusted means; [b] vs placebo; [c] Last-observation-carried-forward analysis; [d] Observed data analysis.

Archer. Desvenlafaxine efficacy and safety for vasomotor symptoms in menopause. Am J Obstet Gynecol 2009.

secutive days with at least 50% reduction from baseline in the daily number of moderate to severe hot flushes.

Comparisons among treatment groups for laboratory tests, vital sign and weight measurements, and electrocardiogram results were done using analysis of covariance. The baseline value served as the covariate. Categorical data, incidence rates for all AEs, and the number of women withdrawing from the study for each reason were compared across treatment groups using Fisher's exact test.

RESULTS

A total of 978 women were screened and 458 were randomly assigned to treatment (Figure 1). Of those, 452 women took at least 1 dose of desvenlafaxine (n = 301) or placebo (n = 151) and were included in the safety population; 436 of 452 women (96.5%) were included in the mITT population for VMS. A total of 393 of 452 participants (86.9%) completed the study. There were no significant differences between groups in the number of women discontinuing overall (desvenlafaxine 100 mg/d, 12.7%; desvenlafaxine 150 mg/d, 16.6%; placebo, 9.9%) or for any specific reason, including AEs (Figure 1). More than 90% of women in all treatment groups were treatment compliant (took at least 80% of study drug tablets per week) during each time interval, with no significant differences among groups.

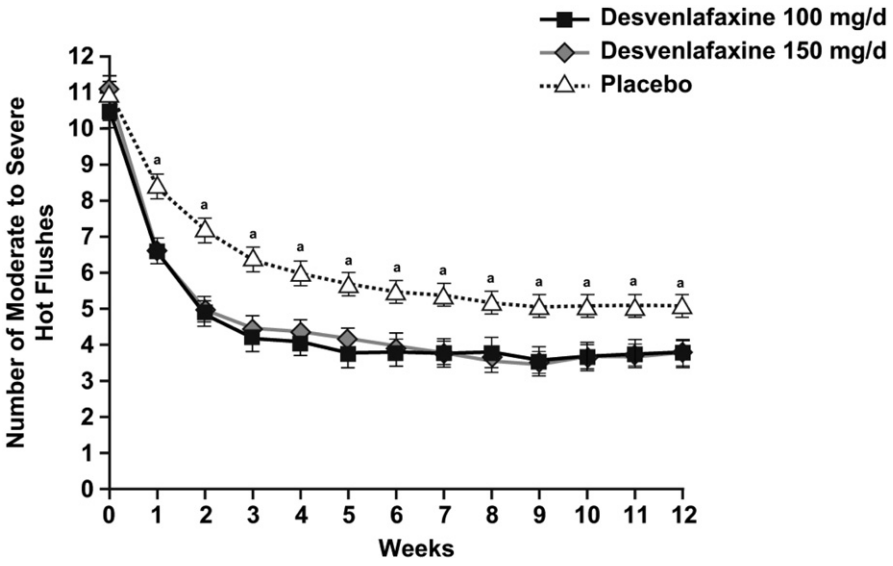
Demographics and baseline clinical characteristics

Participants' demographic characteristics and baseline symptoms are summarized by group in Table 1. There were no statistically significant differences between groups for any demographic characteristics or baseline symptoms.

Efficacy

Desvenlafaxine 100- and 150-mg/d groups showed significant improvement from baseline at week 12 in all efficacy endpoints compared with placebo, as summarized in Table 2. Desvenlafaxine 100- and 150-mg/d doses significantly reduced the number of moderate to severe hot flushes from baseline compared with placebo from week 1 through week 12 (Figure 2), achieving 65.4% and 66.6% reductions from baseline, respectively, at week 12 compared with a 50.8% reduction for placebo ($P = .005$ and $P = .012$, respectively; Table 2). The number of moderate to severe hot flushes experienced per day declined from a mean of 11.1 to 3.8 for women treated with desvenlafaxine 100 mg/d and from 10.5 to 3.8 for those treated with desvenlafaxine 150 mg/d. Placebo treatment was associated with a reduction from 10.9 to 5.1 moderate to severe hot flushes per day. Average daily hot flush severity scores were reduced significantly from baseline for both desvenlafaxine groups compared with placebo at all time points (all comparisons, $P < .001$; Table 2). The

FIGURE 2
Decrease in number of moderate to severe hot flushes over 12 weeks, mITT population, last observation carried forward



[a] The significant decrease for both desvenlafaxine 100- and 150-mg/d groups compared with placebo. *Error bars* indicate standard error. The 100- and 150-mg/d desvenlafaxine groups had significantly greater decreases than the placebo group at all time points (all comparisons, $P \leq .012$). *mITT*, modified intent to treat.

Archer. Desvenlafaxine efficacy and safety for vasomotor symptoms in menopause. Am J Obstet Gynecol 2009.

magnitude of the reductions in both number and severity of hot flushes was similar for the 2 desvenlafaxine doses.

The weekly weighted severity scores for moderate to severe hot flushes were assessed at weeks 4 and 12. Desvenlafaxine 100 and 150 mg/d groups differed significantly from placebo at both time points (all comparisons, $P \leq .025$), each achieving a 73.0% reduction from baseline at week 12, compared with a 60.4% reduction for placebo (Table 2). The desvenlafaxine 100- and 150-mg/d groups also had significant reductions from baseline in average number of mild, moderate, and severe hot flushes compared with placebo at weeks 4 and 12 (all comparisons, $P \leq .036$).

Figure 3 shows the proportion of women in each treatment group who achieved 50% or greater and 75% or greater reductions from baseline in the number of moderate to severe hot flushes at weeks 4 and 12. A significantly greater percentage of women in each desvenlafaxine dose group responded at 50% and 75% levels compared with the placebo group at both time points (all comparisons, $P < .001$; Table 2). The median time to onset of efficacy was significantly shorter for both desvenlafaxine groups (7-8 days) than for placebo (25 days; both $P < .001$; Table 2). The reduction in daily number of nighttime awakenings because of hot flushes for desvenlafaxine 100-mg/d (3.3-1.5 at week 4; 1.3 at week 12) and 150-mg/d (3.1-1.5 at week 4; 1.3 at week 12) doses were significantly greater compared with placebo (3.2-2.0 at week 4; 1.8 at week 12) at both time points (all comparisons, $P \leq .048$).

Participants' assessment of their own symptom improvement was measured using the GCS and the MS-TSQ. The desvenlafaxine 100- and 150-mg/d groups showed significant improvement in GCS total and vasomotor subscale scores from baseline at weeks 4 and 12 compared with placebo (all comparisons, $P < .001$). GCS total scores decreased from 17.1 at baseline to 9.3 at week 12 for the desvenlafaxine 100-mg/d group and from 16.5 to 9.8 for the 150-mg/d group (placebo, 16.2-12.5). At week 12, 70% of women treated with desvenlafaxine 100 mg/d and 68% of women who had received desvenlafaxine 150 mg/d reported they were satisfied or extremely satisfied with treatment overall (4 or 5 on the 5-point MS-TSQ rating scale) compared with 50% of placebo-treated women (both $P \leq .002$).

Greater percentages of women in both desvenlafaxine groups also reported they were satisfied or extremely satisfied with control of hot flushes during the day (desvenlafaxine 100 mg/d, 74%; desvenlafaxine 150 mg/d, 65%) and control of hot flushes at night (desvenlafaxine 100 mg/d, 73%; desvenlafaxine 150 mg/d, 71%) compared with the placebo group at week 12 (day, 47%; night, 44%; all comparisons, $P \leq .001$).

Safety and tolerability

A total of 452 women took at least 1 dose of desvenlafaxine or placebo and were included in the safety analyses. More desvenlafaxine-treated participants (253/301, 84.1%) reported treatment-emergent AEs during the on-therapy period compared with placebo (105/151, 69.5%; overall $P = .002$). The overall difference between groups was primarily driven by a significantly greater proportion of desvenlafaxine-treated women (159/301, 52.8%) reporting treatment-emergent AEs with an onset in the first week of therapy (during dose titration) compared with placebo-treated women (47/151, 31.1%; overall $P < .001$). More than half of all desvenlafaxine-treated women reporting treatment-emergent AEs (55.3%) did so during the first 3 days of the trial while on the desvenlafaxine 50-mg/d dose.

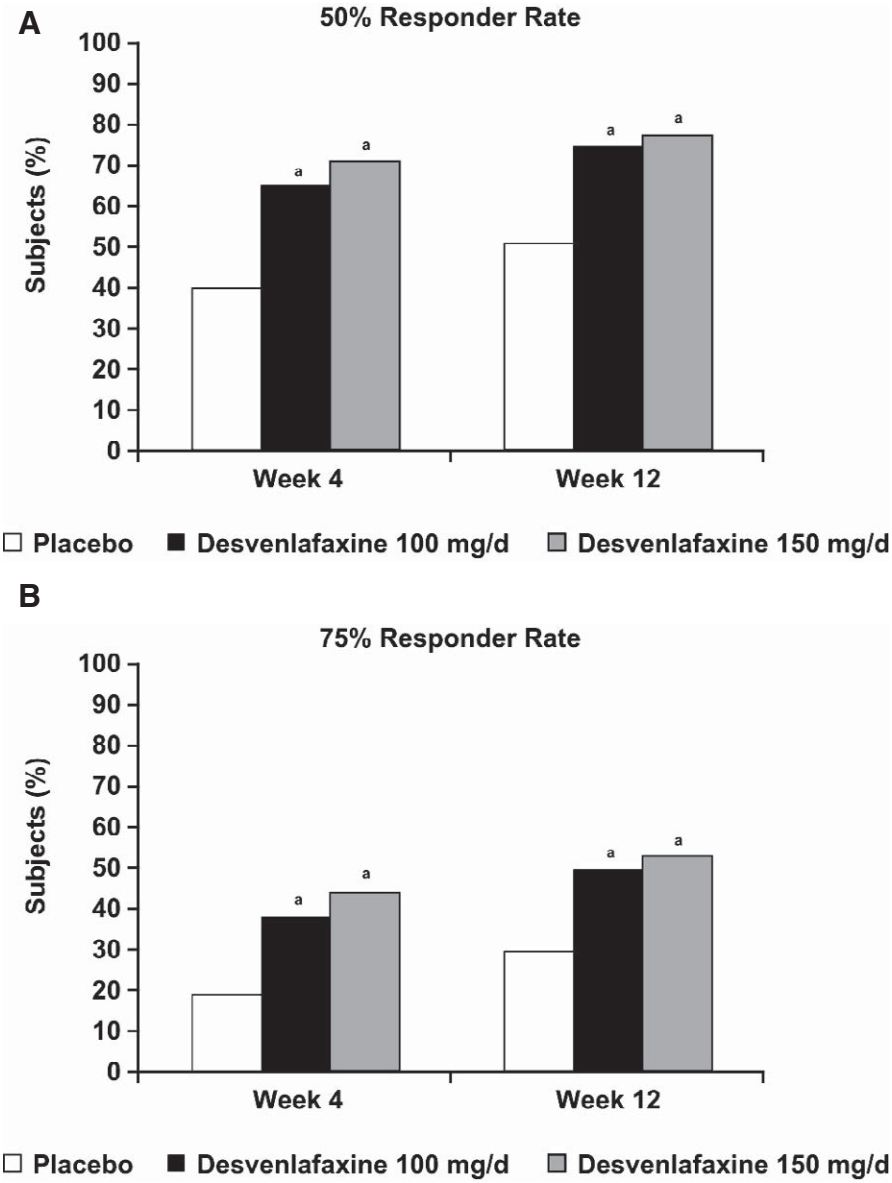
Desvenlafaxine and placebo groups did not differ significantly in the incidence of newly emergent AEs after the first week of therapy (while on maintenance dose). Most treatment-emergent AEs (desvenlafaxine, 83%; placebo, 85%) were mild or moderate in severity and did not lead to discontinuation. Withdrawals because of AEs did not differ significantly among groups during the first week of therapy or at any week during the study, although there were numerically more withdrawals due to AEs in the desvenlafaxine 150-mg/d group overall (Figure 1).

Common ADRs for desvenlafaxine (defined as AEs that are at least possibly causally related to the treatment) are listed in Table 3. Nausea was the most common ADR, reported by 76 of 301 (25.2%) women in the desvenlafaxine groups and 11 of 151 (7.3%) women in the placebo group (overall $P < .001$). Median duration of nausea episodes was 3 days for desvenlafaxine groups and 1.5 days for the placebo group. The overall incidence of AEs was similar for the 2 desvenlafaxine treatment groups; the rates of several ADRs, including dry mouth and mydriasis, were notably higher with desvenlafaxine 100 mg/d than with 150 mg/d. There was no significant weight gain or sexual dysfunction associated with desvenlafaxine treatment (data not shown).

There were 2 serious AEs reported during the trial that were considered possibly related to the study drug: 1 woman (desvenlafaxine 150 mg/d) reported hypertension and 1 woman (placebo) reported bronchospasm. One woman in the placebo group was hospitalized because of depression that was not considered related to the study drug. Systolic blood pressure showed a small but statistically significant increase (4.52 mm Hg) at the final on-therapy evaluation for desvenlafaxine 150 mg/d (but not desvenlafaxine 100 mg/d) compared with placebo ($P = .002$).

Taper/posttherapy-emergent AEs (discontinuation symptoms: AEs that began or worsened during or after the taper period) were reported by significantly more desvenlafaxine-treated participants (100 mg/d, 82/150 [54.7%]; 150 mg/d, 72/151 [47.7%]) compared with placebo (57/151 [37.7%]; $P = .013$). Most discontinuation symptoms were mild or moderate in severity. Dizziness (17.3% of all desvenlafaxine-treated women), nausea (9.3%), hostility (4.0%), and vertigo (4.0%) were the most common discontinuation symptoms that occurred at a frequency of at least twice the rate of the placebo group. The desvenlafaxine 100 mg/d group reported significantly more discontinuation symptoms compared with placebo when tapered to 50 mg/d ($P = .019$) and in the week after taper ($P < .001$) but showed no significant difference compared with placebo 2 weeks after the last tapered dose. The desvenlafaxine 150-mg/d group did not differ from placebo during the 2-week taper period but did report significantly more discontinuation symptoms than the placebo group in the week following complete discontinuation ($P = .011$).

FIGURE 3
Responder analysis, mITT population, last observation carried forward



A, Percentage of women with ≥ 50% decrease in average daily number of moderate to severe hot flushes. **B**, Percentage of women with ≥ 75% decrease in average daily number of moderate to severe hot flushes. The number of women who responded with a decrease of ≥ 50% and ≥ 75% in the average daily number of moderate and severe hot flushes was significantly greater in each desvenlafaxine treatment group than in the placebo group at weeks 4 and 12 (all comparisons, $P < .001$). [a] Significantly different from placebo. *mITT*, modified intent to treat.

Archer. Desvenlafaxine efficacy and safety for vasomotor symptoms in menopause. Am J Obstet Gynecol 2009.

COMMENT

These results confirm previous clinical trial results showing that desvenlafaxine

TABLE 3
Common ADRs (≥ 5% of either desvenlafaxine treatment group)

Variable	Overall *P* value	Desvenlafaxine, 100 mg/d (n = 150)	Desvenlafaxine, 150 mg/d (n = 151)	Placebo (n = 151)
Any AE, n (%)	.002	125 (83.3)	128 (84.8)	105 (69.5)
ADR, n (%)				
Body as a whole				
Asthenia	.021	17 (11.3)	19 (12.6)	6 (4.0)
Cardiovascular system				
Hypertension	.160	8 (5.3)	6 (4.0)	2 (1.3)
Digestive system				
Anorexia	.041	9 (6.0)	6 (4.0)	1 (0.7)
Constipation	< .001	14 (9.3)	20 (13.2)	2 (1.3)
Diarrhea	.407	9 (6.0)	5 (3.3)	5 (3.3)
Dry mouth	< .001	30 (20.0)	19 (12.6)	4 (2.6)
Nausea	< .001	43 (28.7)	33 (21.9)	11 (7.3)
Nervous system				
Dizziness	.349	17 (11.3)	18 (11.9)	11 (7.3)
Insomnia	.122	19 (12.7)	17 (11.3)	9 (6.0)
Somnolence	.002	14 (9.3)	14 (9.3)	1 (0.7)
Special senses				
Mydriasis	.001	8 (5.3)	1 (0.7)	0

ADRs, adverse drug reactions; *AE*, adverse event.

Archer. Desvenlafaxine efficacy and safety for vasomotor symptoms in menopause. Am J Obstet Gynecol 2009.

is an effective and safe nonhormonal treatment for moderate to severe VMS in postmenopausal women. Desvenlafaxine was significantly more effective than placebo at both doses tested and all time points across the trial. The 50% and 75% responder rates were significantly better for desvenlafaxine than for placebo, and onset of efficacy was significantly shorter for desvenlafaxine than placebo. Additional benefits of desvenlafaxine treatment included a reduction in nighttime awakenings because of hot flushes.

The 65-66% reduction in number of moderate to severe hot flushes and 73% reduction in weighted scores at week 12 are consistent with the findings of a previous desvenlafaxine trial[26] and compare favorably with results of other placebo-controlled SSRI and SNRI trials.[18-21] Although the difference in the reduction of numbers of hot flushes between desvenlafaxine and placebo was not large (-1.3 per day at week 12), the results of the GCS and MS-TSQ self-assessment questionnaires suggest that the symptom reduction associated with desvenlafaxine treatment is likely to be clinically meaningful for the subjects: desvenlafaxine-treated women perceived a greater decrease in symptoms compared with placebo-treated women based on the GCS, and significantly more desvenlafaxine-treated participants were satisfied or extremely satisfied with their symptom reduction compared with the placebo group.

Reductions in number and severity of hot flushes affect other areas of functioning, in this study reducing the number of nighttime awakenings by more than 50%, which likely contributes to the satisfaction expressed by the women treated with desvenlafaxine. This perceived impact of desvenlafaxine compared with placebo and the consistent improvements across all measures of efficacy (Table 2) are strengths of the study. Hormone therapy remains the standard and only approved prescription therapy for menopausal VMS, yielding an average reduction of 75.3% in the number of hot flushes in a metaanalysis.[37] However, there are few, if any, nonhormonal treatments for hot flushes that have been demonstrated to be as effective as desvenlafaxine in large, placebo-controlled trials of generally healthy, postmenopausal women with frequent, moderate to severe VMS.[22]

The placebo group in the current trial had larger reductions in the number of moderate to severe hot flushes (50.8%) than those reported in other SSRI and SNRI trials (14-36%)[18-21] but are in line with the typically high placebo responses seen in hormone therapy trials (58% reduction in hot flush frequency) that enrolled women with moderate and severe symptoms.[37] Despite the high placebo response, both desvenlafaxine doses separated from placebo by the end of week 1

and at all time points during the trial. The onset of efficacy for VMS occurred with desvenlafaxine in less than a third of the time it took placebo to reach onset of efficacy.

The tolerability profile of desvenlafaxine is consistent with other SSRIs/SNRIs, but in this trial there was no evidence of weight gain or sexual dysfunction, both of which are side effects typically associated with drugs in this class.[38-44] An episode of hypertension was the single serious AE considered related to the study drug, and there was a small but statistically significant increase in systolic blood pressure for the higher desvenlafaxine dose group. Blood pressure monitoring is recommended during treatment with desvenlafaxine, as it is with other SNRIs.[45,46]

Dose titration was an effective strategy for improving desvenlafaxine tolerability at initiation of therapy. The percentages of desvenlafaxine-treated women reporting common ADRs, particularly nausea (25%) and dizziness (12%), were lower compared with the rates observed at the same desvenlafaxine doses in a previous trial that did not use a dose titration protocol (nausea 43%; dizziness 19%).[26] There was no increase in AEs with increasing dose during titration in this trial. The rate of discontinuation because of AEs for desvenlafaxine-treated women was also substantially lower in this trial (11%) compared with the previous desvenlafaxine trial (30%)[26] and did not differ significantly from placebo during titration or at any time after reaching the assigned maintenance dose.

Dose tapering at discontinuation of treatment is recommended for SSRIs/SNRIs, especially those with short half-lives such as desvenlafaxine.[29,45-47] The 2-week tapering protocol used in this trial did not prevent withdrawal symptoms: symptoms in the current trial were comparable with those reported for other SSRIs/SNRIs[47,48] and did not occur at lower rates than in previous desvenlafaxine trials. However, in this trial, placebo-treated women also reported more discontinuation symptoms than in previous desvenlafaxine trials. The short duration of the taper period was a limitation of the trial; longer and more gradual tapers have been recommended for withdrawing patients from SSRIs/SNRIs and should be considered for desvenlafaxine.[47] An ongoing study assessing various regimens of titration and tapering will provide further information regarding strategies for effectively improving initial tolerability and minimizing discontinuation symptoms with desvenlafaxine treatment.

Results of this trial indicate that desvenlafaxine is an effective and generally well-tolerated nonhormonal treatment for moderate to severe VMS associated with menopause. Desvenlafaxine 100-mg/d is the optimal dose for treating hot flushes, with no greater efficacy found for the desvenlafaxine 150-mg/d dose in this trial. Dose titration improved tolerability of desvenlafaxine and resulted in a low rate of discontinuations due to AEs. ■

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