

Oral Clonidine in Postmenopausal Patients with Breast Cancer Experiencing Tamoxifen-Induced Hot Flashes: A University of Rochester Cancer Center Community Clinical Oncology Program Study

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Background: Hot flashes are the most frequently reported side effect of tamoxifen treatment. Although hormones are an effective treatment, their safety is questionable in women with breast cancer. It is therefore important to evaluate nonhormonal treatments for hot flashes.

Objective: To evaluate the effectiveness of oral clonidine for control of hot flashes associated with tamoxifen therapy in postmenopausal women with breast cancer.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: University of Rochester Cancer Center Community Clinical Oncology Program.

Patients: 194 postmenopausal women with breast cancer who were receiving adjuvant tamoxifen therapy.

Intervention: Oral clonidine hydrochloride, 0.1 mg/d, or placebo for 8 weeks.

Measurements: In a daily diary, patients recorded number, duration, and severity of hot flashes and overall quality-of-life score (on a 10-point scale) during a 1-week baseline period and during the 4th, 8th, and 12th weeks of the study.

Results: Patients in the placebo and treatment groups were similar in age, duration of tamoxifen use, reported frequency and duration of hot flashes at baseline, and dropout rates. One hundred forty-nine patients completed 12 weeks of follow-up. The mean decrease in hot flash frequency was greater in the clonidine group than in the placebo group after 4 weeks of treatment (37% compared with 20% [95% CI for difference, 7% to 27%]) and 8 weeks of treatment (38% compared with 24% [CI for difference, 3% to 27%]). Patients receiving clonidine were more likely than patients receiving placebo to report difficulty sleeping (41% compared with 21%; $P = 0.02$). A significant difference was seen in the mean change in quality-of-life scores (0.3 points in the clonidine group compared with -0.2 points in the placebo group; $P = 0.02$) at 8 weeks, although the median difference was 0 in both groups.

Conclusion: Oral clonidine, 0.1 mg/d, is effective against tamoxifen-induced hot flashes in postmenopausal women with breast cancer.

Hot flashes—a collective term that includes many vasomotor symptoms, such as a feeling of warmth, redness of the face and upper body, sweating, and dizziness—are the most frequent menopausal symptom. Approximately 60% to 70% of women undergoing the climacteric report hot flashes (1). Hot flashes are also the most common side effect associated with use of the antiestrogen tamoxifen; in a recent study, 57% of 1318 women with breast cancer who were receiving the drug reported hot flashes (2). Although most women tolerate this symptom and are able to remain active, others find it distressing. Hot flashes have been reported to interfere with daily activities and sleep, and some women have considered discontinuing therapy or have been less compliant with their daily tamoxifen regimen. These problems have become more pronounced because long-term tamoxifen therapy is now advocated for early-stage breast cancer. It is important to address the continuing problem of vasomotor side effects associated with tamoxifen therapy.

The pathophysiology underlying hot flashes is not entirely clear. Casper and Yen (3) have hypothesized that physiologic levels of estrogen and progesterone maintain endogenous opioid peptide concentrations in the hypothalamus and brain stem. At menopause, these concentrations decrease with decreasing estrogen levels, which releases nonadrenergic activity from its usual tonic inhibition and causes nonadrenergic hyperactivity. This leads to inappropriate activation of the heat loss mechanism in the medial preoptic area and subsequent hot flashes.

Clonidine hydrochloride is a centrally active α -adrenergic agonist that reduces vascular reactivity and is currently used to treat hypertension. Its reported side effects include dry mouth and sleepiness. Several studies have examined its effectiveness in controlling hot flashes caused by natural or surgical menopause. Wren and Brown (4) reported no benefit of clonidine therapy in a placebo-controlled trial, but Clayden and colleagues (5) and Edington and coworkers (6) demonstrated significant benefit in patients receiving oral clonidine. In a dose-escalation study by Laufer and coworkers (7), 10 women

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received two daily doses of clonidine, starting with 0.1 mg/d and increasing to 0.2 mg/d and 0.4 mg/d. Each dose level was maintained for 2 weeks. Four of the 10 participants withdrew because of side effects: 1 at 0.1 mg/d, 1 at 0.2 mg/d, and 2 at 0.4 mg/d. Increasing benefit was noted with increasing dose: At the maximum dose, hot flashes decreased by 46%. In a more recent study, transdermal clonidine was found to be of some benefit for tamoxifen-induced hot flashes (8).

A double-blind crossover pilot study of clonidine, 0.1 mg, or placebo given at bedtime was conducted at the University of Rochester Cancer Center in Rochester, New York (9). Fifteen women receiving tamoxifen for breast cancer entered the study. Of the 13 evaluable women, 9 (69%) preferred clonidine, 2 (15%) had no preference, and 2 (15%) preferred placebo. No adverse side effects, including any related to blood pressure, were reported. The clonidine and placebo groups did not differ significantly with regard to number of hot flashes. However, because the sample was too small and the duration of treatment too short, differences between treatments could not be reliably detected. We performed a larger randomized, controlled trial that studied the effect of clonidine on hot flashes in women receiving tamoxifen for breast cancer.

Methods

Our study was conducted by the University of Rochester Cancer Center and its affiliates under the auspices of the National Cancer Institute's Community Clinical Oncology Program (CCOP). Patients who met eligibility criteria were recruited from clinical practices of medical oncologists from participating CCOPs. Postmenopausal women who had been receiving adjuvant tamoxifen therapy for breast cancer for at least 1 month and reported at least one hot flash per day were eligible. Premenopausal women and women receiving concurrent chemotherapy or other endocrine therapy for breast cancer were ineligible. Patients receiving hypertension therapy or concurrent treatment with monoamine oxidase inhibitors; L-dopa; piribedil; tricyclic antidepressants; or sedatives, such as benzodiazepines or barbiturates, were also ineligible. Patients with coronary insufficiency, recent history of myocardial infarction (within the past 3 months), symptomatic cardiac disease, peripheral or cerebrovascular disease, syncope, or symptomatic hypotension were excluded, as were those with a history of allergy or adverse reaction to clonidine. Normal hepatic and renal function were required. Each patient signed an informed consent document approved by the institutional review board of the participating affiliate.

The National Cancer Institute, Division of Can-

cer Prevention and Control, Bethesda, Maryland, funded all aspects of the study as part of their CCOP. The study was designed, conducted, peer reviewed, and approved at the University of Rochester Cancer Center, a designated research base for CCOP. The University of Rochester Institutional Review Board approved the study.

Treatment

Patients were randomly assigned to receive oral clonidine, 0.1 mg, or placebo at bedtime for 8 weeks. Randomization was done by using a computer program maintained by the University of Rochester Department of Biostatistics and was stratified by time since menopause (≤ 3 years, > 3 years), duration of tamoxifen therapy (≤ 1 year, > 1 year), and baseline frequency of hot flashes (< 10 per day, ≥ 10 per day). Doses were not modified during the study. Patients or physicians could discontinue treatment for any reason. If treatment was discontinued, the reason was recorded on the appropriate study forms.

Treatment Evaluation

Self-report methods were used because the patient's evaluation of symptoms was of principal importance and greatest clinical relevance (10). We obtained data on hot flashes by asking patients to keep a daily diary for 1 week at baseline, during the 4th and 8th weeks of treatment, and during the 4th week after the end of treatment (the 12th week after randomization). The diary consisted of self-administered questionnaires on the number, duration, and severity of hot flashes. Severity was recorded as mild, moderate, severe, or very severe, similar to that reported by the North Central Cancer Treatment Group (8). A separate symptom checklist was used to monitor 18 potential side effects, as adapted from the drug surveillance literature and used in previous studies (11). Potential symptoms were difficulty sleeping, decreased appetite, constipation, diarrhea, hair loss, headache, eye sensitivity to light, dry mouth, night sweats, pain, nausea, vomiting, fatigue, stress incontinence, change in sense of taste or smell, drowsiness, dizziness, and hot flashes. We also asked patients to rate their lives on a scale from 1 (worst possible life) to 10 (best possible life) at each assessment. A brief history and physical examination, including blood pressure measurement, were done at each assessment.

Statistical Analysis

Four measures of hot flash symptoms were used to assess treatment effectiveness: frequency, mean severity grade (calculated by assigning scores of 1, 2, 3, and 4, respectively, to mild, moderate, severe, and very severe hot flashes), a combined score ob-

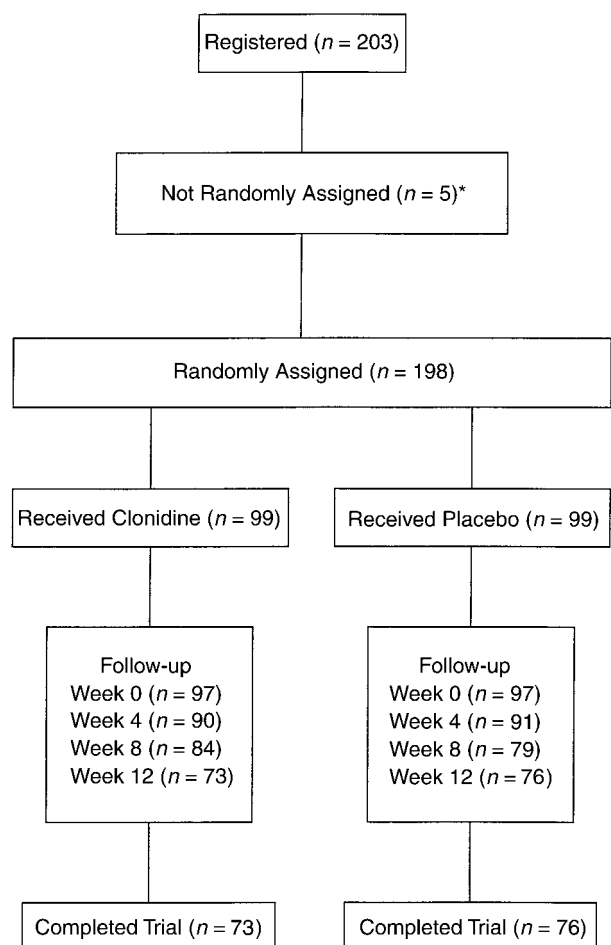


Figure 1. Flow of participants. *Two patients were ineligible, and three declined to participate.

tained by multiplying the mean frequency by the mean severity grade, and mean duration. Symptoms during the 4th, 8th, and 12th weeks were expressed as percentage changes from the baseline week for each woman, and the Wilcoxon test was used to test for differences between the clonidine and placebo groups. Patients' ratings of quality of life at each assessment were expressed as changes from the baseline score, and the Wilcoxon test was used to test for a difference between the clonidine and placebo groups. Repeated measures of analysis of variance were used to test for differences in treatment effects between weeks 4 and 8. Two-way analysis of variance was used to test for differences in treatment effect between subgroups defined by time since menopause, duration of tamoxifen therapy, or baseline frequency of hot flashes. We used SAS (SAS Institute, Inc., Cary, North Carolina) and S-PLUS (MathSoft, Inc., Seattle, Washington) statistical software. All *P* values are two-sided.

Patients reported occurrence and severity of 18 side effects on a scale from 0 (not at all severe) to 4 (extremely severe). The data were summarized as the peak severity of each symptom during treatment

minus its baseline severity. Between-group differences were compared by using the Wilcoxon test.

Results

The flow of patients is shown in **Figure 1**. We randomly assigned 198 women to receive clonidine or placebo. Four women did not provide baseline information about hot flashes and thus were considered unevaluable. The 194 evaluable patients in the clonidine and placebo groups were similar with respect to mean age (53 years compared with 55 years [range, 35 to 77 years]; *P* = 0.15), duration of tamoxifen use (>1 year, 39% compared with 35%; *P* > 0.2), and time since menopause (>3 years, 58% compared with 62%; *P* > 0.2). Forty-five of 194 patients (23%) did not complete the full 12 weeks of the study, and 31 (16%) did not complete the 8-week intervention period. Dropout rates were similar in the two groups and were due to patient preference. Baseline characteristics (age, hot flash symptoms, duration of tamoxifen therapy, time since menopause, and quality-of-life score) were generally similar in patients who completed the study and those who did not. Only one difference was statistically significant: Patients who dropped out had a shorter mean duration of hot flashes at baseline than did the 149 patients who completed the study.

During the baseline week, the mean frequency of hot flashes among the two groups was 8.0 (median, 6.7) per day in the clonidine group and 7.4 (median, 6.3) per day in the placebo group. Mean severity grades were 2.2 and 2.1, respectively (median, 2.1) (**Table**). The median duration of hot flashes was approximately 3 minutes in both groups. The mean duration in the clonidine group was distorted by a single patient who reported very long durations (mean, >88 minutes). Exclusion of this patient caused only minor changes in the differences between treatment groups. Mean quality-of-life scores were between 7.0 and 8.0 for both groups. No statistically significant differences were observed between treatment groups at baseline.

The **Table** and **Figure 2** show changes in the outcome measures from baseline by treatment group and week. Both groups reported milder hot flash symptoms during treatment than during the baseline period, but the reduction was greater in the clonidine group. Patients receiving clonidine had significantly greater benefit with respect to frequency and severity of hot flashes at weeks 4 and 8; 95% CIs for the between-group difference in frequency changes were 7% to 27% at week 4 and 3% to 27% at week 8. Although a nonsignificant difference between the clonidine and placebo groups was observed at week 12 (4 weeks after the end of treatment), the percentage change was greater in the

Table. Comparison of Clonidine and Placebo Groups by Week of Follow-up*

Outcome	Clonidine Group			Placebo Group			P Value†
	Patients	Mean ± SE	Median	Patients	Mean ± SE	Median	
	<i>n</i>			<i>n</i>			
Hot flashes per day							
Baseline, <i>n</i>	97	8.0 ± 0.6	6.7	97	7.4 ± 0.5	6.3	>0.2
Percentage change at week 4	90	-37.0 ± 3.5	-34.2	91	-20.1 ± 3.8	-21.1	0.001
Percentage change at week 8	84	-38.4 ± 4.2	-36.7	79	-23.6 ± 4.3	-16.7	0.006
Percentage change at week 12	73	-23.8 ± 5.2	-25.0	76	-13.9 ± 3.9	-15.0	0.09
Hot flash severity‡							
Baseline	97	2.2 ± 0.1	2.1	97	2.1 ± 0.1	2.1	>0.2
Percentage change at week 4	90	-14.9 ± 2.9	-11.7	91	-9.7 ± 2.6	-8.5	0.18
Percentage change at week 8	84	-21.0 ± 3.3	-17.3	79	-13.1 ± 3.4	-10.5	0.08
Percentage change at week 12	73	-14.6 ± 3.8	-9.3	76	-6.1 ± 3.3	-8.3	>0.2
Hot flash score§							
Baseline	97	18.3 ± 1.6	13.3	97	16.6 ± 1.2	12.6	>0.2
Percentage change at week 4	90	-42.2 ± 4.4	-42.6	91	-23.7 ± 4.6	-24.1	0.002
Percentage change at week 8	84	-45.0 ± 4.9	-50.2	79	-26.4 ± 5.5	-25.8	0.006
Percentage change at week 12	73	-28.6 ± 5.8	-26.6	76	-16.1 ± 4.9	-17.5	0.07
Hot flash duration							
Baseline, <i>min</i>	97	8.4 ± 4.1	2.7	97	4.1 ± 0.3	3.1	>0.2
Percentage change at week 4	90	-15.5 ± 4.2	-11.3	89	-2.8 ± 5.8	-1.5	0.11
Percentage change at week 8	84	-23.2 ± 4.3	-16.7	78	-9.2 ± 5.7	-16.8	0.18
Percentage change at week 12	73	-21.5 ± 5.0	-23.2	75	17.0 ± 19.5	-4.4	0.023
Quality-of-life score							
Baseline	96	7.2 ± 0.2	7.0	97	7.7 ± 0.2	8.0	0.08
Change at week 4	90	0.4 ± 0.1	0.0	88	-0.3 ± 0.2	0.0	0.003
Change at week 8	83	0.3 ± 0.2	0.0	77	-0.2 ± 0.2	0.0	0.022
Change at week 12	75	0.3 ± 0.2	0.0	78	-0.1 ± 0.2	0.0	>0.2

* All changes are relative to baseline.

† Two-sided Wilcoxon test comparing clonidine and placebo groups.

‡ On a scale of 1 to 4.

§ Obtained by multiplying the mean frequency by the mean severity grade.

|| On a scale of 1 to 10.

clonidine group. A significant difference was seen in the mean changes in quality-of-life score at 8 weeks (0.3 points in the clonidine group compared with -0.2 points in the placebo group), although the median difference was 0 in both groups. Treatment effects did not differ significantly between the 4- and 8-week follow-ups for any of the outcome measures ($P > 0.2$ for all treatment-by-week interactions).

To analyze treatment effects, we used all available observations at each follow-up. To assess the sensitivity of the results to alternate ways of handling missing values, we repeated the primary analysis with two variations. In the first, we excluded the 45 patients who dropped out before the end of the 12-week study; that is, only data from those who completed the study were analyzed. In the second, missing values at weeks 8 or 12 were replaced by the preceding nonmissing value for the patient (last observation carried forward). Because outcomes were defined as changes from baseline, we had no value to carry forward for missing data at week 4. However, dropout rates at week 4 were less than 10% and were nearly identical in the two treatment groups. For both alternate analyses, the patterns and magnitudes of treatment effects were similar to those for the reported analyses. Only the following changes in statistical significance were seen: 1) The analysis of persons who completed the study showed less evidence of a treatment effect on quality-of-life score at 8 weeks ($P = 0.082$ compared with $P =$

0.022), and 2) the last-observation-carried-forward analysis identified additional significant differences that showed greater benefit with clonidine for hot flash frequency, hot flash score, and quality-of-life score at 12 weeks. Neither of the alternate analyses is preferable to the available-data analysis, but both illustrate that the main conclusions of the study are not sensitive to the handling of missing data, especially during the 8-week intervention period.

We also tested whether the effects of clonidine at weeks 4 and 8 differed by the stratification variables, which interacted with treatment effect in two statistically significant ways. At week 4, the effect of clonidine on hot flash duration was significantly greater for women receiving tamoxifen for 1 year than for those receiving it for more than 1 year ($P = 0.024$). At week 8, the clonidine effect on hot flash score was significantly greater for women 3 years past menopause than for women more than 3 years past menopause ($P = 0.048$). These results should be interpreted with caution because we tested 30 potential interactions and thus could expect to observe 1 or 2 nominally significant effects by chance.

Patients self-reported the occurrence and severity of potential side effects. Difficulty sleeping was the only variable that differed significantly between groups; 41% of those in the clonidine group and 21% of those in the placebo group reported increased difficulty ($P = 0.02$). Blood pressure was

monitored at each assessment visit, and no adverse effect was noted.

Discussion

Hot flashes are a bothersome side effect of tamoxifen therapy in postmenopausal women with breast cancer. For patients with breast cancer, physicians are usually reluctant to prescribe estrogens because of the possibility of detrimental effects. Low doses of progestational agents, such as megestrol, have been reported to control hot flashes (12–15). It is uncertain, however, whether these agents are safe in women receiving tamoxifen, because both classes of drugs are potentially thrombogenic. Therefore, effective nonhormonal treatments are needed for tamoxifen-induced hot flashes.

A recent prospective study evaluated vitamin E

for hot flashes in survivors of breast cancer (16). A statistically significant reduction in hot flash frequency was seen, but the clinical magnitude was considered marginal because patients experienced only one fewer hot flash per day.

Our trial demonstrates that oral clonidine can decrease the frequency of tamoxifen-induced hot flashes for at least 8 weeks. This is consistent with the reported effectiveness of clonidine in women who experienced natural menopause (5, 6). Transdermal clonidine has also been found to reduce the frequency and, to a lesser extent, the severity of tamoxifen-induced hot flashes over a 4-week period (8). Our results are similar to those seen with transdermal clonidine over the first 4 weeks of administration. In addition, effectiveness was preserved over the 8-week duration of our study; a median of approximately 2.2 fewer hot flashes per day occurred

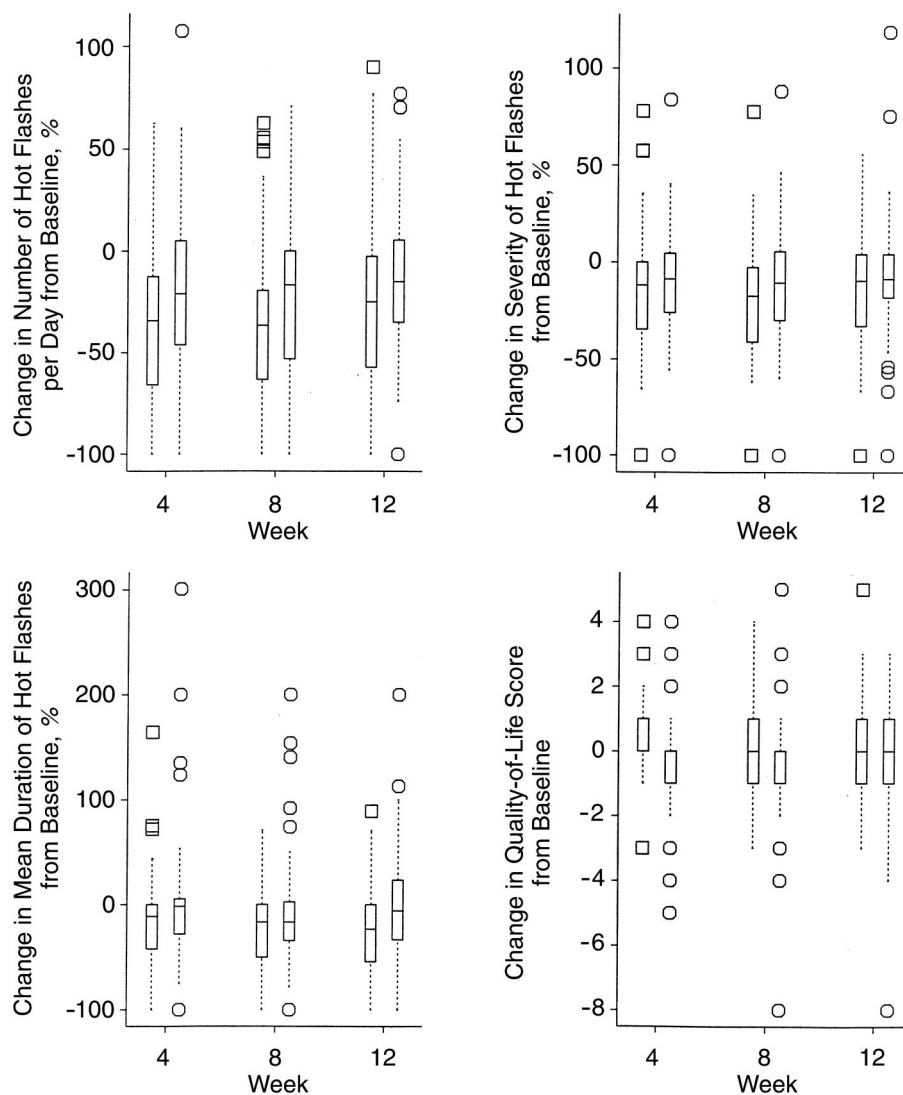


Figure 2. Changes in hot flash symptoms and quality-of-life score compared with baseline values, by treatment group and study week. For each week, the left-hand boxplot with squares represents the clonidine group and the right-hand boxplot with circles represents the placebo group. One observation at week 12 in the placebo group is not included in the plot of hot flash duration because the patient reported a mean duration of 1 minute at baseline and 15 minutes at 12 weeks (an increase of 1400%).

in the treatment group compared with 1.2 fewer hot flashes per day in the placebo group. Clonidine had a small beneficial effect on hot flash duration and severity. Mean quality-of-life scores were significantly better in the oral clonidine group at 4 and 8 weeks, although the between-group difference was small and the median did not differ. **Figure 2** clearly shows that the response to both clonidine and placebo varied considerably. Some women experienced no benefit from clonidine, and others reported substantial improvement with placebo. Large placebo-controlled studies are needed to ascertain the effectiveness of any putative agent in the control of hot flashes, as evidenced by the placebo effect in this study. Baseline frequency of hot flashes did not influence response to clonidine treatment. Our study was not designed for crossover treatment, and therefore patient preference cannot be ascertained. However, in our previous small pilot study, we observed a definite trend in favor of clonidine (9).

The toxicity of oral clonidine was low. Only 1 of 18 potential side effects differed significantly between groups. In contrast, Goldberg and colleagues (8) found statistically significant self-reported side effects of dry mouth, constipation, and drowsiness with transdermal clonidine.

Our study was designed for an intervention period of 8 weeks, during which clonidine was found to be effective. We believe that continued use of clonidine would provide clinical benefit, but we did not examine its long-term effectiveness. Tamoxifen and other selective estrogen receptor modulators are now being tested in healthy postmenopausal women at high risk for breast cancer, and hot flashes are expected to be a side effect requiring special attention. Oral clonidine may be helpful in that setting. We conclude that oral clonidine is useful for controlling tamoxifen-induced hot flashes in postmenopausal women with breast cancer.

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