# Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population

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## ABSTRACT

*Objective:* To evaluate the effectiveness of a selective serotonin reuptake inhibitor (SSRI) (sertraline) in decreasing hot flashes in a general population of women.

*Design:* A double-blind, placebo-controlled, crossover trial was conducted in a southwestern urban setting. A total of 102 women aged 40 to 65 who were experiencing hot flashes and not taking any hormone therapy were recruited. After 1 week of baseline hot flash data collection, study participants were randomized to receive placebo or active drug (sertraline 50 mg) for 4 weeks. This intervention was followed by a 1-week washout and cross over to the opposite treatment for 4 weeks. The number and severity of hot flashes were measured.

*Results:* One hundred two women were enrolled in the study. Five dropped out before providing baseline data. Of the 97 remaining, 52 were randomized to active drug first and 45 to placebo first. Ten dropped out of the study before completing all 10 weeks, leaving 46 in the active drug-first arm and 41 in the placebo-first arm. At baseline, the mean number of hot flashes reported was 45.6 per week (SD = 29.6), ranging from 2 to 148. During the sertraline phase of the study, women experienced five fewer hot flashes per week than they did on the placebo ($P = 0.002$). The severity of hot flashes was not significantly different; however, the hot flash score (number × average severity) was significantly improved during the sertraline phase.

*Conclusion:* Sertraline reduced the number of hot flashes and improved the hot flash score relative to placebo and may be an acceptable alternative treatment for women experiencing hot flashes.

*Key Words:* Menopause – Hot flashes – Selective serotonin reuptake inhibitor.

One of the earliest and most distressing symptoms of menopause is hot flashes. This vasomotor irregularity, along with mood swings, insomnia, depression, and joint pain, can severely affect quality of life and well-being.

More than 15 million women ages 45 to 54 in the United States experience hot flashes.[1] An additional 22 million women who are now ages 35 to 44 will experience menopause over the next 10 to 15 years.[2] Seventy-five percent to 80% of women undergoing the natural course of menopause and 95% to 100% of women who have had their ovaries removed experience physiological and/or psychological problems associated with the decline in ovarian steroids.[3] The data indicate that hot flashes may start much earlier and continue far longer than is commonly recognized by physicians or acknowledged in textbooks of gynecology. The pattern of hot flashes is not static and may change with time. For some women, hot

flashes become less frequent and less intense; for others, hot flashes may continue at hourly intervals well into old age.[1]

Healthcare utilization data reveal that most women seeking care related to menopausal symptoms do so because of the discomfort associated with hot flashes.[4] Therefore, hot flashes are a significant issue for women in midlife and for the healthcare system.

The Study of Women's Health Across the Nation (SWAN) has extensively reported on the demographics and epidemiology of the menopausal syndrome from its multiethnic, multirace, multisite study of 16,065 women ages 40 to 55 years.[5] Vasomotor symptoms, particularly hot flashes and night sweat, were reported more commonly in African-American and white women and less commonly in Japanese and Chinese women.[5] SWAN also reports that menopausal syndrome, independent of other explanatory factors, is associated with self-reported sleep difficulty.[6] While the SWAN results argue against a universal menopausal syndrome, all groups of postmenopausal women reported more vasomotor symptoms than premenopausal women.[7]

A common and effective treatment for the symptoms of menopause is estrogen, either alone or with progesterone, as hormone therapy.[8] Estrogen provides greater than 95% efficacy for relief of vasomotor symptoms.[9] However, recent research has more clearly defined the risks of hormone therapy.[10] The results from the Women's Health Initiative's randomized, controlled trial show an increased risk of breast cancer, coronary heart disease, stroke, and pulmonary embolism in healthy postmenopausal women taking conjugated estrogen and progesterone.[10]

In part because of these recent findings, many women and doctors are looking for nonhormonal ways to manage menopausal symptoms. In the SWAN cohort, a large multiethnic sample of midlife women, 42.1% of participants had used at least one of 16 complementary or alternative medicine therapies in the past year.[11] Clonidine is mildly effective but not well tolerated.[12] Vitamin E, soy, black cohosh, and other botanicals have been tried, but the results are unimpressive.[13] Many researchers have studied the role of complementary alternatives to hormone therapy with mixed results.[14-16]

Antidepressants have been used with some success. Early work in this field studied the role of antidepressants in the care of breast cancer patients for whom hormonal therapy was not appropriate. In a randomized, controlled trial of breast cancer survivors, venlafaxine significantly reduced hot flashes at 75 mg/day.[17,18] Clinical trials have shown improvement in hot flashes with fluoxetine.[19,20] Stearns and colleagues[21,22] have published on the role of paroxetine in the treatment of hot flashes in breast cancer survivors. Finally, Stearns et al[23] recently published results of their work with paroxetine in menopausal women in the treatment of menopausal hot flashes. Her team found "the mean reductions in hot flash frequency composite score from baseline to Week 6 were statistically greater for those receiving paroxetine CR than for those receiving placebo."[23] In another recent study, Evans et al[9] evaluated the effectiveness of extended-release venlafaxine in a 12-week trial in a general population of women experiencing menopausal hot flashes. They studied a single dose of venlafaxine in a double-blind, noncrossover format and found a significant decrease in hot flash frequency but not severity. In Japan, Nagata et al[24] studied whether short-term combination therapy of low-dose estrogen with an SSRI (fluvoxamine) helped oophorectomized women with hot flashes and depressive tendencies. They found the low-dose estrogen therapy in combination with fluvoxamine was more effective than low-dose estrogen alone in relieving hot flashes and depressive symptoms in this population. Sertraline, another SSRI, shows promise as well.

Clinical trials using SSRIs in the treatment of hot flashes have been few in number, with small numbers of patients and of short durations. Most have studied women who are breast cancer survivors. Despite these limitations, SSRIs were generally modestly successful in reducing the frequency and severity of hot flashes in perimenopausal and postmenopausal women and in women with breast cancer. Because of their safety and tolerability profiles, they are a reasonable nonhormonal alternative in treating this very common complaint.[25]

The clinical trials using antidepressants for the treatment of hot flashes have consistently showed a mild improvement in the populations studied. The number of hot flashes decreases significantly, albeit modestly. A closer look at the data, however, suggests that we are witnessing a different phenomenon. The SWAN cohort demonstrates that women experience menopause quite differently.[7] Similarly, data from studies of SSRIs for the treatment of hot flashes suggest that women respond to SSRI treatment differently. Loprinzi et al[19] in the trial of fluoxetine for hot flashes found that 42% of the women treated with fluoxetine had a greater than 50% reduction in hot flashes, 30% of the women had

a less than 50% reduction in hot flashes, and 27% of the women actually had more hot flashes.

We chose to study the effect of sertraline in the treatment of hot flashes with the following objectives: (i) to measure efficacy of sertraline compared to placebo in treating the vasomotor symptoms characteristic of menopause; (ii) to measure efficacy of sertraline compared to placebo in treating the mood disturbances characteristic of menopause; and (iii) to measure quality-of-life indicators related to the use of sertraline compared to placebo at the time of menopause.

## METHODS

We studied sertraline (Zoloft) in the treatment of hot flashes with a crossover, double-blind design in the general, noncancer survivor menopausal population. Women between the ages of 40 and 65 who were having hot flashes were recruited for the study through radio and newspaper advertisements and from flyers at the practices of some of the family physicians and obstetrician-gynecologists in Tucson, AZ. Women were excluded who were currently taking estrogens, antidepressants, or any herbal products for hot flashes that they would not discontinue. In addition, because of possible medication interactions, women taking the following medications were excluded: warfarin, selegiline, sibutramine, buspirone, meperidine, and tramadol. The University of Arizona Human Subjects Protection Program reviewed and approved the project.

A double-blind, randomized, placebo-controlled, crossover design was used. At the beginning of the study, informed consent was obtained and demographic information was collected, including menopausal status. We used the same measurement tools as in the Heart and Estrogen/Progestogen Replacement Study[26] with the 12-item Duke Activity Status Index,[27] the RAND Mental Health Inventory,[28] and depressive symptoms as measured in the Medical Outcomes Study.[29] Using the model from Loprinzi et al,[30] we constructed a hot flash data collection instrument. Using this instrument the patient noted each hot flash, its time of occurrence and assigned it a severity number from 1 (mild) to 4 (very severe). The number of hot flashes per week and average severity were multiplied to arrive at a hot flash score for each week. After 1 week of baseline hot flash data collection, subjects were randomized to placebo or active drug (sertraline 50 mg). The research nurse then administered the three questionnaires (the 12-item Duke Activity Status Index,[27] the RAND Mental

Health Inventory,[28] and depressive symptoms as measured in the Medical Outcomes Study[29]) as a baseline measure, which were administered again at the end of 4 weeks on either sertraline or placebo, at the end of the washout week, and the end of the study. Participants maintained a daily hot flash log documenting time and severity of each hot flash they experienced. They met with the research nurse weekly to review the data and noted any adverse reactions on a scale of 0 (not present) to 10 (extremely severe). At each weekly visit, the research nurse gave the participant one week's supply of active drug or placebo. Active drug and matched placebo were identically appearing small white pills with no markings. After a week of washout, the study participant then crossed over to the other study condition (sertraline or placebo). One week washout was chosen as the half-life of sertraline is 24 hours and would be fully removed within five to six half-lives. The same weekly protocol and data collection continued for another 4 weeks. The study participants received $20 for each week of completed data and $60 additional at the end of data collection for a complete data set.

The needed sample size was calculated using published data from a study with a similar design.[8] Based on an expected reduction of 41% in hot flashes in the active drug condition and a 22% reduction in the placebo condition, with a power of 0.80 and an $\alpha$ of 0.05, 46 women were needed for each study sequence.

Before the start of the study, one of the principal investigators used the Statistical Package for the Social Sciences random selection procedure to assign each study identification number (from 1 to 200) to one of the two arms of the study (sequence 0 or sequence 1). The study pharmacist, who had no contact with any study participants, determined which sequence number corresponded to sertraline-first or placebo-first arm. She then prepared the correct sequence of medication for the 8 intervention weeks and labeled the packet with the study identification number. The research nurse, who was blinded to the sequence, enrolled study participants and distributed the medication.

All study participants and all study personnel who had contact with study participants were blinded both to the participant's sequence (0 or 1) and to the order of medication assigned to that sequence. Other than the study pharmacist, all study personnel were blinded to the sequence of drugs until all data collection was completed.

Pfizer provided funding for the study and matched placebo and active drug. The investigator team independently designed the research hypothesis and protocol. The team at the University of Arizona had complete control of design and conduct of the study and conducted all analyses.

## Statistical analyses

Hot flash data are presented as mean and SD per week for both number of hot flashes and a median for the severity index. Paired *t* tests were used to compare the mean number and severity of hot flashes for the sertraline and placebo conditions, with an average number of hot flashes per week calculated for the 4 weeks on sertraline and for the 4 weeks on placebo. Median and Wilcoxon ranks tests were used with ordinal variables. Pearson's and Spearman's correlations were used as appropriate. $\chi^2$ Analysis was used with noncontinuous demographic characteristics and an *F* test for continuous variables to compare the equivalence of the two randomized study groups and to compare women who left the study early with those who did not. All tests were two tailed with results considered significant if the significance level was less than 0.05. All analyses were done using Statistical Package for the Social Sciences Version 12 for the PC.

## RESULTS

One hundred two women were enrolled in the study. Five dropped out before providing any baseline data. Of the 97 remaining, 10 dropped out of the study before completing all 10 weeks. Table 1 presents the demographic data for those who did and did not complete the full 10 weeks. None of the differences are significant except insurance status. Enrollment began January 2004 and ended May 2004. Data collection ended August 2004.

## Baseline

Ninety-seven women provided a week's baseline data on number and severity of hot flashes. The number reported ranged from 2 to 148, with a mean of 45.6 (SD = 29.6) and a median of 40. The median severity was 2.0. The hot flash score had a median of 79 (range, 3-387) Table 2 presents the comparison of demographic characteristics for women assigned to the two sequences.

The number of hot flashes at baseline was not significantly related to ethnicity, marital status,

education, smoking status, or whether the woman drank alcohol. The number of hot flashes at baseline was negatively related to weight ($R = -0.24$, $P = 0.02$) and to body mass index ($R = -0.21$, $P = 0.05$) and positively related to age ($R = 0.31$, $P = 0.004$). Severity at baseline was related to smoking status (median severity of 2.5 for those who smoke versus 1.9 for those who do not; $P = 0.05$), and the number of packs per day ($R = 0.70$, $P = 0.02$) and to level of education (median of 2.6 for women with a high school degree or less, 2.0 for women with some college or a college degree, 1.8 for women with some graduate school or a graduate degree, $P = 0.05$).

## Intention-to-treat analysis

The first analysis comparing active drug to placebo included all the women, with the last value carried

**TABLE 1.** *Comparison of women with complete and incomplete data*

| | Complete data (n = 87) | Incomplete data (n = 10) | P |
|---|---|---|---|
| Ethnicity (self-reported) (%) | | | 0.84 |
| White non-Hispanic | 80 | 80 | |
| Hispanic | 14 | 10 | |
| Other | 6 | 10 | |
| Marital status (%) | | | 0.16 |
| Married | 55 | 30 | |
| Single | 30 | 60 | |
| Partnered | 15 | 10 | |
| Age (y), mean (SD) | 52.6 (5.1) | 51.9 (6.6) | 0.71 |
| Highest level of education (%) | | | 0.43 |
| High school degree or less | 15 | 20 | |
| Some college or college degree | 61 | 40 | |
| Some graduate school or graduate degree | 24 | 40 | |
| Smoking status, yes (%) | 15 | 30 | 0.22 |
| Drink alcohol status, yes (%) | 78 | 70 | 0.56 |
| Activity level (self-reported) (%) | | | 0.19 |
| Less active than women of same age | 11 | 30 | |
| About the same | 41 | 20 | |
| More active than women same age | 47 | 50 | |
| Insurance status (%) | | | <0.05 |
| Commercial | 76 | 50 | |
| AHCCCS (Arizona Medicaid) | 14 | 10 | |
| None | 10 | 40 | |
| Mean no. of hot flashes/ week at baseline (SD) | 47.3 (29.7) | 31.1 (25.2) | 0.10 |
| Median severity of hot flashes at baseline | 2.0 | 1.9 | 0.76 |

**TABLE 2.** *Characteristics of study groups*

| | Sequence | | |
| --- | --- | --- | --- |
| | Placebo/ sertraline 50 g (n = 41) | Sertraline 50 mg/ placebo (n = 46) | *P* |
| Ethnicity (%) | | | 0.40 |
| White non-Hispanic | 88 | 74 | |
| Hispanic | 12 | 15 | |
| Other | 0 | 11 | |
| Marital status (%) | | | 0.58 |
| Married | 51 | 59 | |
| Single | 29 | 30 | |
| Partnered | 20 | 11 | |
| Age (y), mean (SD) | 52.6 (4.8) | 52.4 (5.4) | 0.83 |
| Highest level of education (%) | | | 0.89 |
| High school degree or less | 12 | 17 | |
| Some college or college degree | 58 | 63 | |
| Some graduate school or graduate degree | 29 | 20 | |
| Smoking status, yes (%) | 17 | 13 | 0.60 |
| Drink alcohol status, yes (%) | 78 | 78 | 0.98 |
| Activity level (self-reported) (%) | | | 0.68 |
| Less active than women of same age | 9 | 17 | |
| About the same | 40 | 39 | |
| More active than women same age | 51 | 44 | |
| Insurance status | | | 0.86 |
| Commercial | 73 | 78 | |
| AHCCCS (Arizona Medicaid) | 15 | 13 | |
| None | 12 | 9 | |
| Mean no. of hot flashes at baseline (SD) | 45.4 (27.9) | 49.0 (31.5) | 0.58 |
| Median severity of hot flashes at baseline | 2.1 | 1.9 | 0.79 |
| Mean no. of hot flashes before crossover (SD) | 38.1 (33.80) | 37.2 (28.8) | 0.90 |
| Median severity of hot flashes before crossover | 2.0 | 1.8 | 0.72 |

forward for those women who did not complete all 10 weeks of the study. The results were virtually the same for the women with complete data and all women; therefore, in the more detailed analyses that follow, only the 87 women with 10 weeks of data have been used.

## Sertraline compared to placebo during the 8 intervention weeks

During the sertraline phase of the study, women experienced five fewer hot flashes per week than they did on the placebo. Repeated-measures analysis indicated that the number of hot flashes per week was significantly lower than baseline during the treatment phase in each week beginning with the first week and continuing through the fourth week. Hot flashes were also grouped into those occurring between 6:00 AM and 5:00 PM and those occurring between 6:00 PM and 5:00 AM. Women reported more hot flashes during the daytime hours (mean = 17.1 vs 14.6 per week on sertraline, 95% CI for the difference, 0.97-4.0; mean = 19.9 vs 16.9 on placebo 95% CI for the difference, 1.4-4.6; both $P \leq 0.001$). The number of hot flashes was lower during the sertraline phase for both day and nighttime periods, although the reduction was greater for the daytime (mean reduction of 2.8 per week during the daytime, 95% CI for the difference, 0.8-4.9; $P = 0.007$; mean reduction of 2.3 for nighttime, 95% CI for the difference, 0.3-4.2; $P = 0.03$). The severity of hot flashes was not significantly different for sertraline and placebo; however, the hot flash score was significantly different with a median of 57 for the placebo condition and 42 for the sertraline condition ($P = 0.001$) (Table 3). Reduction in hot flashes was not significantly related to the number of hot flashes at baseline, although analysis of just the women who had more than 10 hot flashes at baseline indicated a greater reduction (6.9 per week, 95% CI, 2.8-11.00; $P = 0.001$). Figure 1 presents the mean number of hot flashes by week for each of the two sequences. Figure 2 presents the percent reduction in hot flashes from baseline.

### Side effects

A comparison of weekly data on side effects showed no significant differences between the women who were on the active drug and women who were on the placebo, with one exception. In the first week on sertraline, three women reported severe nausea (rated 8 or above). During the first week on the active drug, 49% of all women experienced some nausea compared with 19% on the placebo ($P < 0.001$). The proportion experiencing any nausea on sertraline declined in subsequent weeks, 24% in week 2, 16% in week 3, and 19% in week 4. Weeks

**TABLE 3.** *Hot flash score*

| | Median hot flash score | Interquartile range |
| --- | --- | --- |
| Baseline (n = 87) | 81 | 42-147 |
| Average 4 wk of sertraline[a] (n = 87) | 42 | 18-92 |
| Average 4 wk of placebo (n = 87) | 57 | 21-105 |

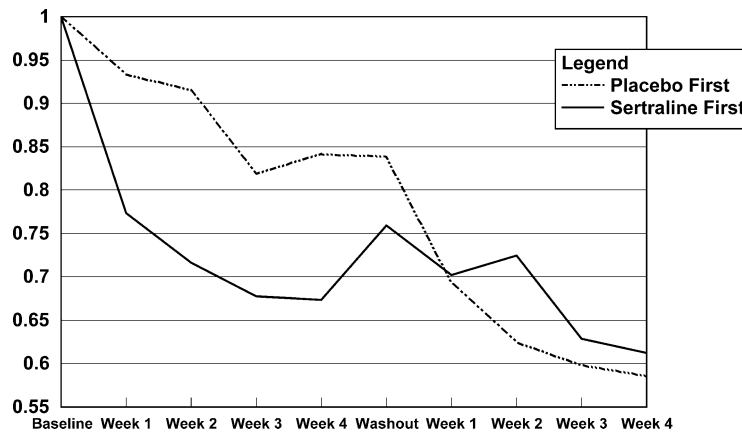[a]Difference between sertraline and placebo significant at $P = 0.001$.

**FIG. 1.** Percentage of reduction in hot flashes from baseline.

2 through 4 were not significantly different than the placebo. There was not a significant difference between active drug and placebo for either sexual functioning or libido in any week of the study.

### Other outcomes

Compared to baseline, women receiving both the placebo and sertraline experienced an improvement in mood. The difference between RAND scores for the sertraline and placebo conditions was not statistically significant. The six Medical Outcomes Study depression items showed a similar pattern. The difference in mood for the sertraline and placebo conditions was not significantly different. The mean activity level based on the 12-item Duke Activity Status Index was not significantly different for the sertraline and placebo conditions.

Self-reported weight at baseline ranged from 105 to 280 lb, with a mean of 158 (SD = 35). Weight at the end of the study was available for 85% of the women. At the end of the study, weight ranged from 107 to 280 lb with a mean of 158 (SD = 35).

### DISCUSSION

This study expands on the previous work of Roth and Scher,[31] who studied sertraline for the treatment of hot flashes in men with prostate cancer and Kimmick et al,[32] who studied sertraline for the treatment of hot flashes in women with early-stage breast cancer. Like other studies using SSRIs or venlafaxine to treat hot flashes, we found that sertraline significantly but modestly decreased the number of hot flashes in this general population of women. The number of hot flashes in the sertraline group decreased by a total of five per week when compared to the placebo group for all women and by 6.9 per week for women with 11 or more hot flashes.

Similar to the findings of Evans et al,[9] the reported severity of the hot flashes did not change with the
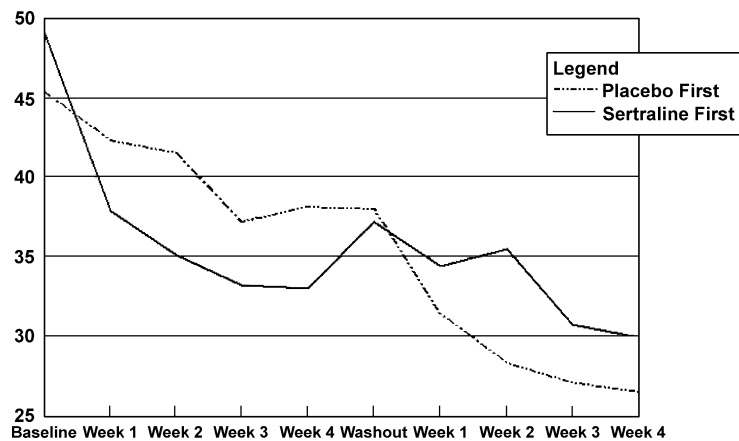


**FIG. 2.** Mean hot flashes per week by medication sequence.

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                              ┌──────────────────┐
                              │   102 Eligible   │
                              └──────────────────┘
┌─────────────────────────────────┐      │
│ 5 dropped out before providing   │──────┤
│ any baseline data – reason unknown│      │
└─────────────────────────────────┘      │
                              ┌──────────────────┐
                              │  97 Randomized   │
                              └──────────────────┘
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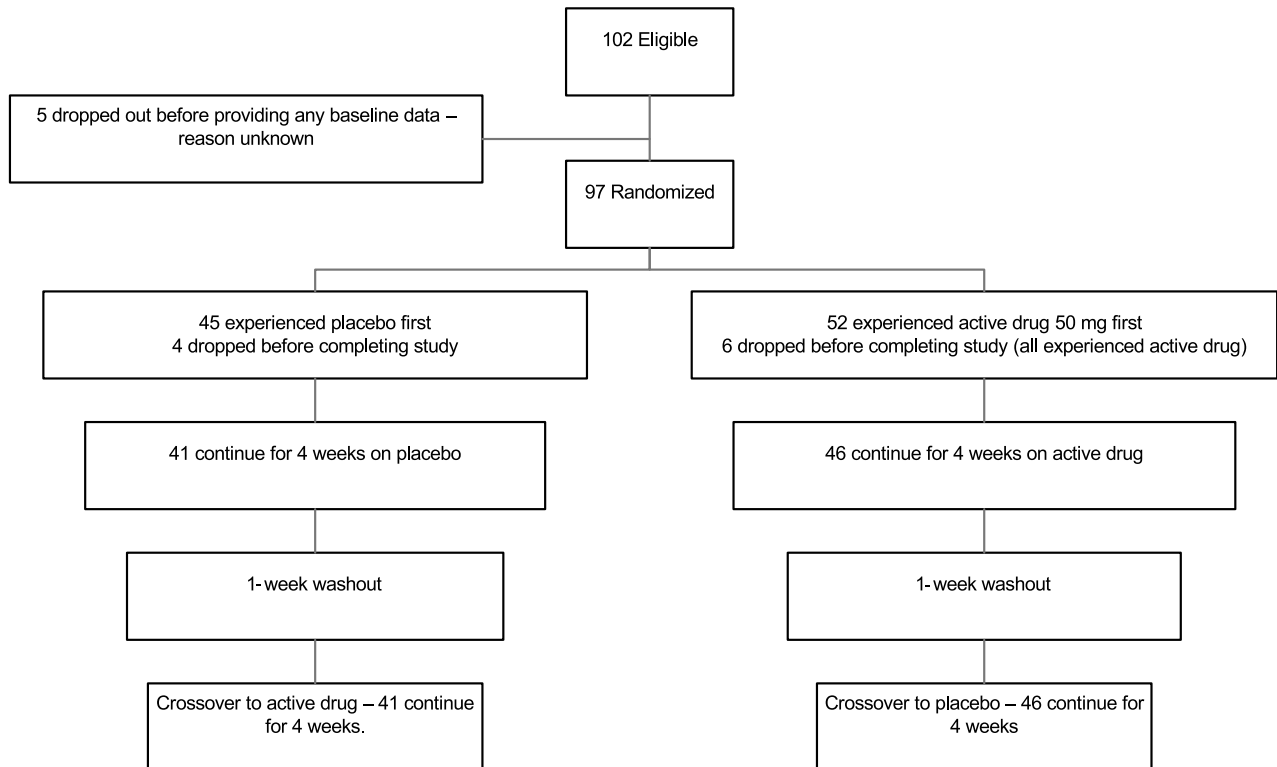| | |
|---|---|
| 45 experienced placebo first<br>4 dropped before completing study | 52 experienced active drug 50 mg first<br>6 dropped before completing study (all experienced active drug) |
| 41 continue for 4 weeks on placebo | 46 continue for 4 weeks on active drug |
| 1-week washout | 1-week washout |
| Crossover to active drug – 41 continue for 4 weeks. | Crossover to placebo – 46 continue for 4 weeks |

**FIG. 3.** Subject flow chart through the study.

active drug; however, the hot flash score (severity $\times$ frequency) did improve significantly.

There were no serious adverse side effects reported. Indeed, unlike previous studies that had a high dropout rate, there was a low dropout rate with sertraline. Of the 95 women who received active drug, only eight participants dropped out (8.4%) (Fig. 3).

Although all the studies discussed found significant differences between the active drug and the placebo, the reductions in number of hot flashes were relatively modest. Patients will ultimately decide whether this modest reduction in hot flash frequency or the improvement in the quality of life is significant to them. For clinicians, these results mean that women do have alternatives to estrogen for the treatment of hot flashes. While the effect on the number of hot flashes was small, the safety and patient comfort with sertraline make it a reasonable alternative. Indeed, a number of study subjects asked their primary care doctors for sertraline to continue their treatment after the termination of the study.

Finally, similar to the findings of Loprinzi et al[19] in the trial of fluoxetine for hot flashes, we found that some women responded vigorously, others modestly, and others negatively. Loprinzi et al found that 42% of the women treated with fluoxetine had a greater than 50% reduction in hot flashes, 30% of the women had a less than 50% reduction in hot flashes, and 27% of the women actually had more hot flashes. We found that 30% of the women in our study had a reduction in hot flashes of 33% or greater, while 30% of the participants had a more modest reduction of 1% to 32%. Forty percent of the participants had no reduction or even had more hot flashes on sertraline than on placebo.

These data, along with those of Loprinzi et al, support the SWAN observation that there is no universal menopausal syndrome. Additionally, there does not seem to be a universal or uniform response to SSRIs for the treatment of hot flashes. Different women respond vigorously, modestly, not at all, or even negatively. Our early efforts to identify those women most likely to respond showed that the amount of benefit was significantly related to education, self-reported activity level, and menopausal status.

Limitations of this study included the relatively brief, 4-week period of treatment, which did not allow assessment of whether or for how long the positive effect of sertraline would continue. In addition, this study only used one dose of sertraline,

50 mg. Although a previous study has looked at two doses of SSRIs,[23] little attention has been paid to the most effective dose.

Future studies should evaluate varying doses of sertraline and, with a longer period of treatment, determine whether the hot flash–lowering effect is maintained over time. If this effect can hold over a longer period of time, the use of SSRIs for women experiencing hot flashes is an important addition to the available therapies. Furthermore, a larger sample size would better define those most likely to respond and therapy could be directed accordingly.

## CONCLUSIONS

This study found a statistically significant although modest reduction in the number of hot flashes while using sertraline compared to placebo. Additionally the hot flash score (number × average severity) was significantly improved during the sertraline phase. Finally, the average reduction in hot flashes while on sertraline varied greatly among groups of women from a mean reduction of 61% to an increase of 29%. A larger study with varying doses may allow us to further characterize those likely to have the greatest benefit. Ultimately, women will decide whether this reduction in the number of hot flashes is clinically significant.

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