

Paroxetine Is an Effective Treatment for Hot Flashes: Results From a Prospective Randomized Clinical Trial

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

In an open-label trial we have previously demonstrated that paroxetine reduces hot flashes. We initiated a stratified, randomized, double-blind, cross-over, placebo-controlled trial to investigate the efficacy of paroxetine 10 mg and 20 mg compared to placebo in reducing hot flash frequency and composite score. A secondary objective was to evaluate quality of life (QOL) parameters.

Patients and Methods

Women who suffered at least two hot flashes a day for 1 month or longer were eligible. Women were randomly assigned to 4 weeks of paroxetine 10 mg or 20 mg followed by placebo for 4 weeks, or placebo for 4 weeks followed by paroxetine 10 mg or 20 mg for 4 weeks. Participants completed baseline daily hot flash diaries for one week prior to the start of the study and throughout the study, and QOL questionnaires at baseline, week 5 and week 9.

Results

279 women were screened, and 151 were randomly assigned. Paroxetine 10 mg reduced hot flash frequency and composite score by 40.6% and 45.6%, respectively, compared to 13.7% and 13.7% for placebo ($P = .0006$ and $P = .0008$, respectively). Paroxetine 20 mg reduced hot flash frequency and composite score by 51.7% and 56.1%, respectively, compared with 26.6% and 28.8% for placebo ($P = .002$ and $P = .004$, respectively). Efficacy was similar between the two doses, but women were less likely to discontinue low-dose paroxetine. Paroxetine 10 mg was associated with a significant improvement in sleep compared with placebo ($P = .01$).

Conclusion

Paroxetine is an effective treatment for hot flashes in women with or without a prior breast cancer.

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INTRODUCTION

Thanks to advances in screening and adjuvant treatments, more than 80% of women with a newly diagnosed breast cancer are expected to survive their disease for 5 years or more. Most breast cancer survivors report excellent quality of life (QOL); however, one of the most common complaints, reported by more than half of the women, is hot flashes.¹ Hot flashes are a common symptom during menopause, but women

with breast cancer may suffer more severe or prolonged symptoms for several reasons.² Women may have discontinued hormone therapy (HT) at the time of breast cancer diagnosis, may have encountered chemotherapy-induced menopause, or initiated antiestrogen therapy.

Short term HT remains the most efficacious treatment for perimenopausal and menopausal women suffering hot flashes. On the basis of recent results from large prospective clinical trials, long-term HT is

not recommended due to increased risk of cardiovascular disease and breast cancer.^{3,4} HT may be particularly risky for women with a prior history of breast cancer. Indeed, the randomized Hormone replacement therapy after breast cancer diagnosis—Is it safe? (HABITS) study was terminated early due to the excess number of breast cancer recurrences in the group randomly assigned to HT compared with the untreated group.⁵ Thus, other treatment options for hot flashes have been investigated.²

We have previously demonstrated in an open-label prospective study that paroxetine is an effective treatment for hot flashes experienced by women with a history of breast cancer.⁶ In the open-label study, women received paroxetine 10 mg for 1 week followed by 4 weeks of paroxetine 20 mg. We have observed that women reported improvement in their hot flashes within days of initiating low-dose paroxetine. We now report results of a prospective, double-blind, randomized cross-over clinical trial designed to evaluate the efficacy of two doses of paroxetine versus placebo. The primary objective was to determine the efficacy of paroxetine relative to placebo in reducing hot flash frequency and composite score. An additional objective was to compare the effectiveness of the standard starting dose of paroxetine for depression and other psychiatric illnesses (20 mg) and low-dose (10 mg) for the treatment of hot flashes. In our pilot trial, we observed a statistically significant improvement in scores of depression, anxiety, sleep, and overall QOL. A secondary objective of the randomized trial was to evaluate the change in depression scores, anxiety scores, sleep, sexual function, and overall QOL in women treated with paroxetine compared with placebo.

PATIENTS AND METHODS

Patients

Eligible patients were recruited from six participating centers in the United States: Lombardi Comprehensive Cancer Center at Georgetown University (Washington, DC), Strang-Cornell Breast Center (New York, NY), Dana-Farber Cancer Institute (Boston, MA), John Wayne Cancer Institute (Santa Monica, CA), Arkansas Cancer Research Center (Little Rock, AR), and the University of Michigan Comprehensive Cancer Center (Ann Arbor, MI). To participate, women must have been 18 years of age or older, with or without a prior history of breast cancer, who could not or did not wish to take HT. The women must have complained of troublesome hot flashes, occurring at least 14 times per week that had lasted 1 month or longer. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and life expectancy greater than 6 months were required. Creatinine and bilirubin must have been less than two times normal level to participate.

Other treatments for hot flashes were not allowed for at least one month before study entry. Vitamin E was allowed, provided it had been used regularly for at least one month, and must have been continued throughout the study period. Simultaneous cytotoxic chemotherapy, radiation therapy, HT (estrogen and/or pro-

gestin), antidepressants, and monoamine oxidase inhibitors were not allowed and must have been discontinued at least 1 month before study entry. Antiestrogen use was allowed but must have been used for at least 1 month before starting the study, and must have been continued throughout the study period.

Study Design and Procedures

Eligible patients who wished to participate in the study signed a written informed consent, approved by each participating center's institutional review board. Before random assignment, all patients underwent baseline history and physical examination, and premenopausal or perimenopausal women underwent a serum pregnancy test.

The patients were stratified by age group (< 60 years, ≥ 60 years) and antiestrogen use (yes, no), and then assigned randomly to one of four treatment arms, so that the design consisted of two cross-over studies, as shown in Figure 1. This was a stratified, randomized, double-blind, placebo-controlled, double cross-over trial of paroxetine hydrochloride at 10-mg and 20-mg doses. The first arm included 4 weeks of paroxetine 10 mg/day followed by 4 weeks of placebo (P10-Pb). The second arm included 4 weeks of paroxetine 20 mg/day followed by 4 weeks of placebo (P20-Pb). The third and fourth arms included 4 weeks of placebo followed by 4 weeks of paroxetine 10 mg/day (Pb-P10) and 20 mg/day (Pb-P20), respectively. The first cross-over trial consisted of arms 1 and 3, and arms 2 and 4 constituted the second cross-over trial. Phase 1 of each cross-over trial consisted of weeks 2 to 5 and phase 2 of weeks 6 to 9 of the study.

A stratified randomization list was generated in RANLST [Brown WB, Lovato J, Rundell B: RANLST software, Houston, TX, The University of Texas, M.D. Andersen Cancer Center, Department of Biomathematics (bwb@odin.mda.uth.tmc.edu), 1992] and the patient assignments were prepared in stratum-specific, consecutively numbered sealed envelopes by the study statistician. The envelopes were maintained at the Research Pharmacy of the Lombardi Comprehensive Cancer Center. When a patient was registered onto the study, the study coordinator faxed on-study information to the pharmacist who determined the arm assignment and prepared the study medication.

Each patient was enrolled in the study for 9 weeks. The patient documented baseline hot flash symptoms using previously validated daily diaries of hot flash frequency and composite score for 7 days.⁷ Each woman noted how many hot flashes she experienced each day and how many were mild, moderate, severe, or very severe. The composite score for each day was calculated by multiplying the number of mild, moderate, severe, or very severe hot flashes by 1, 2, 3 or 4, respectively, and adding the values to obtain a summary score. The patient received two bottles, each containing 28 tablets, and was instructed to take the first drug (designated "drug A") daily during study weeks 2 to 5 and the second ("drug B") daily during study weeks 6 to 9. The women then returned to the clinic for a history and a physical, and returned their daily diaries, questionnaires, and unused study medication. Each woman was asked if she thought that drug A or drug B was more effective and whether she wished to continue taking drug A, drug B, or neither.

The women completed six measurements at baseline, week 5, and week 9. To document baseline and change in symptoms commonly associated with hot flashes and possible adverse events of the study drug, we used a symptom checklist that was previously used to survey a cohort of women who had enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast

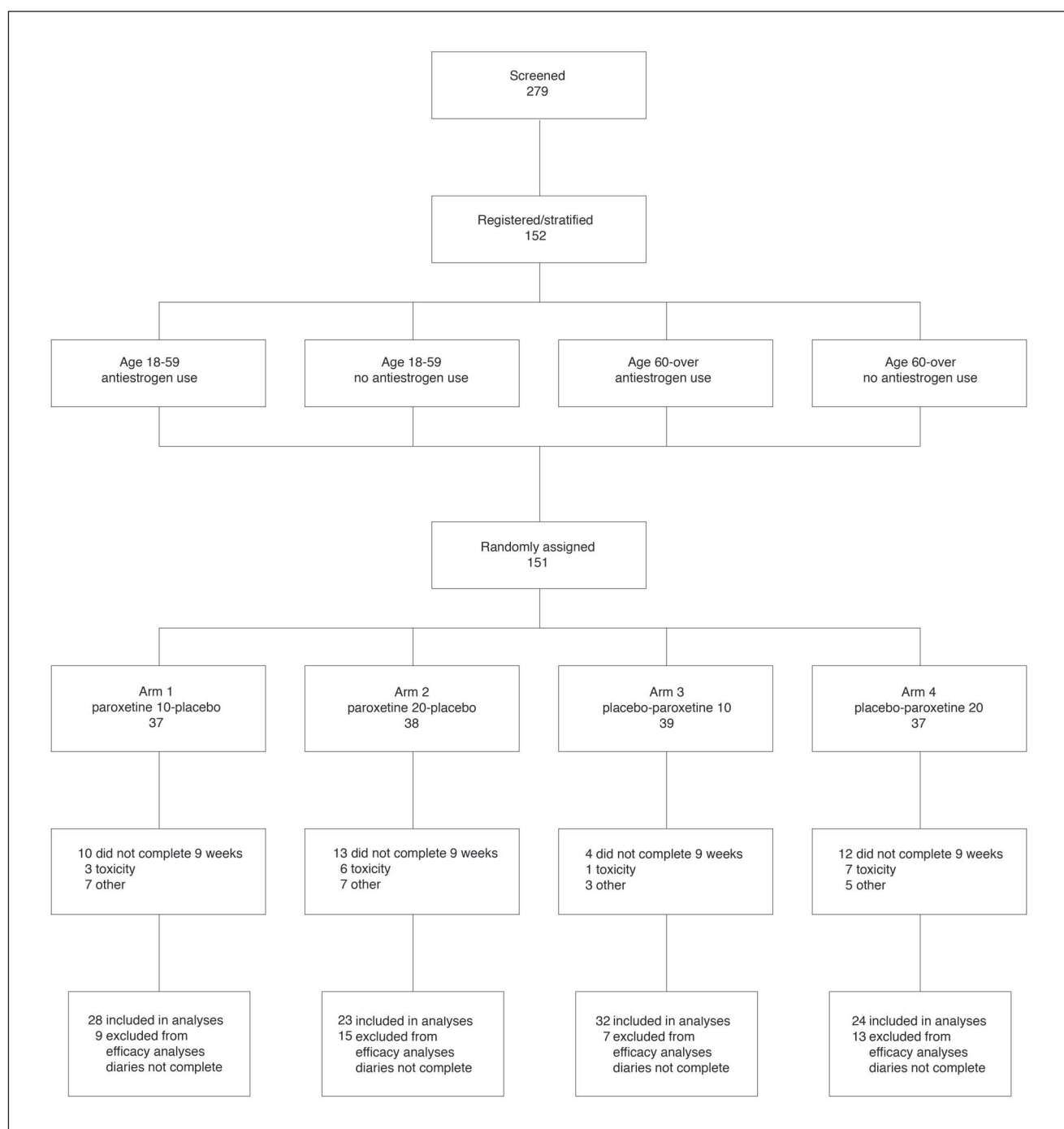


Fig 1. Patient entry, random assignment, and assessability.

Cancer Prevention Trial.⁸ We used five previously validated self-reported QOL tools: The Center for Epidemiologic Studies Depression Scale (CES-D),⁹ Hospital Anxiety and Depression Scale (HADS) 7 anxiety items,¹⁰ the Medical Outcomes Study (MOS) Sleep Problems Index,¹¹ MOS Sexual Problems Index,¹¹ and a self-rating questionnaire of overall health-related QOL standardized in the EuroQOL Linear Rating Scale (LRS).^{12,13}

Drug Formulation and Administration and Safety Monitoring

Immediate-release paroxetine hydrochloride (Paxil IR) formulated in 10-mg and 20-mg tablets and matching placebo were obtained from GlaxoSmithKline Pharmaceuticals (Collegeville, PA). Patients could be taken off study for unacceptable major toxicity or at the patient's request. The safety and tolerability of paroxetine was

monitored on a regular basis by the study coordinator. If a study participant complained of a bothersome adverse effect on a full-tablet study medication (A or B), she could decrease the dose to half a tablet. A history and physical, renal and liver function tests were repeated at study end.

Statistical Considerations

Outcome measures. The primary outcome measures were the percentage reduction in the number and composite scores of hot flashes from the baseline level (week 1) to the number at the end of the final week of treatment in each phase (ie, week 5 for phase 1 and week 9 for phase 2).

Sample size. Previous randomized trials in the same population suggested that patients receiving placebo would have a mean reduction in hot flashes of 27% and standard deviation (SD) of approximately 30% to 35%.¹⁴⁻¹⁶ We hypothesized that either P10 or P20 would lead to a reduction of $\geq 50\%$ in hot flash frequency. A sample size of 38 patients per treatment arm was selected to provide a statistical power of at least 80% to detect the hypothesized 23% difference in the reduction of hot flashes at a two-sided 5% statistical significance level. If data from phase I only are used and a comparison made between the percentage reductions in hot flash frequency for P10 versus P20, having 38 patients per group means the statistical power is 80% for detecting a difference of 23% at a statistical significance level of 5% (two-sided test). This assumes an SD of 35% in both the P10 and P20 groups.

Analysis. The primary analysis was of patients completing both phases of the cross-over study according to methods described by Senn.¹⁷ Conclusions from the primary analysis were checked by comparing P10 and P20 versus placebo in patients completing phase 1 only. Patients withdrawing and not completing the two phases of the study for any cause, and who did not provide daily diaries, and those with incomplete diaries (ie, not completed through week 9) could not be included in the cross-over analyses. For scattered missing observations in otherwise complete diaries, a value was imputed for the missing day by averaging the observations for the day before and after the missing day, or a similar rule for two missing days or a missing day at the end of a sequence. Less than 5% of the total number of daily entries was missing for included patients.

χ^2 tests (using the exact *P* values from StatXact¹⁸) or Fisher's exact tests were used for comparisons of distributions of patient characteristics among treatment arms, patients included versus not included in the analyses, and comparisons of the incidences of adverse effects among treatments. Analysis of variance methods^{19,20} were used to determine if there was a relationship between various covariates and the percentage reduction in hot flashes or composite scores for patients completing phase 1.

For all QOL measures (except the one-item EuroQOL-LRS scale), scale scores were classified as missing for patients with $\geq 25\%$ of item responses missing. Scores for CES-D, HADS, MOS Sleep, MOS Sexuality, and EuroQOL-LRS were classified as same, better, or worse at week 5 compared to baseline. For CES-D, a score changing from 16 or above to below 16 was deemed better and vice versa for worse. HADS scores were classified as normal (0-6), borderline (7-9), and high (> 10). Any transition from one category to another was considered better (worse) if the score decreased (increased). EuroQOL-LRS and MOS Sleep scores were considered better (worse) if the score increased (decreased) by at least 10 points between baseline and week 5, and the same otherwise. MOS Sexuality scores were considered better (worse) if the score decreased (increased) by at least 10 points between baseline

and week 5, and the same otherwise. McNemar's test²¹ was used to determine whether the distribution of patients to better or worse differed for each measure between baseline and week 5. A Kruskal-Wallis test²² was performed to compare each paroxetine dose against placebo.

Data safety monitoring committee. An independent data safety monitoring committee (DSMC) consisting of two medical oncologists, a biostatistician and a patient advocate not involved in the conduct of the trial, met at 12 and 26 months from the date of the study opening. The DSMC monitored patient accrual and assessability of the data. At 26 months, a protocol-stipulated preliminary analysis of each cross-over trial was performed. The study would have been closed if the effect of either treatment relative to placebo was statistically significant at the .001 level (according to the Haybittle-Peto²³ stopping rule).

RESULTS

Patient Population

From September 1999 to September 2002, 279 potential participants were screened. Of those, 152 eligible patients signed an informed consent and 151 were stratified and randomly assigned to treatment (Fig 1). The distribution of patient characteristics among treatment arms is given in Table 1. The majority of study participants were postmenopausal and had suffered hot flashes for 12 months or longer. More than 80% were breast cancer survivors, and 60% were taking an antiestrogen.

A total of 29% (44 of 151) of patients could not be included in the cross-over analyses because of missing or incomplete diaries. The distributions of patient characteristics were similar between the group that was included in the analysis versus not (data not shown). Of these 44 patients, five did not complete diaries because they stopped study early due to protocol violation, three, nine, and three withdrew due to toxicity on P10, P20, and placebo, respectively. Two patients withdrew because hot flashes were too severe while they received placebo; eight completed study medication but did not complete diaries, 11 were lost to follow-up or withdrew consent without stating reason, and three patients withdrew for unrelated personal problems (cancer progression, unrelated pre-existing medical issue, and family crisis).

Outcomes of Cross-over Treatment

Outcomes at weeks 5 and 9. Treatment with paroxetine substantially reduced hot flash frequency and composite score compared with placebo regardless of dose (Figs 2A and 3A). For patients on the 10-mg dose cross-over study, the average percentage reduction of hot flash frequency for P10 was 40.6% (SE, 5.1) compared with 13.7% (SE, 5.6) for placebo, a difference favoring P10 treatment of 27.0% ($P = .0006$). There is an apparent order effect for the P10 arms, but further analyses revealed no explanation for this difference (data not shown). For patients on the 20 mg dose cross-over

Table 1. Patient Characteristics of Randomly Assigned Patients by Treatment Arm

Characteristic	Arm 1 P10-Pb (n = 37)		Arm 2 P20-Pb (n = 38)		Arm 3 Pb-P10 (n = 39)		Arm 4 Pb-P20 (n = 37)		P
	No.	%	No.	%	No.	%	No.	%	
Age, years									.19
Median	53		50		55		52		
Range	43-76		27-67		41-76		36-75		
Menopausal status									.34
Pre	1	3	0	0	0	0	2	5	
Peri	7	19	7	18	4	10	3	8	
Post	29	78	31	82	35	90	32	86	
Natural	10	34	11	35	21	60	18	56	
Surgical	12	41	14	45	10	29	5	16	
Chemotherapy-induced	6	21	5	16	3	9	9	28	
Not specified	1	3	1	3	1	3	0	0	
Duration of hot flashes									.98
< 3 mo	4	11	4	11	4	10	3	8	
3-6 mo	5	14	2	5	5	13	6	16	
7-12 mo	4	11	6	16	5	13	5	14	
> 12 mo	24	65	26	68	25	64	23	62	
Prior hormone replacement therapy	21	57	12	32	26	67	17	46	.02
History of breast cancer	29	78	31	82	31	79	32	86	.83
Concurrent antiestrogen therapy	23	62	26	68	23	59	25	68	.80
Tamoxifen	21	91	24	92	18	78	25	100	
Raloxifene	2	9	0	0	3	13	0	0	
Aromatase inhibitor	0	0	2	8	0	0	0	0	
Not specified	0	0	0	0	2	9	0	0	
Concurrent vitamin E	20	54	20	53	20	51	15	41	.64
Baseline daily hot flash frequency*									0.86
Mean	7.3		6.9		7.1		7.8		
SE	0.7		0.8		0.7		0.7		
Baseline daily composite severity score*									.73
Mean	14.9		13.9		14.4		16.7		
SE	1.9		1.8		1.7		2.0		
Baseline CES-D*									.40
Mean	16.4		12.9		11.7		12.1		
SE	2.5		2.4		1.7		1.8		
Baseline HADS*									.40
Mean	5.7		6.7		5.2		5.2		
SE	0.60		0.85		0.63		0.78		
Baseline sleep (MOS)*									.74
Mean	78.8		75.2		78.4		74.3		
SE	2.7		4.4		2.6		4.0		
Baseline sexual function (MOS)*									.90
Mean	29.9		36.3		37.5		33.3		
SE	6.5		8.6		7.1		7.8		
Baseline EuroQOL-LRS*									.72
Mean	79.7		82.8		83.8		82.7		
SE	3.2		2.7		2.4		2.2		

Abbreviations: P10, paroxetine 10 mg dose; P20, paroxetine 20 mg dose; Pb, placebo; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; LRS, Linear Rating Scale; MOS, Medical Outcomes Study; QOL, quality of life.

*Baseline data are provided only for those patients who returned their baseline hot flash diaries and symptom questionnaires. n = 30, 29, 36, and 30 for arms 1, 2, 3, and 4, respectively, for hot flash frequencies and composite severity scores. Numbers are slightly smaller and variable for each quality-of-life measure.

study, the average percentage reduction for P20 treatment was 51.7% (SE, 5.3) compared with 26.6% (SE, 7.0) for placebo, a difference of 25.2% favoring P20 treatment ($P = .002$).

Average percentage reductions in hot flash composite score were similar to the hot flash frequency data (Figs 2B and 3B). Patients receiving P10 had an average percentage

reduction in composite score of 45.6% (SE, 5.8) compared to 13.7% (SE, 6.9) for patients receiving placebo ($P = .0008$), and those receiving P20 had an average percentage reduction in composite score of 56.1% (SE, 6.7) compared with 28.5% (SE, 7.9) for patients receiving placebo ($P < .001$).

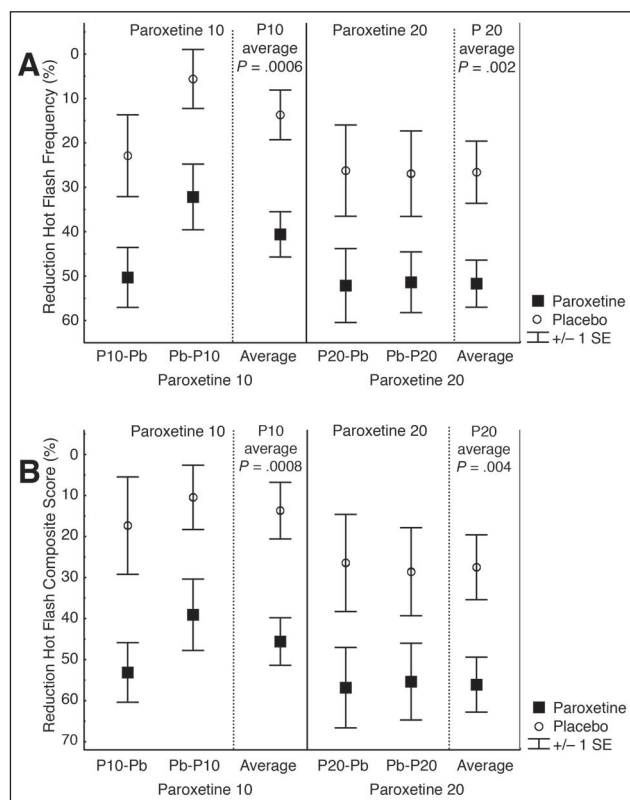


Fig 2. (A) Average percentage reduction in hot flash frequency; (B) average percentage reduction in hot flash composite score.

Outcomes at week 5. An additional nine patients had complete diaries through week 5 (ie, phase I data only available), totaling 29, 27, 32, and 28 patients in arms 1 (P10), 2 (P20), 3 (Pb), and 4 (Pb), respectively. Patients randomly assigned to P10, P20 in phase I had percentage reductions in the number of hot flashes of 51.0% (SE, 6.6), and 50.0% (SE, 7.3), respectively, and these results were significantly superior to the 16.1% (SE, 5.3) average reduction for the combined placebo treatment arms ($P < .0001$ for both comparisons). The percentage reductions in composite scores were 53.9% (SE, 7.0) for P10 and 54.3% (SE, 8.2) for P20, both highly significantly superior to the 19.1% (SE, 6.1) reduction for the combined placebo treatment arms ($P < .0001$ for both comparisons). Hence, the results in hot flash frequency and composite score data favoring P10 and P20 treatment to placebo are consistent whether the full results from the 9 weeks of the cross-over study are analyzed or only the 5 week data from the first portion of the study.

Comparison of results for P10 versus P20. The trial design, a random assignment to one of four treatment sequences in a double blind cross-over study, allowed a comparison between the P20 versus P10 treatment sequences. The average percentage reductions in hot flash frequency relative to placebo for P10 (27.0%) and for P20 (25.2%)

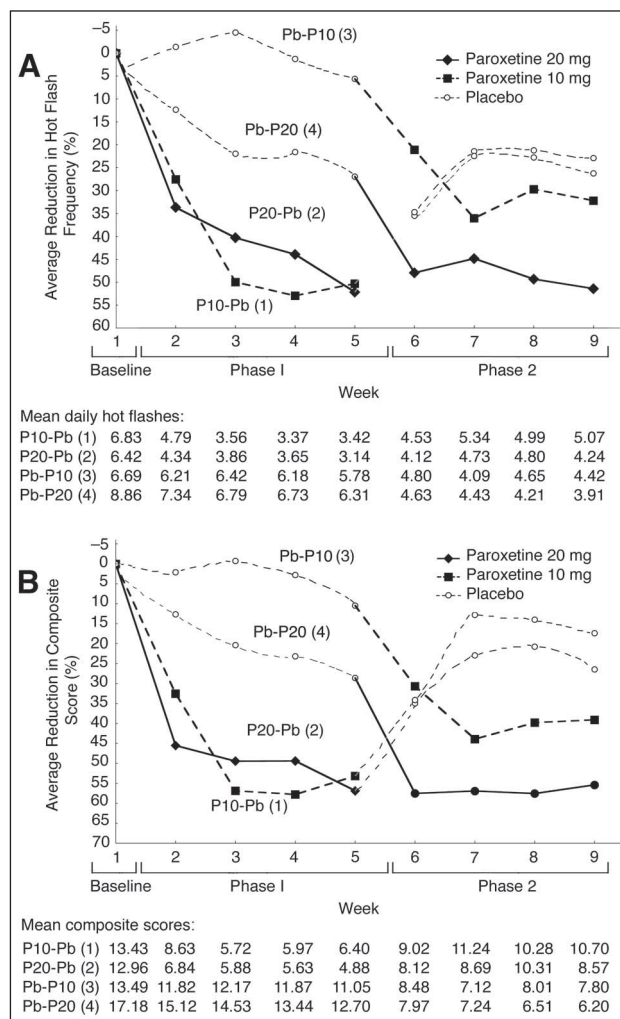


Fig 3. (A) percent reduction in average daily hot flash by treatment and week; (B) percent reduction in average daily severity score by treatment and week.

showed a difference of 1.8%. These reductions are very similar with a 95% CI for the difference between P10 and P20 treatment of -18.9% to 22.5% . Also, the decreases in composite score for P10 versus P20 treatment of 31.9% versus 28.6% were similar (difference is 3.3%) with a 95% CI for the difference between P10 and P20 of -22.1% to 29.0% . Hence, we conclude that P10 and P20 treatment were similar in effectiveness for reducing hot flash frequency and composite scores.

Relationship Between Patient Characteristics and Outcomes

Because results were similar for patients receiving P10 or P20 treatment, the data on both treatments were combined to investigate the relationship between various patient characteristics and hot flash outcomes. Analyses were also performed separately by treatment and conclusions are the same (data not shown). Reductions in hot flash frequency were not significantly related to patient characteristics

such as age, menstrual status, prior HT, prior breast cancer, baseline hot flash frequency or composite score, or baseline mean CES-D or HADS scores (Table 2). Although concurrent antiestrogen use was strongly associated with current age ($P = .06$) and history of breast cancer ($P < .001$), there is no difference detected in the percentage reduction in hot flash frequency for these characteristics between patients with and without concurrent antiestrogen use (data not shown). Likewise, differences in reductions in composite scores were not statistically significantly different among the subgroups (data not shown).

Safety and Tolerability

One hundred seventeen women comprise the safety population, including 104 patients from the efficacy analysis and 13 additional women with data provided through week 5. The ten most common symptoms experienced by women at baseline included fatigue (53%), headaches (49%), weight gain (31%), constipation (31%), weakness (28%), increased appetite (27%), vaginal discharge (27%), mouth dryness (25%), blurred vision (24%), and dizziness (21%), and none were significantly different among the four arms. We evaluated changes in status in symptoms that may be related to paroxetine (ie, better, same, worse) from

Table 2. Relationship Between Various Patient Characteristics and Percentage Reductions in Hot Flash Frequency for Paroxetine Versus Placebo

Table 2. Relationship Between Various Patient Characteristics and Percentage Reductions in Hot Flash Frequency for Paroxetine Versus Placebo								
Characteristic	No. of Patients	Reduction in Hot Flash Frequency						P*
		P10 and P20 Treatment		Placebo		Difference		
		%	SE	%	SE	%	SE	
Age, years								0.73
< 50	35	49.5	6.2	27.2	8.5	22.3	9.8	
50-59	54	43.9	5.4	17.4	5.3	26.5	7.4	
≥ 60	18	42.6	9.5	9.9	12.9	32.7	11.4	
Menopausal status								0.56
Pre/Peri	19	68.5	5.9	35.7	9.4	32.9	11.4	
Post	88	40.5	4.2	15.8	4.9	24.7	5.9	
Duration of hot flashes								0.44
≤ 12 mo	38	47.8	5.3	27.1	7.2	20.7	10.0	
> 12 mo	69	44.3	5.0	15.1	5.5	29.2	6.0	
Prior hormone replacement therapy								0.68
No	54	49.3	5.3	25.3	6.2	24.0	6.8	
Yes	53	41.7	5.3	13.3	6.3	28.4	8.1	
History of breast cancer								0.95
No	20	43.7	8.0	18.3	13.0	25.5	14.5	
Yes	87	45.9	4.2	19.6	4.6	26.3	5.6	
Concurrent antiestrogen therapy								0.53
No	40	44.2	6.4	22.3	8.5	21.9	9.2	
Yes	67	46.3	4.6	17.6	5.0	28.7	6.3	
Concurrent vitamin E								0.63
No	51	44.0	5.8	20.5	6.4	23.5	7.7	
Yes	56	46.9	4.8	18.3	6.1	28.6	7.1	
Average daily hot flash frequency at baseline								0.89
< 5	39	43.4	7.2	9.6	9.4	33.8	10.2	
5-9.9	44	41.3	5.6	24.9	5.6	16.4	7.9	
≥ 10	24	56.7	5.9	24.9	7.0	31.8	7.5	
Mean daily composite score at baseline								0.39
< 10	43	41.0	6.6	8.7	8.4	32.2	9.1	
10-19.9	38	45.9	6.1	24.0	6.2	21.8	9.4	
≥ 20	26	52.5	6.2	30.1	6.8	22.4	7.4	
Mean CES-D score at baseline								0.43
< 16	65	44.8	4.8	14.8	5.5	30.0	6.3	
≥ 16	32	45.8	7.2	25.1	7.3	20.8	10.7	
Mean HADS score at baseline								0.23
≤ 10	96	42.8	4.0	18.8	4.7	24.0	5.5	
> 10	11	68.8	7.5	24.1	13.2	44.7	15.6	
Abbreviations: P10, paroxetine 10 mg dose; P20, paroxetine 20 mg dose; Pb, placebo; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; LRS, Linear Rating Scale; MOS, Medical Outcomes Study; QOL, quality of life.								
*The P value is testing whether the difference between placebo and treatment differs by patient characteristics.								

Abbreviations: P10, paroxetine 10 mg dose; P20, paroxetine 20 mg dose; Pb, placebo; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; LRS, Linear Rating Scale; MOS, Medical Outcomes Study; QOL, quality of life.

*The P value is testing whether the difference between placebo and treatment differs by patient characteristics.

baseline to week 5 for P10, P20, and placebo treatment (Fig 4). Most often, the symptom status remained the same and the distribution of changes was similar for P10, P20, and placebo. The only statistically significant increase in symptom status occurred on P20, with nausea getting worse in 41% (11 of 27) of patients in contrast to 10% (7 of 73) of patients on placebo getting worse ($P < .001$), and 4% (1 of 26) on P10 ($P = .002$). A higher proportion of women on P20 arms withdrew due to toxicity (13 [17%] of 75) compared with the P10 arms (4 [5%] of 76; $P = .02$). The most common reasons for withdrawal were drowsiness and nausea.

Effects that may have been related to paroxetine were mostly mild. Only one grade 3 toxicity was reported. The

study participant complained of progressive shortness of breath while receiving drug A (placebo) and she subsequently stopped the study drug after 2 days of drug B (P20). The patient was subsequently diagnosed with congestive heart failure. She had a remote history of Hodgkin's Disease treated with radiation therapy and then a diagnosis of breast cancer treated with four cycles of combination doxorubicin and cyclophosphamide (total doxorubicin cumulative dose 240 mg/m²). Although her symptoms were likely due to prior anticancer therapy and not the study drug, data of prior anticancer therapy and potential cardiotoxic drugs were determined thereafter for all study participants at the recommendation of the DSMC.

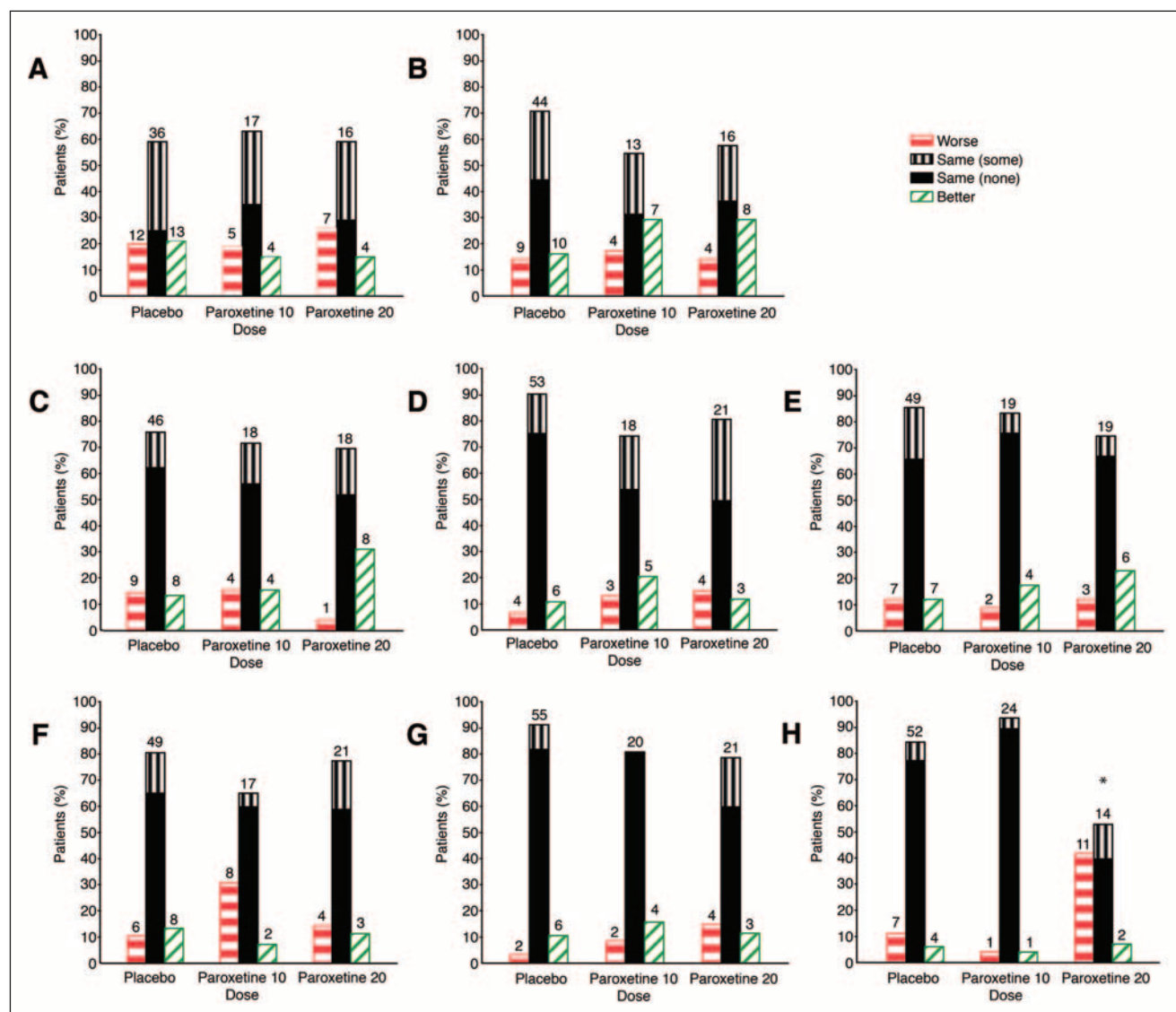


Fig 4. Changes in symptoms reported subjectively by patients at baseline and week 5 for eight symptoms that may be related to paroxetine. (*) Nausea was significantly worse among patients taking paroxetine 20 compared to baseline ($P < .001$). Same (none) means patients experienced the symptom neither at baseline nor week 5. Same (some) means that the patient experienced the symptom at the same level for baseline and week 5. (A) Fatigue/drowsiness; (B) headache; (C) weight gain; (D) constipation; (E) fatigue/weakness; (F) mouth dryness; (G) blurred vision; (H) nausea.

Quality of Life

Baseline means for the QOL scales were similar across the four treatment arms (Table 1). At week 5, there were no significant statistical differences in the distribution of patients for either paroxetine dose versus placebo who experienced improvement or worsening of CES-D, HADS, or MOS Sexuality scores (Fig 5). All three groups had substantial improvements of at least 10 points from baseline in MOS sleep scores; however, the improvement observed on P10 was statistically significantly better than the improvement observed with placebo ($P = .01$). EuroQOL-LRS scores improved or remained the same with treatment in all arms, including placebo, and the distribution of patients to better, same, or worse was similar among all treatment arms. However, for patients taking P10, all patients im-

proved or stayed the same ($P = .05$), but this improvement was not significantly different from the improvement observed with placebo.

Patient Preference to Continue Medication

A total of 106 patients responded to the question “which drug is more effective?” and “which drug would you like to continue?” by indicating drug A, drug B, or neither. A similar percentage of women in the P10 arms (42 [72%] of 58) and on the P20 arms (34 [71%] of 48) believed that paroxetine was more effective than placebo. However, a higher percentage of women who preferred P10 (34 [81%] of 42) wished to continue P10, compared to those on the P20 arms (22 [65%] of 34). Of the patients believing that P10 was more effective than placebo, 7 (17%) were not

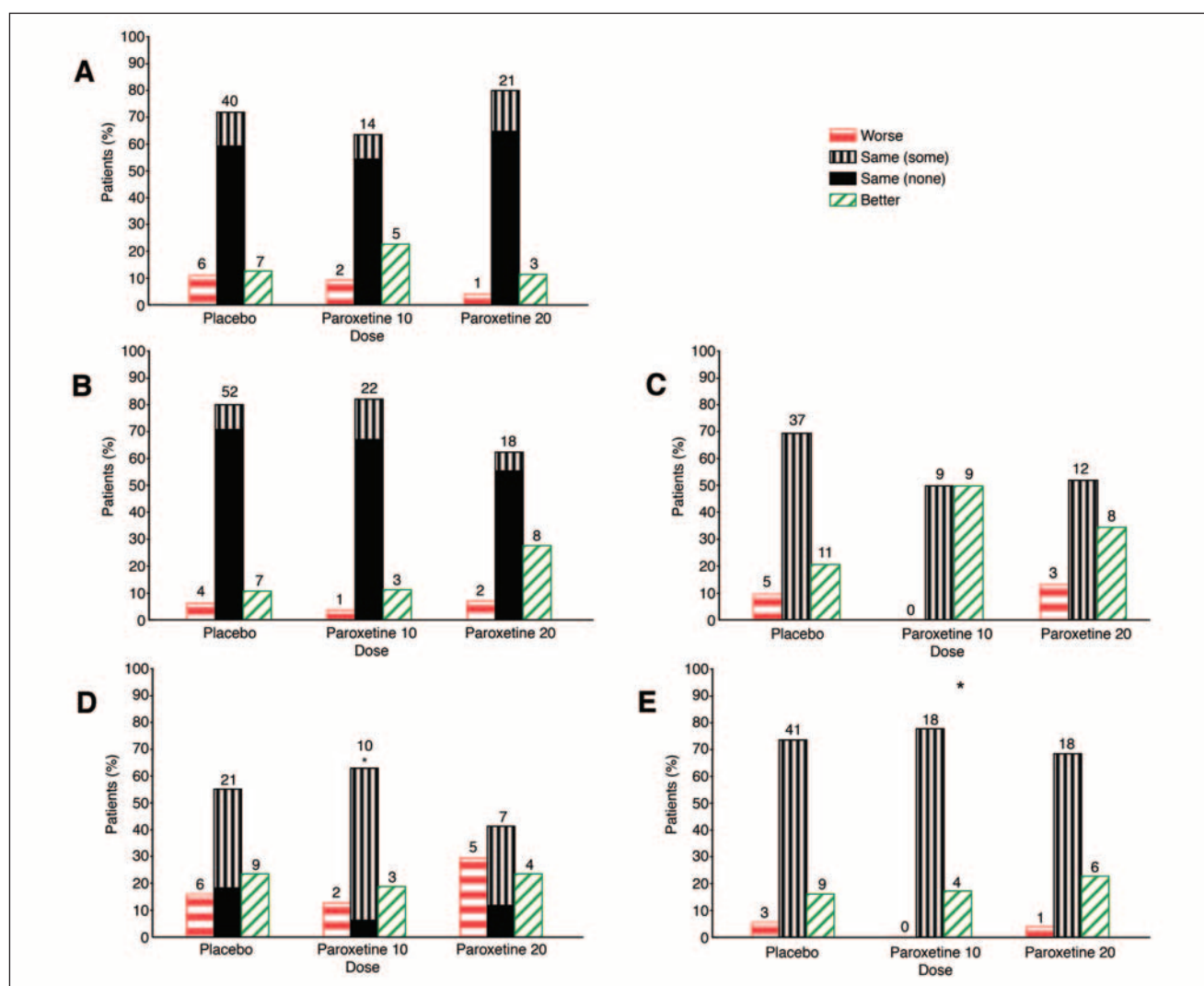


Fig 5. Change in quality-of-life measures at week 5 by treatment. (*) Sleep and EuroQOL-Linear Rating Scale were significantly better among patients receiving paroxetine 10 compared with baseline ($P = .003$ and $P = .05$, respectively). No other symptoms showed significant changes for the 10 mg or 20 mg dose. Same (none) means patients experienced the symptom neither at baseline nor week 5. Same (some) means that the patient experienced the symptom at the same level for baseline and week 5. (A) CES-D depression; (B) HADS anxiety; (C) sleep score; (D) EuroQOL-Linear Rating Scale.

interested in continuing either compared with 12 (35%) patients who believed P20 was more effective but did not wish to continue either treatment. Approximately 25% of patients on P10 and P20 treatment thought that placebo was more effective than paroxetine. Remarkably, of patients believing that placebo was the more effective treatment, 10 (71%) were interested in continuing on the placebo in the P10 group compared with six (50%) in the P20 group.

DISCUSSION

In this prospective randomized clinical trial we have demonstrated that both P10 and P20 were statistically and clinically significantly more effective than placebo in reducing the frequency and composite score of hot flashes. P10 was similar in effectiveness to P20 in reducing hot flash frequency and composite score, but the toxicity profile was more favorable and women were more likely to choose continuation of P10. Participants benefited from paroxetine equally regardless of age, menopausal status, a prior history of breast cancer, prior HT use, or concurrent antiestrogen use.

Our results are consistent with three other reported randomized clinical trials that evaluated the effectiveness of selective serotonin or noradrenergic reuptake inhibitors (SSRI/SNRI) for the treatment of hot flashes. Loprinzi et al compared 3 doses of venlafaxine (37.5 mg, 75 mg, and 150 mg) to placebo. Venlafaxine 75 and 150 mg reduced hot flash composite score by 61% each and was significantly more effective than placebo ($P < .0001$).²⁴ Venlafaxine 75 mg provided similar benefit to the higher dose and was recommended for clinical use. In a separate trial by the same investigators, fluoxetine was modestly more effective than placebo in reducing hot flash composite score, (50% v 36%, respectively; $P = .02$).²⁵ In another study, we have evaluated the efficacy of two doses of paroxetine controlled release (12.5 mg and 25 mg paroxetine; CR) in reducing hot flashes in women who were postmenopausal, over 90% of whom did not have a history of breast cancer and were not taking a concomitant antiestrogen. Paroxetine CR 12.5 mg and 25 mg provided similar benefit for post menopausal hot flashes, reducing hot flash composite score by 62% and 64%, respectively ($P = .03$ and $.007$, respectively). However, the low dose was associated with fewer adverse effects and a smaller likelihood of drug discontinuation.²⁶

Our results, taken together with other published reports, establish the effectiveness of a low-dose SSRI/SNRI for the control of hot flashes. Women who take a low-dose preparation are as likely to gain benefit from the agent and less likely to discontinue it, providing a greater clinical benefit to low-dose treatment. The mechanism of action of SSRI for the treatment of hot flashes is not known. The benefit observed in studies of SSRI for hot flashes is seen

earlier than the expected time required to assess efficacy in the treatment of psychiatric syndromes. In addition, hot flashes improved regardless of depression and anxiety scores, suggesting that the mechanism of action of SSRI in the treatment of hot flashes may differ from the effects seen in the treatment of depression and other psychiatric illnesses. Different SSRI/SNRI agents may be associated with a slightly different safety profile. Thus, it is possible that if a woman cannot tolerate one agent, she may tolerate a different compound. Whether agents from the same family would provide similar benefits to the same individual is not known.

Although our prior open-label pilot study suggested that women treated with paroxetine had improvement in depression scores, anxiety symptoms, sleep, and overall QOL compared to baseline scores, these changes were observed only for sleep at the P10 dose in the placebo-controlled trial. Our results coupled with the other three randomized trials²⁴⁻²⁶ suggest that the effectiveness of SSRI for the treatment of hot flashes was not related to improvement in depression, anxiety, or sleep disturbance.

SSRI treatment has been associated with sexual dysfunction in women treated for depression.²⁷ In the randomized trials of venlafaxine and fluoxetine for hot flashes, women on the treatment group had an improvement in libido compared with the placebo group. In our study, we asked specific questions regarding sexual function including sexual interest, difficulty in becoming sexually aroused, ability to relax and enjoy sex, and difficulty having orgasm. A significant difference was not detected between paroxetine and placebo treatments in any of these parameters.

The study has two main limitations. First, 39 women (26%) did not complete the 9 weeks of therapy required for the cross-over analysis. Second, 26 women (17%) did not return their diaries. It is possible that a simpler study design would have provided improved compliance. In our study, we demonstrated that the positive effects of paroxetine were similar when the 9 weeks of study were included or when only the first 5 weeks of the study were analyzed. Similarly, the randomized reports of venlafaxine and paroxetine CR did not have a cross-over design and demonstrated similar benefits to those observed in our current trial. Therefore, we recommend the use of a randomized parallel groups design for future investigations of promising agents for the treatment of hot flashes.

Several questions remain unanswered. We have not studied escalating doses of paroxetine and cannot recommend an increase in the dose more than 20 mg/day. In addition, like other studies of SSRI, our study evaluated changes in symptoms over a short duration. The long-term treatment benefit of paroxetine and other agents is not known. Finally, SSRI inhibit cytochrome P450 2D6 isoenzyme (CYP2D6). We have demonstrated that paroxetine inhibits the metabolism of tamoxifen to its

antiestrogen metabolite endoxifen.²⁸ Others have recently presented a preliminary report suggesting that tamoxifen-treated women with a CYP2D6 variant, which is a surrogate for an enzyme with low or no activity, had a worse disease-free survival compared to women with the wild type genotype.²⁹ We have further demonstrated that paroxetine is a strong inhibitor of the CYP2D6 enzyme compared with venlafaxine and sertraline.³⁰ However, a direct correlation between inhibition of tamoxifen metabolism and long-term breast cancer outcomes has not been reported. Until definitive data are available, clinicians should consider this information when recommending treatments for hot flashes in women who are taking tamoxifen.

Taken together, our data and those of others demonstrate that paroxetine and other SSRIs are effective treat-

ment for hot flashes in women with or without a prior breast cancer. We recommend prescribing low-dose of paroxetine (10 mg) to women who desire a nonhormonal pharmacologic treatment for their hot flashes.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Vered Stearns			Wyeth (A)			GlaxoSmithKline (C)		
Dollar Amount Codes (A) < \$10,000 (B) \$10,000-99,999 (C) ≥ \$100,000 (N/R) Not Required								

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