

# Symptom Experience After Discontinuing Use of Estrogen Plus Progestin

Judith K. Ockene, PhD, MEd

David H. Barad, MD, MS

Barbara B. Cochrane, PhD, RN

Joseph C. Larson, MS

Margery Gass, MD

Sylvia Wassertheil-Smoller, PhD

JoAnn E. Manson, MD, DrPH

Vanessa M. Barnabei, MD, PhD

Dorothy S. Lane, MD, MPH

Robert G. Brzyski, MD, PhD

Milagros C. Rosal, PhD

Judy Wylie-Rosett, EdD

Jennifer Hays, PhD

**R**ECOMMENDED GUIDELINES AND prescribing practices for menopausal hormone therapy (MHT) have changed significantly<sup>1,2</sup> since publication of the Women's Health Initiative (WHI) estrogen plus progestin (E + P) trial findings that the overall health risks of taking conjugated equine estrogens and medroxyprogesterone acetate for disease prevention exceed the benefits.<sup>3</sup> Management of vasomotor and vaginal dryness symptoms remains the cornerstone of opinion in favor of MHT use. Women frequently cite relief from vasomotor symptoms<sup>4,5</sup> and improvement in well-being as reasons for starting or continuing MHT.<sup>6,7</sup>

Current recommendations for MHT focus on treatment of symptoms at the lowest effective dosage for the shortest duration possible,<sup>8-10</sup> yet there is little information about the effects of stop-

**For editorial comment see p 245.**

**Context** Little is known about women's experiences after stopping menopausal hormone therapy.

**Objective** To describe women's symptoms and management strategies after stopping the intervention in a large estrogen plus progestin trial.

**Design, Setting, and Participants** Cross-sectional survey of 8405 women (89.9%; N = 9351) at 40 clinical centers who were still taking study pills (conjugated equine estrogens plus medroxyprogesterone [CEE + MPA] or placebo) when the estrogen plus progestin intervention (Women's Health Initiative) was stopped. Surveys were mailed 8 to 12 months after the stop date. Logistic regression was used to model vasomotor symptoms and pain or stiffness symptoms as functions of former treatment and baseline symptoms, adjusted for appropriate covariates.

**Main Outcome Measures** Symptoms (vasomotor or pain and stiffness) and management strategies.

**Results** Respondents' mean (SD) age at trial stop date was 69.1 (6.7) years. They averaged 5.7 years of taking study pills. Moderate or severe vasomotor symptoms after discontinuing study pill use were reported by 21.2% of former CEE + MPA and 4.8% of placebo group respondents overall and by 55.5% and 21.3%, respectively, with these symptoms at baseline (randomization). Compared with respondents in the former placebo group, moderate or severe vasomotor symptoms (adjusted odds ratio [AOR] 5.82; 95% confidence interval [CI], 4.92-6.89) and pain or stiffness symptoms (AOR, 2.16; 95% CI, 1.95-2.40) were more likely in respondents in the former CEE + MPA group. Both vasomotor symptoms (AOR, 5.36; 95% CI, 4.51-6.38) and pain or stiffness symptoms (AOR, 3.21; 95% CI, 2.90-3.56) also were more likely in women with these symptoms at baseline. Women reported a wide range of strategies to manage symptoms.

**Conclusions** More than half of the women with vasomotor symptoms at randomization to active CEE + MPA also reported these symptoms after discontinuing use of the study pills. However, these participants did not include women who were unwilling to be randomized or who had stopped taking the study pills earlier. These findings should be considered when advising women to treat menopausal symptoms with hormone therapy for as short duration as possible. Investigation of alternative strategies to manage menopausal symptoms is warranted.

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**Author Affiliations:** Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester (Drs Ockene and Rosal); Departments of Obstetrics and Gynecology and Women's Health (Dr Barad) and Epidemiology and Population Health (Drs Wassertheil-Smoller and Wylie-Rosett), Albert Einstein College of Medicine, Bronx, NY; Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Wash (Dr Cochrane and Mr Larson); Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr Gass); Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical

School, Boston, Mass (Dr Manson); Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee (Dr Barnabei); Department of Preventive Medicine, State University of New York, Stony Brook (Dr Lane); Department of Obstetrics and Gynecology, University of Texas Health Science Center, San Antonio (Dr Brzyski); and Department of Medicine, Baylor College of Medicine, Houston, Tex (Dr Hays).

**Corresponding Author:** Judith K. Ockene, PhD, MEd, University of Massachusetts Medical School, Division of Preventive and Behavioral Medicine, 55 Lake Ave N, Worcester, MA 01655 (Judith.Ockene@umassmed.edu).

ping MHT on either symptoms or health-related quality of life. Many possible alternative but largely untested strategies have been proposed for symptom relief after stopping MHT.<sup>11</sup> Newton et al<sup>12</sup> found that women generally view such alternative strategies as helpful. Unfortunately there is little information about the efficacy of many of these proposed alternatives.

The WHI E + P trial participants represent a large, unique cohort of women who have undergone sudden withdrawal from active combined hormone therapy or placebo. This article reports on vasomotor (hot flashes or night sweats) and other symptoms, use of alternative strategies for managing symptoms, and the perceived effectiveness of these strategies in those E + P trial participants who responded to a survey mailed 8 to 12 months after they were instructed to stop taking their study pills. These data are compared with baseline and year 1 postrandomization data from the same participants.

## METHODS

Details of the E + P trial design, recruitment, screening, randomization, baseline characteristics, and comparison of participants receiving active treatment with those receiving placebo are described elsewhere.<sup>3,13-15</sup> Relevant to the current analysis, participants with menopausal symptoms at baseline were generally not excluded from participating. Women who were taking hormones at screening were required to undergo a 3-month washout. Those women who completed the washout were asked if they were having postmenopausal symptoms, such as hot flashes or night sweats. Women who reported that they were having mild or moderate symptoms during the washout were cautioned that they could be randomized to placebo and that their symptoms could continue for the rest of the study. Women who reported that they were having severe menopausal symptoms during the washout were ineligible for the study. Participants who had not had a hysterectomy at baseline and were still interested in and eligible for the E + P trial provided writ-

ten informed consent and were assigned to 0.625 mg/d of conjugated equine estrogens plus 2.5 mg/d of medroxyprogesterone acetate (CEE + MPA) or placebo at 40 clinical centers across the United States. All participants completed self-administered questionnaires that included health-related quality of life and symptom items at baseline (before randomization) and at 1-year postrandomization.<sup>13,14,16,17</sup> Some of the participants who were taking hormones at screening may have completed these questionnaires before washout. Race/ethnicity was self-reported by participants who were given choices on a form.

In May 2002, the WHI data and safety monitoring board concluded that the risks of CEE + MPA treatment outweighed the benefits and recommended early stopping of the E + P trial.<sup>3,18</sup> The National Heart, Lung, and Blood Institute concurred, and in a centralized mailing timed to be received by participants on July 8, 2002 (average intervention duration was 5.6 years), E + P participants were informed of the findings and instructed to stop taking their study pills. The WHI clinical center staff subsequently met with each E + P participant, confirmed that she had stopped taking the study pills, obtained a medical history update, informed her of her treatment assignment, and discussed the findings of the study.

Participants who were still taking study pills on July 8, 2002, when the E + P trial intervention was stopped (n=9351 or 56% of the 16 608 women randomized in the E + P trial) were eligible to complete a survey mailed 8 to 12 months after the stop date. For women who stopped taking the study pills earlier, their recall of symptoms may have been distorted by time. Therefore, the remaining 7257 participants (44%), who had permanently discontinued use of the study pills before the stop date or were deceased, were excluded from this analysis.

## Survey Instruments

The E + P survey instrument was designed to collect self-report data after the WHI E + P trial intervention was

stopped. The survey was pretested at 4 WHI clinical centers using cognitive interviewing techniques<sup>19,20</sup> with 56 age-eligible women who had not been enrolled in the WHI. Survey items were based on previously standardized scales, expert clinician input, and a review of the relevant literature.<sup>12,21-23</sup> Some items have been described previously, including the depression and symptom checklist,<sup>10,23</sup> which had 8 items appended to capture additional menopausal symptoms and treatment effects.

Anxiety was measured using the 7-item Anxiety Disorder subscale of the Patient Health Questionnaire.<sup>24</sup> For each symptom of anxiety, respondents rated on a 3-point scale ("not at all" to "more than half the days") the extent to which they had experienced the symptom during the last 4 weeks. Panic attacks were assessed similarly by a single item from the Patient Health Questionnaire that asked if the participant had "an anxiety attack, suddenly feeling fear or panic."

Symptom management strategies included a checklist of 25 items reported by or recommended for women to cope with symptoms.<sup>12,22,23</sup> For each strategy, the respondent noted whether she had tried the strategy, and if so, how helpful she perceived it to be on a 3-point scale (from "helped" to "made things worse").

Hormone use items were based on questions included on other WHI surveys. Respondents also were asked about reasons for starting or continuing to take hormone medications since the intervention stop date.

Following review and approval by the institutional review boards for the clinical coordinating center and the local clinical centers, a cover letter, E + P survey, and prepaid return envelope were mailed out to all eligible E + P participants who had been taking study pills, either active or placebo, as of July 8, 2002. A subsequent follow-up mailing and telephone call were used to enhance response rates. The current analysis represents all eligible responses received and entered into the WHI database between the first mailing on March 15, 2003, and August 31, 2003.

## Data Analysis

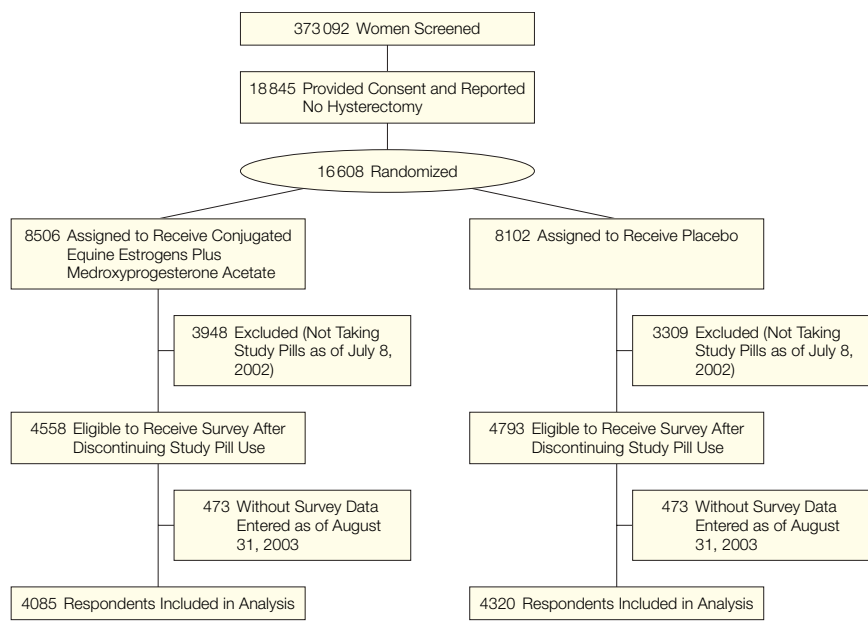
To characterize survey respondents more fully and improve the generalizability of study findings, we examined baseline demographic and health characteristics of survey respondents, eligible nonrespondents, and E + P participants who were not eligible to complete the survey because they had stopped taking the study pills before July 8, 2002. Participants who reported moderate or severe vasomotor symptoms (hot flashes or night sweats) within the 4 weeks before their screening visit were considered to have vasomotor symptoms at baseline (randomization or study entry).

The percentage of study pills taken was calculated from the actual weight of returned pills or the participant's estimate of remaining pills if they were not returned. Adherence was defined as taking 80% or more of the standard study pill regimen. The last adherence rate was based on the last actual or estimated pill collection before a participant stopped taking her study pills.

Symptoms were selected for analysis from the 42-item checklist based on previous research on symptoms of menopause, adverse effects of treatment, other treatment effects attributed to exogenous hormones, and symptoms identified in the earlier E + P trial analyses of health-related quality of life and symptoms.<sup>16,17</sup> Descriptive statistics and graphic displays of symptoms and symptom management strategies were reviewed.

Logistic regression was used to model the occurrence of selected symptoms since discontinuing study pill use as a function of both the baseline report of the same symptom and treatment group. These models were run separately for individual symptoms, including moderate or severe vasomotor symptoms and pain or stiffness. With the symptom of interest after discontinuing study pill use as the response, the models were adjusted for the baseline variables of age, race/ethnicity, prior hormone use, smoking, alcohol use, and body mass index (calculated as weight in kilograms divided by the square of

**Figure.** Survey Respondents After Discontinuing Use of Study Pills



height in meters). Receiver operating characteristic curves were checked graphically and used in conjunction with the Hosmer-Lemeshow  $\chi^2$  test<sup>25</sup> to assess the model fit. Collinearity was checked by examining correlation tables of the variables involved in the model, and overfitting was evaluated by looking at reduced models and checking for similar results.

In addition to these models, logistic models stratified by vasomotor symptom history (present at baseline vs not present at baseline) were run to assess the interaction between baseline vasomotor symptoms and treatment assignment with the presence of moderate or severe symptoms after stopping. Parameter estimates for all models were tested with a 2-tailed Wald test from a  $\chi^2$  statistic. For all testing,  $P < .05$  was identified as significant. All analyses were conducted with SAS version 9.0 (SAS Institute Inc, Cary, NC).

## RESULTS

A total of 9351 participants (4558 in the CEE + MPA group and 4793 in the placebo group), representing 56.3% of all participants in the E + P trial, were still taking study pills when the E + P trial

was stopped and were, therefore, eligible to receive the survey (FIGURE). Of these participants, 8405 (representing 89.6% of those formerly assigned to CEE + MPA and 90.1% to placebo) returned their surveys and are included in this data set.

Mean (SD) age at the time participants discontinued study pill use was 69.1 (6.7) years. TABLE 1 shows baseline characteristics of survey respondents, eligible nonrespondents, and ineligible participants who discontinued use of study pills prior to the stop date of the E + P trial. Respondents compared with eligible nonrespondents were older and more likely to be white, high school or college graduates, or married; have past or current MHT use at baseline; drink alcohol; and were former smokers. Respondents also were more likely to be adherent at their last pill collection before the stop date, to have longer follow-up, and were less likely to have had a history of hypertension, cardiovascular disease, or treated diabetes at baseline. Comparisons of survey respondents with E + P participants ineligible for this survey indicate differences similar to those described above. However, survey

**Table 1.** Baseline Characteristics\*

	No. (%) Eligible for Survey (n = 9351)		P Value for Respondents vs Nonrespondents	No. (%) Ineligible for Survey† (n = 7257)	P Value for Eligible vs Ineligible for Survey
	Respondents (n = 8405)	Nonrespondents (n = 946)			
Age, y					
50-54	1003 (11.9)	156 (16.5)	<.001	870 (12.0)	<.001
55-64	3839 (45.7)	432 (45.7)		3006 (41.4)	
65-74	3139 (37.3)	297 (31.4)		2771 (38.2)	
75-79	424 (5.0)	61 (6.4)		610 (8.4)	
Race/ethnicity					
White	7337 (87.3)	672 (71.0)	<.001	5936 (81.8)	<.001
Black	421 (5.0)	137 (14.5)		566 (7.8)	
Hispanic	329 (3.9)	82 (8.7)		477 (6.6)	
Asian/Pacific Islander	193 (2.3)	32 (3.4)		138 (1.9)	
American Indian	26 (0.3)	1 (0.1)		29 (0.4)	
Unknown	99 (1.2)	22 (2.3)		111 (1.5)	
Education					
College degree or higher	3079 (36.6)	305 (32.2)	<.001	2369 (32.6)	<.001
Beyond high school	3173 (37.7)	370 (39.1)		2872 (39.6)	
High school diploma or equivalent	1709 (20.3)	156 (16.5)		1357 (18.7)	
<High school diploma or equivalent	403 (4.8)	107 (11.3)		604 (8.3)	
Marital status					
Married or living as married	5246 (62.4)	491 (51.9)	<.001	4208 (58.0)	<.001
Widowed	1542 (18.3)	181 (19.1)		1414 (19.5)	
Divorced or separated	1243 (14.8)	214 (22.6)		1317 (18.1)	
Never married	353 (4.2)	57 (6.0)		276 (3.8)	
Alcohol use					
Current	6111 (72.7)	637 (67.3)	.003	5013 (69.1)	<.001
Past	1307 (15.5)	178 (18.8)		1322 (18.2)	
Never or rarely	932 (11.1)	123 (13.0)		855 (11.8)	
Smoking					
Current	769 (9.1)	119 (12.6)	<.001	830 (11.4)	<.001
Past	3254 (38.7)	328 (34.7)		2937 (40.5)	
Never	4292 (51.1)	487 (51.5)		3398 (46.8)	
Menopausal hormone therapy use					
Current	609 (7.2)	44 (4.6)	.009	392 (5.4)	<.001
Past	1563 (18.6)	171 (18.1)		1525 (21.0)	
Never	6230 (74.1)	730 (77.2)		5337 (73.5)	
History of cardiovascular disease‡					
Present	186 (2.2)	24 (2.5)	.49	241 (3.3)	<.001
Absent	8137 (96.8)	901 (95.2)		6929 (95.5)	
Diabetes					
Present and treated§	287 (3.4)	65 (6.9)	<.001	382 (5.3)	<.001
Absent	8116 (96.6)	881 (93.1)		6867 (94.6)	
Hypertension					
Treated	1551 (18.4)	194 (20.5)	.009	1526 (21.0)	<.001
Untreated	600 (7.1)	86 (9.1)		580 (8.0)	
Never hypertensive	5591 (66.5)	583 (61.6)		4435 (61.1)	
Last adherence rate to estrogen plus progestin					
≥80%	7273 (86.5)	674 (71.2)	<.001	2794 (38.5)	<.001
<80%	998 (11.9)	254 (26.8)		4152 (57.2)	
Hot flashes					
Moderate or severe	734 (8.7)	115 (12.2)	<.001	695 (9.6)	.27
Missing, none, or mild	7670 (91.3)	831 (87.8)		6562 (90.4)	
Night sweats					
Moderate or severe	689 (8.2)	116 (12.3)	<.001	722 (9.9)	.003
Missing, none, or mild	7715 (91.8)	830 (87.7)		6535 (90.0)	
Hot flashes and night sweats at baseline					
Moderate or severe	950 (11.3)	146 (15.4)	<.001	950 (13.1)	.008
Missing, none, or mild	7454 (88.7)	800 (84.6)		6307 (86.9)	

\*Frequencies may not add up to sample totals due to missing covariate data.

†Defined as estrogen plus progestin trial participants who had discontinued use of the study pills prior to the actual stop date of the trial (July 8, 2002).

‡Includes reported history of coronary heart disease, revascularization procedure, stroke, congestive heart failure, and peripheral vascular disease.

§Refers to self-report of diabetes treated with medication (pills or shots).

||Refers to self-report of current hypertension treated with medication.

respondents were younger than women who were ineligible to receive the survey, and there was no significant difference in cardiovascular disease prevalence at baseline.

Women who were taking hormones at baseline represented 7.2% of survey respondents compared with 4.6% of eligible nonrespondents ( $P = .009$ ) and 5.4% of E + P trial participants ineligible to receive the survey ( $P < .001$ ). The percentage of respondents who had moderate or severe vasomotor symptoms at baseline (11.3% overall; 12.3% of CEE + MPA group and 10.4% of placebo group) was significantly lower ( $P < .001$ ) than the percentage of eligible nonrespondents (15.4% overall; 16.1% of CEE + MPA

group and 14.8% of placebo group) and the percentage of women ineligible to receive the survey (13.1% overall; 12.5% of CEE + MPA group and 13.8% of placebo group;  $P = .008$ ) with these symptoms.

Among those participants ineligible to receive the survey because they had discontinued study pill use prior to July 8, 2002, only 10 reported vasomotor symptoms as a reason for stopping study pill use (0.1% of CEE + MPA group and 0.2% of placebo group). More survey-ineligible participants reported discontinuing study pill use because of vaginal bleeding (14.1% of CEE + MPA group and 0.9% of placebo group) or breast tenderness (6.8% of CEE + MPA group and 1.2% of pla-

cebo group) than because of vasomotor symptoms.

Survey respondents reported a wide array of symptoms after discontinuing study pill use. Respondents formerly randomized to the CEE + MPA group had a higher prevalence of each symptom since discontinuing study pill use than those randomized to placebo (TABLE 2). In addition, the total number of moderate or severe symptoms reported by women after discontinuing use of CEE + MPA was greater than the number of symptoms reported by women after discontinuing use of placebo, with 36.7% and 59.5%, respectively, reporting no symptoms.

Symptoms reported by more than 10% of respondents after discontinuing use of

**Table 2.** Symptoms Reported by Survey Respondents by Age After Discontinuing Use of Study Pills\*

Symptom	All Women, % (N = 8405)		Women Aged 55-59 y, % (n = 598)		Women Aged 60-69 y, % (n = 3859)		Women Aged ≥70 y, % (n = 3948)	
	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo
Hot flashes and night sweats	21.2	4.8	35.8	11.0	28.0	6.8	11.5	2.2
Hot flashes	15.3	2.9	29.3	6.5	20.6	4.1	7.1	1.3
Night sweats	17.1	3.6	28.7	9.5	22.9	5.1	8.9	1.6
Pain and stiffness	36.8	22.2	37.3	20.9	38.3	23.2	35.2	21.4
Joint pain or stiffness	26.4	14.4	29.6	11.0	27.6	15.4	24.6	13.9
General aches or pains	22.0	11.5	23.0	9.9	23.6	12.5	20.0	10.8
Low back pain	16.3	10.4	16.4	9.1	16.1	10.3	16.6	10.7
Neck pain	9.2	5.1	12.8	6.1	9.1	5.4	8.7	4.8
Feeling tired	21.3	11.6	24.2	11.4	21.6	11.7	20.4	11.6
Headaches or migraines	4.9	3.1	8.7	4.2	5.3	3.8	3.8	2.4
Difficulty sleeping	17.7	8.4	23.3	11.8	19.2	9.5	15.1	6.9
Mood swings	8.4	2.7	16.1	6.1	9.4	3.3	5.9	1.8
Difficulty concentrating	5.6	2.7	7.8	3.0	5.8	3.0	5.0	2.3
Irritability	5.1	2.1	8.7	4.6	6.1	2.1	3.4	1.8
Depression†	10.5	7.2	14.6	12.2	11.7	8.1	8.4	5.7
Generalized anxiety‡	2.0	1.1	3.0	3.0	2.5	1.2	1.3	0.8
Panic attack§	7.3	5.7	11.0	8.8	7.2	5.7	6.7	5.3
Vaginal or genital								
Dryness	9.8	5.1	9.6	8.4	13.0	6.4	6.5	3.6
Irritation, itching	4.5	2.5	3.0	3.8	5.5	2.6	3.8	2.3
Discharge	1.4	0.6	2.4	0.4	1.6	0.6	1.0	0.6
Weight gain	9.5	4.6	14.0	4.9	10.5	5.4	7.6	3.9
Increased appetite	7.2	2.6	10.2	3.0	8.9	2.9	4.8	2.3
Breast tenderness	3.4	1.2	3.0	2.3	4.4	1.4	2.4	0.9
Bloating or gas	11.5	7.7	13.1	8.0	11.4	8.2	11.4	7.3
Swelling of hands or feet	6.7	4.2	6.3	4.9	6.9	4.1	6.6	4.3

Abbreviations: CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

\*For all symptoms and for the combined age groups, all  $\chi^2$  tests comparing the proportion of symptomatic estrogen plus progestin participants with placebo participants were significant at the .01 level. Symptoms were reported as moderate or severe since discontinuing use of study pills unless otherwise indicated.

†In the past week (>5 score on Center for Epidemiologic Studies Depression Scale Short Form).

‡In the past 4 weeks (Patient Health Questionnaire).

§From anxiety at least several times in the past 4 weeks (Patient Health Questionnaire).

CEE + MPA included (in descending frequency) pain or stiffness, feeling tired, vasomotor symptoms, difficulty sleeping, and bloating or gas. Symptoms reported by more than 10% of respondents after stopping placebo were pain or stiffness and feeling tired. The percentage of respondents with scores on the Center for Epidemiologic Studies Depression Scale above the cut point for depression was greater for women after discontinuing use of CEE + MPA (10.5%) than placebo (7.2%) ( $P < .001$ ). Younger women reported more frequent emotional or neurological symptoms, headaches, breast tenderness, vaginal symptoms, and vasomotor symptoms.

TABLE 3 shows moderate or severe symptoms in participants after discontinuing study pill use stratified by whether or not women had these symptoms at baseline. Women who reported having moderate or severe symptoms at baseline were more likely to report these symptoms after discontinuing study pill use regardless of treatment group. Overall, 91.1% of women in the former CEE + MPA group who reported vasomotor symptoms after discontinuing MHT had also experienced them in the past.

TABLE 4 shows the adjusted odds ratios for specific moderate or severe vasomotor symptoms and pain or stiffness after discontinuing study pill use. The strongest determinant of these symptoms after discontinuing study pill use was their presence at baseline even after adjusting for former treatment assignment, age at stop date, baseline MHT use, body mass index, alcohol use, and smoking status. After adjusting for all other variables, respondents formerly assigned to CEE + MPA compared with those formerly assigned to placebo were also more likely to have these symptoms after discontinuing study pill use. Other factors that increased the likelihood of experiencing vasomotor symptoms after discontinuing study pill use in these adjusted models were taking hormones prior to study enrollment and current smoking. Higher body mass index, past or current alcohol use, and current smoking increased the likelihood of pain or stiffness after discontinuing study pill use in these adjusted models.

An additional model was run to evaluate an interaction between the effects of treatment assignment and history of vasomotor symptoms. This

model included all of the covariates presented in Table 4 with the addition of an interaction term. The interaction between treatment assignment and baseline vasomotor symptoms proved to be significant ( $P = .02$ ). To determine the nature of this interaction, separate models were created for the subgroups of participants based on vasomotor symptom status at baseline. Among respondents in both former treatment groups who reported vasomotor symptoms at baseline, those women previously assigned to CEE + MPA were 4.4 times more likely than those assigned to placebo to have vasomotor symptoms after discontinuing study pill use. Among respondents in both former treatment groups who reported none or only mild vasomotor symptoms at baseline, those women previously assigned to CEE + MPA were 7 times more likely than those assigned to placebo to have these symptoms after discontinuing study pill use.

Among survey respondents reporting any mild, moderate, or severe symptoms after discontinuing study pill use, the percentage that reported specific lifestyle and medical strategies to manage their symptoms are included in

**Table 3.** Symptoms Reported by Survey Respondents at Baseline and After Discontinuing Use of Study Pills

Symptom After Discontinued Use*	All Women, % (N = 8405)		Women Aged 55-59 y, % (n = 598)		Women Aged 60-69 y, % (n = 3859)		Women Aged ≥70 y, % (n = 3948)	
	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo	CEE + MPA	Placebo
<b>Vasomotor</b>								
Present at baseline†	55.5 (n = 503)	21.3 (n = 447)	57.0	22.7	57.2	23.1	47.0	16.1
Prior to baseline only‡	21.6 (n = 2077)	3.7 (n = 2358)	31.9	7.1	27.2	4.9	13.6	1.9
No prior symptoms§	6.4 (n = 1114)	1.2 (n = 1230)	10.3	3.1	10.3	2.3	3.6	0.5
<b>Pain or stiffness¶</b>								
Present at baseline§	54.7 (n = 1396)	38.3 (n = 1445)	50.4	41.0	57.6	39.8	52.5	36.5
No prior symptoms‡	27.5 (n = 2688)	14.1 (n = 2875)	29.9	12.4	28.5	14.4	26.0	13.9
<b>Depression#</b>								
Present at baseline	31.8 (n = 327)	25.5 (n = 334)	29.3	43.8	35.6	24.7	26.6	22.0
No prior symptoms§	8.6 (n = 3758)	5.6 (n = 3986)	12.6	7.8	9.2	6.5	7.3	4.6
<b>Vaginal or genital dryness</b>								
Present at baseline	29.1 (n = 388)	24.2 (n = 318)	26.3	17.7	34.6	26.0	21.8	23.2
No prior symptoms§	7.8 (n = 3696)	3.6 (n = 4002)	7.4	7.7	10.3	4.8	5.2	2.1

Abbreviations: CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

\*Symptoms reported as moderate or severe since discontinuing use of study pills unless otherwise indicated.

† $P < .001$  for comparison between CEE + MPA and placebo groups in the all category and in the aged 55-59 y and aged 60-69 y categories.

‡ $P < .001$  for comparison between CEE + MPA and placebo groups in the all category and in each age category.

§ $P < .001$  for comparison between CEE + MPA and placebo groups in the all category and in the aged 60-69 y and ≥70 y categories.

||No symptoms at baseline.

¶Defined as moderate or severe general aches and pains, joint pain or stiffness, low back pain, or neck pain.

#Did not occur in the past 4 weeks before screening visit (>5 score on Center for Epidemiologic Studies Depression Scale Short Form).

**TABLE 5.** More than half of the respondents with symptoms in either treatment group reported use of at least 1 management strategy. However, many of the management strategies were tried by 10% or fewer of the respondents. More respondents who had been assigned to CEE + MPA than those assigned to placebo tried at least 1 of any management strategy and, specifically, at least 1 lifestyle (49.1% vs 41.2%, respectively;  $P < .001$ ) or 1 medical (48.0% vs 37.1%, respectively;  $P < .001$ ) management strategy. Among women who reported only mild symptoms, 42% had tried 1 or more management strategies as opposed to 68% of women with any moderate or severe symptoms.

The most frequent lifestyle management strategies that women reported trying were drinking more fluids and starting or increasing exercising, which were reported by more than 20% of women in each treatment group. More than 86% of the women in each treatment group who tried these strategies reported that they helped to reduce symptoms.

The most frequent medical management strategy that women reported trying was talking to a clinician, which was used by 23.2% of the CEE + MPA group and 17.0% of the placebo group. Use of prescription MHT was not common in either the CEE + MPA group (4.3%) or the placebo group (1.2%). Among women in each treatment group who tried prescription hormones, 87% reported that they helped.

A separate question asked women whether they started taking prescription hormones (not necessarily as a management strategy) after discontinuing study pill use. A total of 5% of all respondents chose to start MHT after stopping their study pills for any reason, with CEE + MPA participants more likely to report starting MHT compared with placebo participants (7.6% vs 2.6%, respectively;  $P < .001$ ). **TABLE 6** lists the reasons these women gave for starting MHT after discontinuing study pill use. The most frequent reasons for starting MHT were symptom management (55.2% of CEE +

**Table 4.** Adjusted Odds Ratios for Symptoms Reported by Survey Respondents After Discontinuing Use of Study Pills\*

	Adjusted Odds Ratio (95% Confidence Interval)†	
	Vasomotor Symptoms	Pain or Stiffness Symptoms‡
Symptom at baseline		
Missing, none, mild	1.00	1.00
Baseline	5.36 (4.51-6.38)	3.21 (2.90-3.56)
Former treatment assignment in trial		
Placebo	1.00	1.00
CEE + MPA	5.82 (4.92-6.89)	2.16 (1.95-2.40)
Age at stopping		
55-59 y	1.00	1.00
60-69	0.81 (0.64-1.01)	1.07 (0.88-1.31)
≥70	0.35 (0.27-0.45)	1.02 (0.83-1.25)
Baseline menopausal hormone therapy use		
Never used	1.00	1.00
Current	1.46 (1.15-1.85)	0.97 (0.80-1.18)
Past	1.26 (1.05-1.51)	0.98 (0.86-1.12)
Body mass index (per unit)	1.01 (1.00-1.02)	1.04 (1.03-1.05)
Baseline alcohol use		
Never or rarely drink	1.00	1.00
Current	1.30 (1.00-1.69)	1.20 (1.01-1.42)
Past	1.35 (1.00-1.83)	1.34 (1.09-1.64)
Smoking		
Never smoked	1.00	1.00
Current	1.54 (1.22-1.95)	1.54 (1.29-1.83)
Past	1.19 (1.02-1.39)	1.06 (0.95-1.18)

Abbreviations: CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

\*Symptoms reported as moderate or severe since discontinuing use of study pills.

†Adjusted for former treatment assignment, age at stopping, baseline menopausal hormone therapy use, body mass index, alcohol use, and smoking status.

‡Defined as moderate or severe general aches and pains, joint pain or stiffness, low back pain, or neck pain.

MPA group) and physician advice (59.5% of placebo group). Compared with women who reported none or only mild vasomotor symptoms at baseline, a higher percentage of women with moderate or severe baseline symptoms also reported that they started MHT after discontinuing study pill use to deal with symptoms. This difference was greater for women in the former CEE + MPA group (77.8% of those with moderate or severe vasomotor symptoms vs 49.4% of those who reported none or only mild symptoms) than for women in the former placebo group (26.7% and 25.0%, respectively).

## COMMENT

This article provides the first published data on symptoms and management strategies reported by a large and diverse sample of relatively healthy

postmenopausal women after discontinuing CEE + MPA or placebo. These findings offer preliminary insights about the symptom experience women might anticipate after discontinuing MHT and are timely in light of recent recommendations to limit MHT primarily to the treatment of moderate to severe menopausal symptoms at the lowest effective dose for the shortest duration possible.<sup>9,10</sup>

Respondents who reported moderate or severe menopausal symptoms at study entry are somewhat comparable with women who might take prescription hormones to treat vasomotor symptoms. Our finding that respondents were more likely to report such symptoms after discontinuing hormone use even after more than 5 years of treatment is consistent with results from a recent cross-sectional survey of postmenopausal women in which

**Table 5.** Management Strategies After Discontinuing Use of Study Pills as Reported by Survey Respondents\*

	CEE + MPA (n = 3646)		Placebo (n = 2857)		Total (n = 6503)	
	No. (%) Tried	Helped, %†	No. (%) Tried	Helped, %†	No. (%) Tried	Helped, %†
<b>Lifestyle Management</b>						
Drank more fluids	1015 (27.8)	86.6	722 (25.3)	88.9	1737 (26.7)	87.6
Started or increased exercising	926 (25.4)	87.3	630 (22.1)	92.5	1556 (23.9)	89.4
Used fans or air conditioners	673 (18.5)	94.4	358 (12.5)	95.0	1031 (15.9)	94.6
Changed diet	554 (15.2)	80.9	431 (15.1)	86.1	985 (15.1)	83.1
Tried self-help techniques‡	379 (10.4)	92.9	247 (8.6)	95.5	626 (9.6)	93.9
Used layered or cotton clothing	385 (10.6)	90.9	213 (7.5)	95.8	598 (9.2)	92.6
Drank less caffeine	329 (9.0)	80.9	262 (9.2)	85.5	591 (9.1)	82.9
Socialized more	290 (8.0)	91.0	208 (7.3)	95.2	498 (7.7)	92.8
Drank less alcohol	66 (1.8)	77.3	56 (2.0)	78.6	122 (1.9)	77.9
Smoked less	39 (1.1)	61.5	47 (1.6)	66.0	86 (1.3)	64.0
Any lifestyle management strategy§	1792 (49.1)	NA	1178 (41.2)	NA	2970 (45.7)	NA
<b>Medical Management</b>						
Talked to clinician	847 (23.2)	80.6	485 (17.0)	87.0	1332 (20.5)	83.0
Took vitamin E	586 (16.1)	71.7	354 (12.4)	78.0	940 (14.5)	74.0
Used vaginal lubricants	401 (11.0)	92.0	241 (8.4)	92.9	642 (9.9)	92.4
Took other medicine	391 (10.7)	87.7	339 (11.9)	93.2	730 (11.2)	90.3
Took sleeping medicine	384 (10.5)	85.9	220 (7.7)	93.2	604 (9.3)	88.6
Tried alternative medical techniques	228 (6.3)	85.5	160 (5.6)	86.9	388 (6.0)	86.1
Took depression medicine	190 (5.2)	81.1	155 (5.4)	88.4	345 (5.3)	84.3
Took herbal or natural hormones	242 (6.6)	69.0	71 (2.5)	81.7	313 (4.8)	71.9
Took prescription hormones	157 (4.3)	92.4	33 (1.2)	87.9	190 (2.9)	91.6
Any medical management strategy¶	1751 (48.0)	NA	1059 (37.1)	NA	2810 (43.2)	NA

Abbreviations: CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; NA, not able to calculate.

\*Respondents who reported mild, moderate, or severe symptoms are included.

†Perceived the strategy "helped" (see "Methods").

‡Included yoga, meditation, or breathing exercises.

§P<.001 for comparison of treatment assignment with trying any lifestyle management strategy.

||Included acupuncture, massage, or chiropractic techniques.

¶P<.001 for comparison of treatment assignment with trying any medical management strategy.

**Table 6.** Reasons for Starting Menopausal Hormone Therapy After Discontinuing Use of Study Pills as Reported by Survey Respondents\*

Reason	Total No. of Respondents Who Reported This Reason	No. (%) of Respondents		P Value
		CEE + MPA (n = 310)	Placebo (n = 111)	
Deal with symptoms	199	171 (55.2)	28 (25.2)	<.001
Moderate or severe vasomotor symptoms at baseline	53	49 (77.8) [n = 63]	4 (26.7) [n = 15]	<.001
None or only mild vasomotor symptoms at baseline	146	122 (49.4) [n = 247]	24 (25.0) [n = 96]	<.001
Advice from clinician	188	122 (39.3)	66 (59.5)	<.001
To feel better	148	138 (44.5)	10 (9.0)	<.001
To treat or prevent osteoporosis	74	65 (21.0)	9 (8.1)	.002
To look better	40	36 (11.6)	4 (3.6)	.01
To prevent Alzheimer disease or dementia	38	33 (10.6)	5 (4.5)	.05
To treat or prevent colorectal cancer	20	20 (6.4)	0	<.001
Advice from family or friends	15	15 (4.8)	0	.02
Information in the media	14	13 (4.2)	1 (0.9)	.09
Information on the Internet	1	0	1 (0.9)	.10
Other	115	79 (25.5)	36 (32.4)	.18

Abbreviations: CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

\*Reasons are not mutually exclusive; respondents could list more than 1 reason for starting menopausal hormone therapy after discontinuing use of study pills.

troublesome symptoms after discontinuing hormone use were more prevalent among women who had started MHT for symptoms than in those who started MHT to prevent disease.<sup>26</sup> Although discontinuing CEE + MPA may be associated with a recurrence or persistence of vasomotor symptoms, we also noted this same phenomenon in a smaller percentage of respondents formerly assigned to the placebo group.

For women who do not have vasomotor symptoms before they start MHT, it appears that discontinuing use does not induce these symptoms. Among women formerly receiving active treatment in our study who reported none or only mild vasomotor symptoms at baseline, few reported these symptoms after discontinuing study pill use. These findings are consistent with the only clinical trial to date that looked at symptoms after discontinuing MHT and found that abruptly stopping a sequential regimen of combined hormone therapy after 14 weeks was not associated with an induction of vasomotor symptoms in women who had never had these symptoms.<sup>27</sup>

We presume that moderate or severe symptoms that occur after stopping CEE + MPA eventually diminish. In fact, the symptoms reported by the WHI participants since stopping use may have disappeared by the time respondents actually completed the survey 8 to 12 months after discontinuing study pill use. A recent study examining the occurrence of vasomotor symptoms in 266 blinded women transitioning from CEE + MPA to either placebo or raloxifene or continuing CEE + MPA found that vasomotor symptoms reported by 50% to 70% of those women transitioning off CEE + MPA were generally reported to be mild to moderate and peaked at 8 weeks into the transition.<sup>28</sup> That study followed up participants for only 12 weeks and did not report symptoms after discontinuing study pill use as a function of baseline symptoms. Grady et al<sup>26</sup> reported that symptoms were still troublesome in 73% of their study participants who discontinued MHT several months before. Addi-

tional research on the timing of onset and duration of symptoms after discontinuing use of MHT is warranted.

The higher prevalence of pain or stiffness in former CEE + MPA respondents compared with placebo respondents after discontinuing study pill use suggests an additional beneficial effect of CEE + MPA or a rebound symptom response to discontinuing use. These findings are consistent with WHI data reported by Barnabei et al,<sup>16</sup> which suggest that CEE + MPA may decrease or prevent musculoskeletal symptoms in postmenopausal women. The high rate of this withdrawal symptom rivals the report of vasomotor symptoms and has not been well documented in the past. Other MHT trials have not shown a beneficial effect of hormones on musculoskeletal symptoms,<sup>29,30</sup> except in a separate analysis of adherent participants. The presence of estrogen receptors in cartilage is generally acknowledged,<sup>31</sup> and animal models suggest that estradiol and progesterone influence pain latency as a factor contributing to an analgesic effect of these hormones.<sup>32</sup> However, a recent review of MHT effects on osteoarthritis by the American College of Obstetricians and Gynecologists noted that research in this area is limited and conflicting. These reviewers concluded that there is no beneficial role of combined hormone therapy or estrogen alone in the prevention or treatment of osteoarthritis or rheumatoid arthritis.<sup>33</sup> The current finding of an increase in pain or stiffness after discontinuing active study pill use may be an effect of aging. However, it is intriguing and warrants further research because the common wisdom has held that vasomotor symptoms are more strongly linked to hormonal effects of menopause despite increased reporting of joint stiffness or soreness in middle-aged women across racial/ethnic groups.<sup>34</sup>

Current hormone prescribing guidelines to limit MHT to the treatment of moderate to severe vasomotor symptoms is supported by our finding that few women with only mild symptoms regardless of treatment group sought

treatment for managing these symptoms. In fact, the number of former CEE + MPA participants who obtained prescription hormones to manage symptoms is considerably smaller than the 21.2% of patients surveyed by Grady et al.<sup>26</sup> Also consistent with current MHT prescribing guidelines is that most respondents regardless of treatment group started taking prescription hormones to deal with symptoms. Our rates correspond to those found by Grady et al,<sup>26</sup> who found that 57% of women reported that they restarted MHT for relief of symptoms.

Similar to findings reported in a telephone survey of alternative therapies for managing menopausal symptoms,<sup>21</sup> most commonly recommended medical and self-help strategies for controlling menopausal symptoms were viewed as helpful in both treatment groups. Although a higher percentage of placebo group respondents identified that the strategies they tried actually helped, this finding may be due to the fact that the symptoms reported by former placebo group respondents were more often mild or absent after discontinuing study pill use.

Complementary and alternative treatments for MHT have gained increasing attention since the release of the WHI E + P trial results, but the use of herbal or natural hormones by respondents in the current study was reported as one of the least effective strategies. Scientific data about the efficacy of many of these kinds of treatments are limited and women often receive information about alternative strategies from lay sources.<sup>35</sup> In prior qualitative research, menopausal women reported limited discussion with clinicians on lifestyle or self-care alternatives and a lack of knowledge and support for such alternatives.<sup>36</sup> Although the effectiveness women attributed to any strategies they tried may be related to a potential placebo effect,<sup>12</sup> the differences seen in the therapies tried and the relative effectiveness of each are important discussion points in clinical practice. Further studies on alternative therapies are warranted.

The generalizability of these findings is limited in several ways. Despite the high response rate of almost 90% in both treatment groups, there were significant differences between the baseline characteristics of respondents and eligible nonrespondents. These differences may have influenced the results.

An important study limitation is that the survey was sent only to those participants who were still taking study pills when the intervention was stopped. More than 40% of trial participants had already discontinued study pill use for personal or protocol-related reasons and were not included in this survey. These excluded women may have had different symptom experiences before, during, and after discontinuing study pill use compared with the survey respondents who took study pills for a longer period. Although there were no significant differences in the proportions of survey-ineligible participants and respondents who had moderate or severe hot flashes at baseline, a significantly greater proportion of survey-ineligible participants than respondents did have moderate or severe night sweats at baseline. It may be that night sweats, more than hot flashes, were disruptive to participants' daily lives during follow-up and therefore prompted more women with these symptoms to discontinue study pill use before the stop date. During follow-up, survey-ineligible participants, particularly those assigned to active CEE + MPA, more often identified symptoms associated with MHT (eg, breast changes and vaginal bleeding) rather than menopausal symptoms as reasons for discontinuing study pill use. Although vasomotor symptoms and vaginal changes were given as reasons for discontinuing study pill use early by similarly low numbers of both CEE + MPA and placebo participants, the experience of stopping study pills in these survey-ineligible participants may have been different from the experience of survey respondents.

Participants who enrolled in the E + P trial and continued taking study pills until July 2002 undoubtedly do not represent the full spectrum of symptom severity. The WHI clinical trial protocol

excluded the randomization of women who were unable to tolerate discontinuing MHT. The mean age of women in this study was considerably older than the age at which women typically begin MHT to treat menopausal symptoms. Less than 7% of all E + P participants reported current MHT use at baseline, but these participants represented a higher proportion of survey respondents than survey-ineligible participants in both treatment groups, and significantly more CEE + MPA than placebo respondents were taking hormones at baseline. Participants were unblinded to their former treatment assignment well before they completed these surveys, which also may have influenced their recall of symptoms since discontinuing study pill use.

Most of these limitations would argue against survey respondents reporting a heightened symptom experience after stopping study pills compared with survey-ineligible participants or the typical woman who starts MHT to treat menopausal symptoms. However, nearly 13% of respondents overall (21.2% of those formerly assigned to CEE + MPA) reported moderate or severe vasomotor symptoms after stopping study pill use. More than half of the youngest age group of CEE + MPA respondents who had these symptoms at baseline—those most comparable with the typical woman who begins MHT for symptom management—also experienced these symptoms after discontinuing use.

Participants in a randomized clinical trial of CEE + MPA and placebo, who had been taking study pills an average of 5.7 years, reported a range of symptoms experienced and strategies for managing symptoms after the intervention was stopped. While most respondents regardless of treatment assignment did not experience moderate to severe vasomotor symptoms after discontinuing study pill use, a history of vasomotor symptoms greatly increased the likelihood of experiencing symptoms after discontinuing use and participants randomized to active CEE + MPA were more likely to report re-

currence or persistence of these symptoms after discontinuing study pill use. Short-term use of CEE + MPA may only alleviate symptoms temporarily for many women, including older women, who may experience a return of menopausal symptoms after stopping MHT. A wide range of lifestyle and medical strategies to manage symptoms may help. Further testing of the efficacy of these management strategies for women whose symptoms recur after discontinuing short-term MHT is warranted.

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**Study concept and design:** Ockene, Barad, Cochrane, Larson, Gass, Wassertheil-Smoller, Manson, Barnabei, Lane, Rosal, Wylie-Rosett, Hays.

**Acquisition of data:** Ockene, Barad, Gass, Wassertheil-Smoller, Manson, Lane, Brzyski.

**Analysis and interpretation of data:** Ockene, Barad, Cochrane, Larson, Gass, Wassertheil-Smoller, Manson, Barnabei, Lane, Brzyski, Rosal, Hays.

**Drafting of the manuscript:** Ockene, Barad, Cochrane, Larson, Barnabei, Lane.

**Critical revision of the manuscript for important intellectual content:** Ockene, Barad, Cochrane, Larson, Gass, Wassertheil-Smoller, Manson, Barnabei, Lane, Brzyski, Rosal, Wylie-Rosett, Hays.

**Statistical analysis:** Barad, Larson, Wassertheil-Smoller.

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**Clinical Centers:** Albert Einstein College of Medicine, Bronx, NY (Sylvia Wassertheil-Smoller); Baylor College of Medicine, Houston, Tex (Jennifer Hays); Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (JoAnn Manson); Brown University, Providence, RI (AnnLouise R. Assaf); Emory University, Atlanta, Ga (Lawrence Phillips); Fred Hutchinson Cancer Research Center, Seattle, Wash (Shirley Beresford); George Washington University Medical Center, Washington, DC (Judith Hsia); Harbor-

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## REFERENCES

- Blumel J, Castelo-Branco C, Chedraui P, et al. Patients' and clinicians' attitudes after the Women's Health Initiative study. *Menopause*. 2004;11:57-61.
- Hersh A, Stefanick M, Stafford R. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291:47-53.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled clinical trial. *JAMA*. 2002;288:321-333.
- Greendale G, Reboussin B, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol*. 1998;92:982-988.
- Barnabei V, Grady D, Stovall D, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstet Gynecol*. 2002;100:1209-1218.
- Rothert M, Padonu G, Holmes-Rovner M, et al. Menopausal women as decision makers in health care. *Exp Gerontol*. 1994;29:463-468.
- Zethraeus N, Johannesson M, Henriksson P, Strand R. The impact of hormone replacement therapy on quality of life and willingness to pay. *Br J Obstet Gynaecol*. 1997;104:1191-1195.
- North American Menopause Society. Estrogen and progestin use in peri- and postmenopausal women: September 2003 position statement. Available at: <http://www.menopause.org/positionstatement.pdf>. Accessed September 17, 2003.
- American College of Obstetricians and Gynecologists. Questions and answers on hormone therapy in response to the Women's Health Initiative Study results on estrogen and progestin hormone therapy. Available at: [http://www.acog.org/from\\_home/publications/press\\_releases/nr08-30-02.cfm](http://www.acog.org/from_home/publications/press_releases/nr08-30-02.cfm). Accessed March 29, 2004.
- Food and Drug Administration. FDA updates hormone therapy information for post menopausal women. Available at: <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01022.html>. Accessed March 20, 2004.
- Treatment of menopause-associated vasomotor symptoms: position statement of the North American Menopause Society. *Menopause*. 2004;11:11-33.
- Newton K, Buist D, Keenan N, Anderson L, LaCroix A. Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol*. 2002;100:18-25.
- Hays J, Hunt J, Hubbell F, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13:S18-S77.
- Matthews K, Shumaker S, Bowen D, et al. Women's Health Initiative: why now? what is it? what's new? *Am Psychol*. 1997;52:101-116.
- Stefanick M, Cochrane B, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(suppl 9):S78-S86.
- Barnabei V, Cochrane B, Aragaki A, et al. The effects of estrogen plus progestin on menopausal symptoms and treatment effects among participants of the Women's Health Initiative. *Obstet Gynecol*. In press.
- Hays J, Ockene J, Brunner R, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med*. 2003;348:1839-1854.
- Freedman L, Anderson G, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. *Control Clin Trials*. 1996;17:509-525.
- Collins D. Pretesting survey instruments: an overview of cognitive methods. *Qual Life Res*. 2003;12:229-238.
- Drennan J. Cognitive interviewing: verbal data in the design and pretesting of questionnaires. *J Adv Nurs*. 2003;42:57-63.
- Barrett-Connor E, Hendrix S, Ettinger B, et al. *Best Clinical Practices*. Washington, DC: National Institutes of Health; 2002.
- National Institute on Aging. *Menopause: One Woman's Story, Every Woman's Story: A Resource for Making Healthy Choices*. Washington, DC: National Institutes of Health; 2001.
- North American Menopause Society. *Menopause Guidebook*. Cleveland, Ohio: North American Menopause Society; 2003.
- Spitzer R, Kroenke K, Williams J. Validation and utility of a self-report version of PRIME-MD: the PHQ Primary Care Study. *JAMA*. 1999;282:1737-1744.
- Hosmer D, Lemeshow S. *Applied Logistic Regression*, 2000. New York, NY: John Wiley & Sons; 2000.
- Grady D, Ettinger B, Tosteson A, Pressman A, Macer J. Predictors of difficulty when discontinuing postmenopausal hormone therapy. *Obstet Gynecol*. 2003;102:1233-1239.
- Hammar M, Ekblad S, Lönnberg B, et al. Postmenopausal women without previous or current vasomotor symptoms do not flush after abruptly abandoning estrogen replacement therapy. *Maturitas*. 1999;31:117-122.
- Gordon S, Walsh B, Ciaccia A, et al. Transition from estrogen-progestin to raloxifene in postmenopausal women: effect on vasomotor symptoms. *Obstet Gynecol*. 2004;103:267-273.
- Nevitt M, Felson D, Williams E, Grady D; Heart and Estrogen/Progestin Replacement Study Research Group. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women. *Arthritis Rheum*. 2001;44:811-818.
- Hannan M, Felson D, Anderson J, Naimark A, Kannel W. Estrogen use and radiographic osteoarthritis of the knee in women: the Framingham Osteoarthritis Study. *Arthritis Rheum*. 1990;33:525-532.
- Reginster J-Y, Kvasz A, Bruyere O, Henrotin Y. Is there any rationale for prescribing hormone replacement therapy (HRT) to prevent or to treat osteoarthritis? *Osteoarthritis Cartilage*. 2003;11:87-91.
- Gordon F, Soliman M. The effects of estradiol and progesterone on pain sensitivity and brain opioid receptors in ovariectomized rats. *Horm Behav*. 1996;30:244-250.
- American College of Obstetricians and Gynecologists. Osteoarthritis. *Obstet Gynecol*. 2004;104:625-655.
- Avis N, Stellato R, Crawford S, et al. Is there a menopausal syndrome? menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med*. 2001;52:345-356.
- Conboy L, Domar A, O'Connell E. Women at mid-life: symptoms, attitudes, and choices, an Internet-based survey. *Maturitas*. 2001;38:129-136.
- Will C, Fowles W. Woman to woman: complementary therapy use in menopause. *J Holist Nurs*. 2003;21:368-382.

### Author in the Room

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