

# Pooled Analysis of Six Pharmacologic and Nonpharmacologic Interventions for Vasomotor Symptoms

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**OBJECTIVE:** To describe the effects of six interventions for menopausal vasomotor symptoms relative to control in a pooled analysis, facilitating translation of the results for clinicians and symptomatic women. The Menopause Strategies: Finding Lasting Answers for Symptoms and Health network tested these interventions in three randomized clinical trials.

**METHODS:** An analysis of pooled individual-level data from three randomized clinical trials is presented. Participants were 899 perimenopausal and postmenopausal women with at least 14 bothersome vasomotor symptoms per week. Interventions included 10–20 mg escitalopram per day, nonaerobic yoga, aerobic exercise, 1.8 g per day omega-3 fatty acid supplementation, 0.5 mg low-dose oral 17-beta-estradiol (E2) per day, and 75 mg low-dose venlafaxine XR per day. The main outcome measures were changes from baseline in mean

daily vasomotor symptom frequency and bother during 8–12 weeks of treatment. Linear regression models estimated differences in outcomes between each intervention and corresponding control group adjusted for baseline characteristics. Models included trial-specific intercepts, effects of the baseline outcome measure, and time.

**RESULTS:** The 8-week reduction in vasomotor symptom frequency from baseline relative to placebo was similar for escitalopram at –1.4 per day (95% confidence interval [CI] –2.7 to –0.2), low-dose E2 at –2.4 (95% CI –3.4 to –1.3), and venlafaxine at –1.8 (95% CI –2.8 to –0.8); vasomotor symptom bother reduction was minimal and did not vary across these three pharmacologic interventions (mean –0.2 to –0.3 relative to placebo). No effects on vasomotor symptom frequency or bother were seen with aerobic exercise, yoga, or omega-3 supplements.

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**CONCLUSION:** These analyses suggest that escitalopram, low-dose E2, and venlafaxine provide comparable, modest reductions in vasomotor symptom frequency and bother among women with moderate hot flashes.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00894543 (MsFLASH 01), NCT01178892 (MsFLASH 02), and NCT01418209 (MsFLASH 03).

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The National Institutes of Health 2005 State-of-the-Science Conference on Management of Menopause-Related Symptoms concluded that although hormone therapy is effective, demonstration of treatment-related adverse events in the Women's Health Initiative trials warranted the conduct of rigorous trials to evaluate safety and effectiveness of alternative therapies for vasomotor and other menopausal symptoms.<sup>1,2</sup> Increased testing of nonhormonal treatments for vasomotor symptoms<sup>3–6</sup> has followed the publication of Women's Health Initiative results, and the U.S. Food and Drug Administration (FDA) recently approved one selective serotonin reuptake inhibitor for vasomotor symptom treatment.<sup>6,7</sup>

The Menopausal Strategies: Finding Lasting Answers to Symptoms and Health network, created in response to the State-of-the-Science conference, has conducted three large randomized clinical trials for treatment of menopausal vasomotor symptoms. The trials tested six interventions in nearly 900 women, including a selective serotonin reuptake inhibitor, a serotonin norepinephrine reuptake inhibitor, oral low-dose estrogen, yoga, aerobic exercise, and omega-3 fatty acid supplementation.<sup>8–12</sup> Before the first trial was launched, Menopausal Strategies: Finding Lasting Answers to Symptoms and Health investigators developed network standards for study design, eligibility and exclusion criteria, and study measures.<sup>13</sup>

Even with standardized Menopausal Strategies: Finding Lasting Answers to Symptoms and Health trial methodology, there were design differences across trials that raise questions regarding direct comparisons of these intervention effects. This article addresses that issue with a novel comparative effectiveness analysis that pools each trial's individual-level data and adjusts for differences between studies. Our primary objective was to describe the magnitude of treatment effects for all six interventions relative to control within the same analysis to facilitate translation of our findings into clinical recommendations.

## MATERIALS AND METHODS

Descriptions of our standardized trial methods are published.<sup>13,14</sup> The studies were approved by the institutional review boards of each clinical site and the Data Coordinating Center. All participants provided written informed consent. The analyses presented here were not prespecified in study protocols, although Menopausal Strategies: Finding Lasting Answers to Symptoms and Health trials were designed to permit eventual pooled analysis.

Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01 was a randomized, placebo-controlled, double-blind clinical trial that aimed to recruit approximately equal numbers of African American and white women to the study population. Eligible women were randomized in a 1:1 ratio to receive 10 mg escitalopram per day or a matching placebo capsule for 8 weeks. If a woman did not report a reduction in vasomotor symptom frequency of 50% or greater or a decrease in vasomotor symptom severity after 4 treatment weeks, her study medication dose was increased to 20 mg per day (or matched placebo) without unblinding the randomization.

Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02 was a three×two factorial, randomized controlled trial. Eligible women were randomized in a 3:3:4 ratio to 12 weeks of yoga, exercise, or usual activity and simultaneously randomized in a 1:1 ratio to 1.8 g per day of omega-3 fish oil capsules or identical-looking placebo capsules. The yoga intervention emphasized a practice of “cooling” breathing exercises, 11–13 poses (Asanas) previously suggested for vasomotor symptom relief, and guided meditation (Yoga Nidra). Instruction was provided during 12 weekly, 90-minute classes. Daily home practice was expected for 20 minutes on the other 6 days of the week. The exercise intervention consisted of 12 weeks of three individualized, cardiovascular conditioning training sessions per week at local fitness facilities supervised by trained, certified exercise trainers. The target training heart rate was 50–60% of the heart rate reserve for the first month and 60–70% for the remainder of the intervention with 40–60 minutes per session to achieve the energy expenditure goal of 16 kcal/kg. Women in the usual activity group were asked not to engage in yoga or to change their exercise routines; at study end they were offered their choice of a 3-hour yoga workshop or a 1-month gym membership. The 1.8-g/day omega-3 fatty acids supplements were taken three times a day for 12 weeks and contained 425 mg ethyl eicosapentaenoic acid, 100 mg docosahexaenoic acid, and 90 mg other



omega-3s. Data collection was performed by research assistants blinded to behavioral intervention assignment. The omega-3 component of the trial was double-blind.

Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 03 was a randomized, placebo-controlled, double-blind, 8-week trial of 0.5 mg low-dose oral 17-beta-estradiol (E2) per day, venlafaxine XR (37.5 mg/d for the first week, then 75 mg/d), or placebo in a 2:2:3 ratio.

Randomization was accomplished through a secure web-based database maintained by the Data Coordinating Center utilizing a dynamic randomization algorithm.<sup>15</sup> The randomization was stratified by clinical site and race for Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01 and by clinical site only for Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02 and 03. Design differences between trials are described in Table 1. Common to all studies was a 6-week outcome assessment and a minimum eligibility criterion of 14 hot flushes per week.

Participants were recruited from July 2009 to October 2012 by mass mailings to age-eligible women using purchased mailing lists and health plan enrollment files. There were five Menopausal Strategies: Finding Lasting Answers to Symptoms and Health network sites. All sites participated in at least two trials and each trial was implemented at three or four sites (Table 2). Eligibility criteria common to all trials included: women aged 40–62 years; in the menopause transition (amenorrhea 60 days or more in the past year), or postmenopausal (12 months or more since last menstrual period or bilateral oophorectomy), or had a hysterectomy with one or both ovaries remaining and follicle-stimulating hormone greater than 20 milli-international units/mL and 50 pg/mL E2 or less; and in general good health as determined by medical history, a brief physical examination, and standard blood tests. In addition to the screening vasomotor symptom frequency requirement (Table 1), vasomotor symptoms had to be rated as bothersome or severe on at least 4 days or nights per week, and the frequency in screening week 3 could not decrease greater than 50% from the mean weekly levels in screening weeks 1 and 2.

Exclusion criteria common to all trials included: use of prescription or over-the-counter treatments for hot flushes (past 30 days); use of exogenous sex steroid hormones or hormonal contraceptives (past 2 months); pregnancy or breastfeeding; any current severe or unstable medical conditions; drug or alcohol abuse (past year); history of myocardial infarction, angina, or cerebrovascular events; or a major depressive

episode (past 3 months). Additional trial-specific exclusion criteria are described in Table 1.

After telephone screening, women completed a 2-week vasomotor symptoms diary and a questionnaire. Women who remained eligible attended an in-person visit that included a blood draw, physical measures, and another questionnaire. After that visit, women completed the week 3 vasomotor symptoms diary and then returned to the clinic for determination of eligibility and randomization. Telephone contacts to encourage study compliance and assess adverse events were made 1 or 2 weeks after randomization and then again midway through the intervention. Follow-up clinic visits were conducted at 4 and 8 weeks (Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01 and 03) or 6 and 12 weeks (Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02) postrandomization.

Vasomotor symptoms counts were collected on the diary two times per day as daytime hot flushes recorded in the evening and night sweats recorded in the morning. Vasomotor symptom bother corresponding to these counts was rated in the daily diaries from 1 to 4 (none, a little, moderately, a lot). The outcomes of interest for the pooled analysis were differences between the 7-day means of vasomotor symptom frequency and bother at weeks 4, 6, 8, 12, and the 14-day baseline means. Adverse events were assessed at each contact using a self-administered questionnaire listing specific expected side effects for the intervention (s) as well as open-ended questions.

The intent-to-treat analysis included all randomized participants who provided follow-up vasomotor symptom diary data, regardless of adherence to treatment assignment (see the figure in Appendix 1, available online at <http://links.lww.com/AOG/A655>). Baseline demographic and clinical characteristics as shown in Table 2 were summarized in combined treatment arms and compared across trials with homogeneity assessed using  $\chi^2$  or F-test.

Linear regression models were applied to estimate differences between each intervention and its corresponding control group in changes from baseline in vasomotor symptom frequency or bother at weeks 4, 6, 8, and 12 with adjustment for clinical site and baseline age, race, education, smoking, and body mass index (calculated as weight (kg)/[height (m)]<sup>2</sup>). The models included trial as a covariate to allow trial-specific intercepts and incorporated trial-specific effects of the baseline outcome measure and time. Robust standard errors were calculated by generalized estimating equations.



**Table 1. Menopause Strategies: Finding Lasting Answers for Symptoms and Health Trial Designs**

| Trial | Total Enrollment | Design  | VMS Eligibility   | Trial-Specific Exclusion Criteria  | Intervention Length (wk) | VMS Assessment  | Reference (s)*   |
|-------|------------------|---|-------------------|--|--------------------------|-----------------|------------------|
| 01    | 205              | 2-arm: escitalopram vs placebo  | 28 VMS or more/wk | Use of psychotropic medications (past 30 d)<br>Use of gabapentin, pregabalin, triptans, warfarin, or St. John's Wort<br>Use of selective estrogen receptor modulators or aromatase inhibitors (past 60 d)<br>Suicide attempt in the past 3 y<br>History of endometrial or ovarian cancer   | 8                        | Weekly          | <sup>9</sup>     |
| 02    | 355              | 3×2 factorial: aerobic exercise and yoga vs usual activity, plus omega-3 supplementation vs placebo | 14 VMS or more/wk | BMI greater than 37 kg/m <sup>2</sup><br><br>Contraindications to yoga, exercise training, or omega-3<br>Current participation in yoga or regular exercise<br>Current use of omega-3 supplements<br>Consumption of 4 or more servings of fish/wk   | 12                       | Week 6, week 12 | <sup>10-12</sup> |
| 03    | 339              | 3-arm: low-dose oral E2 and venlafaxine vs placebo  | 14 VMS or more/wk | Hypersensitivity or contraindication to study medications<br>Use of psychotropic medications (past 30 d)<br>Use of selective estrogen receptor modulators or aromatase inhibitors (past 60 d)<br>Suicide attempt in the past 3 y<br>History of thrombotic or endometrial disease, pre-breast cancer conditions, or breast cancer | 8                        | Weekly          | <sup>13</sup>    |

VMS, vasomotor symptoms; BMI, body mass index; E2, estradiol.

\* See Appendix 3, available online at <http://links.lww.com/AOG/A657>, for reproductions of published primary results tables.

The planned sample size of each trial was determined by the primary trial endpoints<sup>8-12</sup>; our pooled sample size provided at least 80% power to detect a 0.45 standard deviation unit effect size for each intervention based on a *t* test with a two-sided .001 level of significance. Analyses were conducted using SAS 9.3.

## RESULTS

The 899 Menopausal Strategies: Finding Lasting Answers to Symptoms and Health trial participants

were randomized as follows: 104 to escitalopram and 101 to placebo (Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01); 106 to exercise, 107 to yoga, and 142 to usual activity, and, simultaneously, 177 to omega-3 and 178 to placebo (Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02); and 97 to E2, 96 to venlafaxine, and 146 to placebo (Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 03). Follow-up data collection retention



**Table 2. Baseline Demographic and Clinical Characteristics by Trial**

| Baseline Characteristic  | MsFLASH 01 (n=205) | MsFLASH 02 (n=355) | MsFLASH 03 (n=339) | P     |
|--|--------------------|--------------------|--------------------|-------|
| Age at screening (y)   | 53.9±4.1           | 54.7±3.7           | 54.6±3.8           | .19   |
| Younger than 50  | 24 (12)            | 19 (5)             | 30 (9)             |       |
| 50–54  | 95 (46)            | 162 (46)           | 147 (43)           |       |
| 55–59  | 66 (32)            | 130 (37)           | 123 (36)           |       |
| 60 or older  | 20 (10)            | 44 (12)            | 39 (12)            |       |
| Race   |                    |                    |                    | <.001 |
| African American   | 95 (46)            | 93 (26)            | 116 (34)           |       |
| White  | 102 (50)           | 228 (64)           | 203 (60)           |       |
| Other*   | 8 (4)              | 34 (10)            | 20 (6)             |       |
| Hispanic   | 0                  | 6 (2)              | 1 (<1)             |       |
| Native American  | 1 (<1)             | 8 (2)              | 2 (1)              |       |
| Asian or Pacific Islander  | 3 (1)              | 12 (3)             | 5 (1)              |       |
| Undisclosed  | 4 (2)              | 8 (2)              | 12 (4)             |       |
| Education  |                    |                    |                    | <.001 |
| High school diploma or less or high school equivalency certificate | 38 (19)            | 21 (6)             | 55 (16)            |       |
| Post-high school   | 87 (42)            | 112 (32)           | 111 (33)           |       |
| College graduate   | 80 (39)            | 221 (62)           | 172 (51)           |       |
| Smoking  |                    |                    |                    | <.001 |
| Never  | 99 (48)            | 232 (66)           | 174 (52)           |       |
| Past   | 59 (29)            | 89 (25)            | 107 (32)           |       |
| Current  | 47 (23)            | 32 (9)             | 55 (16)            |       |
| BMI (kg/m <sup>2</sup> )   | 29.1±6.5           | 27.0±4.4           | 28.3±6.8           | .005  |
| Less than 25   | 54 (26)            | 123 (35)           | 118 (35)           |       |
| 25 to less than 30   | 72 (35)            | 144 (41)           | 107 (32)           |       |
| 30 or greater  | 78 (38)            | 88 (25)            | 107 (32)           |       |
| Menopause status   |                    |                    |                    | .27   |
| Postmenopausal   | 142 (69)           | 266 (75)           | 256 (76)           |       |
| Perimenopausal   | 41 (20)            | 65 (18)            | 52 (15)            |       |
| Indeterminate  | 22 (11)            | 24 (7)             | 31 (9)             |       |
| Site   |                    |                    |                    | —     |
| Boston   | 43 (21)            | 0                  | 100 (29)           |       |
| Indianapolis   | 35 (17)            | 118 (33)           | 0                  |       |
| Oakland  | 57 (28)            | 110 (31)           | 0                  |       |
| Philadelphia   | 70 (34)            | 0                  | 121 (36)           |       |
| Seattle  | 0                  | 127 (36)           | 118 (35)           |       |
| VMS/d  |                    |                    |                    |       |
| Frequency  | 9.8±5.6            | 7.6±3.8            | 8.1±5.3            | <.001 |
| Bother   | 3.1±0.5            | 3.0±0.5            | 3.0±0.5            | <.001 |

MsFLASH, Menopause Strategies: Finding Lasting Answers for Symptoms and Health; BMI, body mass index; VMS, vasomotor symptoms. Data are mean±standard deviation or n (%) unless otherwise specified.

The dash indicates that no hypothesis testing was performed.

\* Test for heterogeneity based on collapsed race categories (African American, white, and other).

was high in all trials: 201 (98%) of 205 women randomized provided week 4, week 8, or week 4 and week 8 vasomotor symptom diary data in Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01; 346 (97%) of 355 women randomized provided vasomotor symptom diary data at week 6, week 12, or week 6 and week 12 in Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02; and 330 (97%) of 339 women randomized provided follow-up vasomotor symptom diary data at week 4, week 8, or week 4 and week 8 in Menopausal Strategies: Finding Lasting

Answers to Symptoms and Health 03 (Appendix 1, <http://links.lww.com/AOG/A655>). Data completeness was comparable across study arms in all trials.

Age was similar across trials with an overall mean age of 54.5 years (standard deviation 3.8, range 42–62 years) (Table 2). The distributions of race, education levels, and smoking prevalence varied across studies, corresponding to the clinical site locations and goals of the trials, although more than 35% of the women in each trial were nonwhite. Mean body mass index was lower in Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02 compared with



**Table 3. Changes From Baseline in Daily Mean Vasomotor Symptom Frequency and Bother in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health Trial Control Groups**

| Outcome          | Change From Follow-Up to Baseline |          |                     |          |
|------------------|-----------------------------------|----------|---------------------|----------|
|                  | Week 4                            |          | Week 6              |          |
|                  | Mean (95% CI)                     | % Change | Mean (95% CI)       | % Change |
| No. of VMS/d     |                                   |          |                     |          |
| Trial 01         | -2.5 (-3.3 to -1.7)               | -29      | -3.0 (-3.9 to -2.1) | -32      |
| Trial 02         | —                                 | —        | -1.8 (-2.6 to -1.1) | -14      |
| Trial 03         | -1.9 (-2.5 to -1.3)               | -25      | -2.0 (-2.5 to -1.4) | -27      |
| VMS bother (1-4) |                                   |          |                     |          |
| Trial 01         | -0.3 (-0.4 to -0.2)               | -12      | -0.4 (-0.5 to -0.2) | -17      |
| Trial 02         | —                                 | —        | -0.4 (-0.6 to -0.3) | -20      |
| Trial 03         | -0.3 (-0.4 to -0.2)               | -12      | -0.3 (-0.4 to -0.2) | -14      |

CI, confidence interval; VMS, vasomotor symptoms. Dashes indicate the timepoints at which data were not collected.

the other trials in large part because enrollment in that trial was restricted to women who were physically able and willing to exercise or practice yoga. The distribution of menopausal status was similar across trials. Mean baseline vasomotor symptom frequency and bother were higher in Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01 than in the later trials as a result of more stringent vasomotor symptom eligibility criteria (Table 1).<sup>13</sup>

Vasomotor symptom frequency and bother responses in the control arms were fairly similar across trials. Mean relative percentage reductions from baseline in the control groups ranged from 14% to 34% for vasomotor symptom frequency and 12–30% for vasomotor symptom bother (Table 3). The control group responses for vasomotor symptom bother (in units of mean relative percentage change from baseline) were generally smaller in magnitude than the corresponding vasomotor symptom frequency responses, except in the Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02 trial.

Reductions in vasomotor symptom frequency from baseline of similar size and statistical significance were observed in the escitalopram, E2, and venlafaxine groups relative to control (Fig. 1; Table 4). Although most of the benefit was gained by week 4 for escitalopram and venlafaxine, participants in the E2 group continued to improve over the intervention period, yielding comparable week 8 intervention effect estimates for these three medications. Decreases ranged from 1.4 to 2.4 fewer vasomotor symptoms per day, or 18–37% lower vasomotor symptom daily frequency, relative to control (Table 4) (Appendix 2, available online at <http://links.lww.com/AOG/A656>). Although low-dose E2 appeared to produce slightly greater

reductions in the number of hot flushes than escitalopram or venlafaxine, the confidence intervals for the estimated effects of these three medications overlapped substantially. The patterns of vasomotor symptom bother change from baseline in the medication treatment groups relative to control were more varied than for vasomotor symptom frequency (Fig. 2). However, again, the intervention effects were quite similar at week 8, ranging from 0.2 to 0.3 point lower bother scores, or 11–15% lower vasomotor symptom daily bother, relative to control (Table 4) (Appendix 2, <http://links.lww.com/AOG/A656>). The Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 02 interventions of yoga, exercise, and omega-3 showed little effect in reducing vasomotor symptom frequency or bother relative to control, findings unchanged from the original published analyses.<sup>9–11</sup>

No serious adverse events resulting from study interventions were reported during the three trials.<sup>9–13</sup> All study medications were well tolerated: seven (6.7%) escitalopram, one (0.6%) omega-3, four (4.1%) E2, five (5.2%) venlafaxine, and four (1.3% of n=318) placebo participants stopped treatment as a result of adverse events. No participants stopped treatment as a result of side effects from behavioral interventions or usual activity. Notable adverse events on the Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 03 trial included the following: three participants reported suicidal ideation while on study medication (2.1% on E2, 0.7% on placebo, none on venlafaxine); 12 women developed systolic blood pressure greater than 165 mm Hg or diastolic blood pressure greater than 95 mm Hg (2.1% on E2, 10.4% on venlafaxine, 0 on placebo), all of whom had baseline systolic blood pressure or



| Change From Follow-Up to Baseline |          |                     |          |
|-----------------------------------|----------|---------------------|----------|
| Week 8                            |          | Week 12             |          |
| Mean (95% CI)                     | % Change | Mean (95% CI)       | % Change |
| -3.2 (-4.2 to -2.2)               | -34      | —                   | —        |
| -2.2 (-2.8 to -1.6)               | -29      | -2.5 (-3.3 to -1.8) | -26      |
| -0.4 (-0.5 to -0.2)               | -16      | —                   | —        |
| -0.4 (-0.5 to -0.2)               | -16      | -0.6 (-0.7 to -0.4) | -30      |

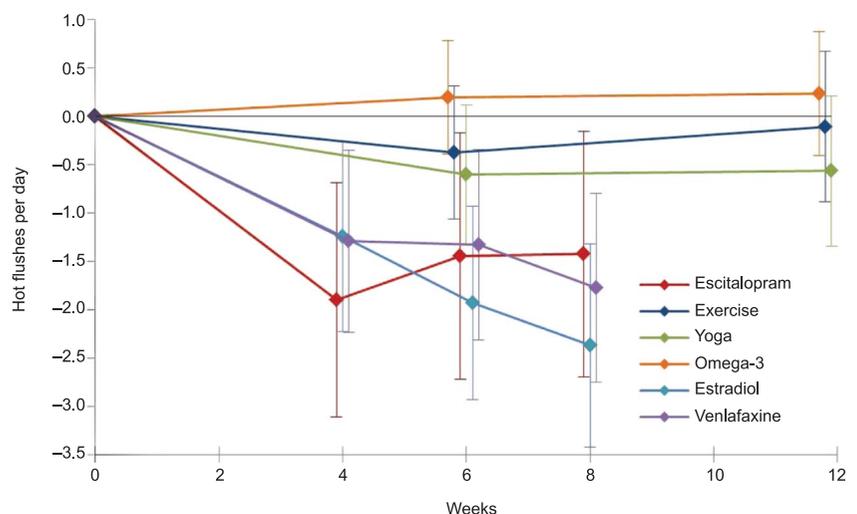
diastolic blood pressure above the study population mean; and among women with a uterus, 6 of 73 (8.2%) on E2, 2 of 124 (1.6%) on placebo, and none on venlafaxine developed abnormal vaginal bleeding (any bleeding in postmenopausal women; two+ cycles less than 21 days in perimenopausal women) on treatment, which was evaluated with a transvaginal ultrasonogram. Three of six E2-treated participants with abnormal bleeding had an endometrial echo complex greater than 5 mm and underwent an endometrial biopsy, all of whom revealed no evidence of hyperplasia or malignancy.<sup>12</sup>

## DISCUSSION

In analyses of pooled individual-level data from three Menopausal Strategies: Finding Lasting Answers to Symptoms and Health clinical trials, the reduction in vasomotor symptom frequency and bother in midlife women was similar for escitalopram, oral low-dose E2,

and low-dose venlafaxine. These interventions conveyed between 18% and 37% improvement in daily frequency relative to the placebo group (Appendix 2, <http://links.lww.com/AOG/A656>) and had minimal effect on bother. Intervention effect estimates in these pooled analyses did not qualitatively diverge from the results of each individual trial,<sup>8-12</sup> implying that between-trial differences did not substantially affect the trials' comparability.

Strengths of this pooled analysis include the use of standardized methods for measurement of vasomotor symptoms and participant characteristics, similar inclusion and exclusion criteria, and the enrollment of many minority women. The Menopausal Strategies: Finding Lasting Answers to Symptoms and Health trials were designed to be comparable, although not identical, making this multivariable analysis an important step in comparing effectiveness of the six interventions. A single trial designed to provide direct



**Fig. 1.** Effect of each intervention on changes from baseline in daily mean vasomotor symptom frequency relative to control.

Guthrie. Pooled Analysis of Six Hot Flush Interventions. *Obstet Gynecol* 2015.



**Table 4.** Effect of Each Intervention on Changes From Baseline in Daily Mean Vasomotor Symptom Frequency and Bother Relative to Control

| Outcome          | Intervention | Change From Follow-Up to Baseline |                     |                     |                    |
|------------------|--------------|-----------------------------------|---------------------|---------------------|--------------------|
|                  |              | Week 4                            | Week 6              | Week 8              | Week 12            |
| No. of VMS/d     |              |                                   |                     |                     |                    |
| Trial 01         | Escitalopram | -1.9 (-3.1 to -0.7)               | -1.4 (-2.7 to -0.2) | -1.4 (-2.7 to -0.2) | —                  |
| Trial 02         | Exercise     | —                                 | -0.4 (-1.1 to 0.3)  | —                   | -0.1 (-0.9 to 0.7) |
|                  | Yoga         | —                                 | -0.6 (-1.3 to 0.1)  | —                   | -0.6 (-1.3 to 0.2) |
|                  | Omega-3      | —                                 | 0.2 (-0.4 to 0.8)   | —                   | 0.2 (-0.4 to 0.9)  |
| Trial 03         | E2           | -1.2 (-2.2 to -0.3)               | -1.9 (-2.9 to -0.9) | -2.4 (-3.4 to -1.3) | —                  |
|                  | Venlafaxine  | -1.3 (-2.2 to -0.4)               | -1.3 (-2.3 to -0.3) | -1.8 (-2.8 to -0.8) | —                  |
| VMS bother (1–4) |              |                                   |                     |                     |                    |
| Trial 01         | Escitalopram | -0.3 (-0.5 to -0.1)               | -0.2 (-0.4 to 0)    | -0.3 (-0.5 to -0.1) | —                  |
| Trial 02         | Exercise     | —                                 | -0.1 (-0.2 to 0.1)  | —                   | 0.0 (-0.2 to 0.1)  |
|                  | Yoga         | —                                 | 0.0 (-0.2 to 0.1)   | —                   | -0.1 (-0.2 to 0)   |
|                  | Omega-3      | —                                 | 0.0 (-0.1 to 0.1)   | —                   | 0.1 (-0.1 to 0.2)  |
| Trial 03         | E2           | -0.2 (-0.4 to 0)                  | -0.2 (-0.5 to 0)    | -0.3 (-0.5 to -0.1) | —                  |
|                  | Venlafaxine  | -0.1 (-0.3 to 0.1)                | -0.1 (-0.3 to 0.1)  | -0.2 (-0.4 to 0)    | —                  |

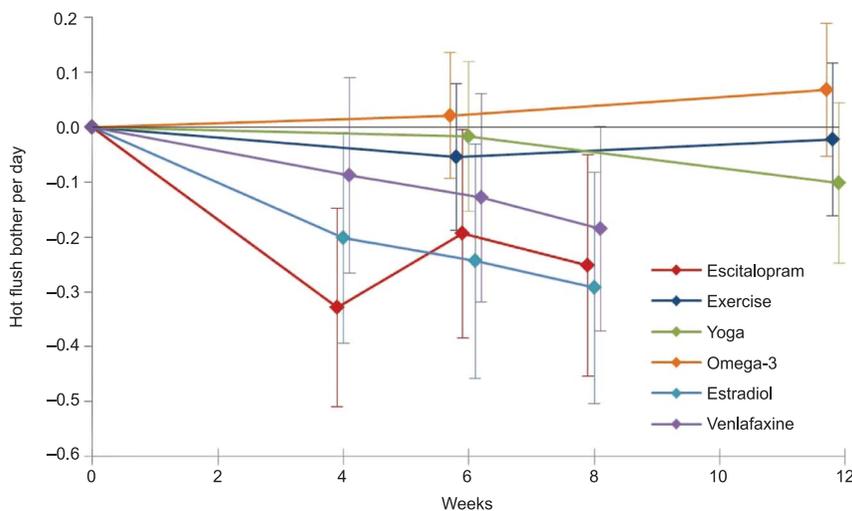
VMS, vasomotor symptoms; E2, estradiol.  
Data are mean (95% confidence interval).  
Dashes indicate the timepoints at which data were not collected.

head-to-head comparisons of all six interventions would have required considerably larger sample sizes that were not possible within time and cost constraints. Furthermore, intervention-specific exclusion criteria and women’s preferences would have made recruitment to a single trial testing all interventions impractical. The analyses presented here bridge the gap between the feasible, individual trials and an idealistic trial providing direct comparisons.

A strong placebo response is common in vasomotor symptom trials with reductions varying from 20% to 60% from baseline<sup>16–20</sup> with possible causes including regression to the mean, natural resolution of symptoms, a true physiologic response to the placebo

interventions, and fatigue with symptom recording over time. We sought to minimize the placebo response by excluding women whose vasomotor symptom frequency decreased more than 50% over the 3-week screening period. The success of this approach is reflected in the fact that the vasomotor symptom frequency reductions from baseline in our placebo groups (14–34%) were at the low end of the range compared with other vasomotor symptom trials.

The magnitude of each pharmacologic agent’s effect is consistent with the benefits observed for oral low-dose E2,<sup>21–23</sup> venlafaxine,<sup>24,25</sup> escitalopram, and other selective serotonin reuptake inhibitors<sup>6</sup> on vasomotor symptom frequency in prior randomized trials.



**Fig. 2.** Effect of each intervention on changes from baseline in daily mean vasomotor symptom bother relative to control.

Guthrie. Pooled Analysis of Six Hot Flush Interventions. *Obstet Gynecol* 2015.



We studied low-dose E2 because the FDA recommends use of the lowest dose possible.<sup>26</sup> Previous studies have highlighted that oral E2 efficacy is dose-dependent for both 17-beta- E2 and conjugated equine E2.<sup>21-23,27,28</sup> Although more rapid onset is achieved with 1- and 2-mg doses, lower doses still will have significant effects and have been shown to have lower risks.<sup>26</sup> Our findings for E2 may be specific to the selection of 17-beta E2, the oral route of administration, and the use of unopposed estrogen rather than estrogen progestin combined, which may produce greater reductions in vasomotor symptoms.<sup>21</sup>

To minimize potential side effects, venlafaxine was also studied at the lowest dose previously shown to be effective in randomized controlled trials.<sup>24,25,29</sup> Escitalopram had undergone limited pilot investigation<sup>30,31</sup> before Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01, so the magnitude of benefit and expected therapeutic dose was not previously known. Thus, we used the FDA-approved dose range for treatment of depression and anxiety (10–20 mg/d). Although the maximum escitalopram and venlafaxine treatment responses appeared to be achieved at 4 weeks in our analysis, whereas vasomotor symptom frequency showed continued improvement between 4 and 8 weeks with low-dose E2, most hormonal studies show little additional benefit beyond 8 weeks.<sup>22,27,32-34</sup> Selective serotonin reuptake inhibitor and serotonin norepinephrine reuptake inhibitor trials show sustained benefit beyond 8 weeks.<sup>6,35</sup>

Findings from these pooled analyses allow for a more informed discussion between women and their health care providers about their treatment options. These data suggest use of escitalopram, oral low-dose E2, or low-dose venlafaxine based on individual risk profiles and side effect concerns is a reasonable starting point for treating women with bothersome hot flashes. In fact, the 8-week reductions in vasomotor symptom frequency from baseline relative to placebo with the medications in Menopausal Strategies: Finding Lasting Answers to Symptoms and Health 01 and 03 trials (–1.4/d with escitalopram, –2.4 with low-dose E2, and –1.8 with venlafaxine) were comparable with recent data on intervention effects with gabapentin (–1.7/d at week 4 and –1.1 at week 12)<sup>36</sup> and larger than the effects of paroxetine 7.5 mg (–1.4/d at week 4 and –0.9 at week 12).<sup>6</sup> Behavioral interventions and nutritional supplements studied to date cannot compete with low-dose E2 or serotonergic medications for relief of moderate vasomotor symptom frequency or bother.<sup>9-11,34,37</sup> These recommendations are based on the short-term expo-

sure studies here. Longer-term studies evaluating the risks and benefits of these treatments are warranted.

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