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ORIGINAL REPORT

Randomized Trial of a Hypnosis Intervention for Treatment of Hot Flashes Among Breast Cancer Survivors

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ABSTRACT

Purpose
Hot flashes are a significant problem for many breast cancer survivors. Hot flashes can cause discomfort, disrupted sleep, anxiety, and decreased quality of life. A well-tolerated and effective mind-body treatment for hot flashes would be of great value. On the basis of previous case studies, this study was developed to evaluate the effect of a hypnosis intervention for hot flashes.

Patients and Methods
Sixty female breast cancer survivors with hot flashes were randomly assigned to receive hypnosis intervention (five weekly sessions) or no treatment. Eligible patients had to have a history of primary breast cancer without evidence of detectable disease and 14 or more weekly hot flashes for at least 1 month. The major outcome measure was a bivariate construct that represented hot flash frequency and hot flash score, which was analyzed by a classic sums and differences comparison. Secondary outcome measures were self-reports of interference of hot flashes on daily activities.

Results
Fifty-one randomly assigned women completed the study. By the end of the treatment period, hot flash scores (frequency × average severity) decreased 68% from baseline to end point in the hypnosis arm ($P < .001$). Significant improvements in self-reported anxiety, depression, interference of hot flashes on daily activities, and sleep were observed for patients who received the hypnosis intervention ($P < .005$) in comparison to the no treatment control group.

Conclusion
Hypnosis appears to reduce perceived hot flashes in breast cancer survivors and may have additional benefits such as reduced anxiety and depression, and improved sleep.

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INTRODUCTION

Hot flashes (or vasomotor symptoms) are a major clinical problem for many women as they enter menopause and for breast cancer survivors. Hot flashes occur as a result of estrogen depletion,[1] can significantly alter daily activities, and can affect perceptions of mood and sleep.[2,3] Furthermore, hot flashes are a common adverse effect of ovarian ablation, tamoxifen, and aromatase inhibitors used in breast cancer treatment. It has been demonstrated that up to 78% of female chemotherapy recipients and 72% of tamoxifen recipients experience hot flashes.[4] Estrogens have been the treatment of choice for hot flashes, but estrogens have been associated with an increased risk of breast cancer and, therefore, are generally avoided for breast cancer survivors.[5] Nonhormonal pharmacologic agents are either not effective for some women or have adverse effects. Given the limited safe and effective options, it is imperative that effective new interventions with minimal adverse effects be developed to help breast cancer survivors who experience hot flashes.

Hypnosis is a mind-body therapy that has few negative adverse effects and that may be of significant benefit in reducing the frequency and severity of hot flashes in breast cancer survivors. Several small studies have suggested that hypnosis intervention may have a positive effect on the reduction of hot flashes. An early study by Stevenson and Delprato[6] reported that four women were able to reduce self-reported hot flashes by 41% to 90% from baseline when provided with instruction in relaxation, self-suggestions of cool thoughts, and temperature biofeedback. Three reports have indicated that hypnosis may be an especially promising intervention for hot flashes.[7-9] We have developed a well-defined hypnosis intervention in our laboratory; recently, in

a small exploratory study,[8] we reported a reduction in hot flashes in 16 women after hypnosis intervention. Pursuant to this, the present study was developed to additionally assess the efficacy of hypnosis intervention for the treatment of hot flashes in a randomized, prospective study.

PATIENTS AND METHODS

Eligible patients were at least 18 years of age, had a history of primary breast cancer without evidence of detectable disease, and had a self-reported history of at least 14 hot flashes per week for a period of at least 1 month before study entry. Patients were not allowed to receive any chemotherapy, androgens, estrogens, progestational drugs, or any treatment for hot flashes. Women taking antihormonal agents for breast cancer (eg, tamoxifen, raloxifene) were permitted into the study if they had been taking the drug for at least 1 month before enrollment and had remained on a stable dose. Patients were asked to not participate in any other mind-body therapy (ie, relaxation therapy, biofeedback, yoga) and to not use any other complementary or alternative therapy during the study period.

Participants were equally and randomly assigned to either hypnosis or to a no-treatment control arm. Random assignment was made sequentially from a confidential, computer-generated list of permuted blocks of varying size. All patients were required to give their written informed consent as dictated by federal guidelines and approved by an institutional review board. After random assignment, patients were asked to complete a daily hot flash diary for 1 week before any treatments for hot flashes. Baseline measures also included the Hot Flash Related Daily Interference Scale (HFRDIS),[2] Center for Epidemiologic Studies Depression Scale (CES-D),[10] Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A),[11] and Medical Outcomes Study Sleep Scale (MOS-Sleep Scale).[12] Patients then received either the hypnosis intervention or remained on a no-treatment waiting list for 5 weeks. At the end of the study period, all participants repeated the measures for a second time.

The hypnosis intervention followed a treatment manual that was developed specifically for this study and was delivered by a clinician with a doctoral degree in psychology who had completed at least 40 hours of training in hypnotherapy provided by the principal investigator. Training followed the guidelines and learning objectives outlined in the publication, *Standards of Training in Clinical Hypnosis*.[13]

Patients in the hypnosis intervention condition were scheduled for five weekly sessions, each to last approximately 50 minutes. At each session, a hypnotic induction was completed according to a standard transcript. (The treatment manual is available from G.E. on request). Hypnotic suggestions for each session included the following: hypnotic induction; mental imagery and suggestions for relaxation; mental imagery for coolness; deepening hypnosis and dissociation from hot flashes; positive suggestions and imagery for the future; self-hypnosis; and the alert, "In a few moments, return to conscious alertness."

In addition, participants were given instruction in self-hypnosis practice and were provided with an audiocassette tape recording of a hypnotic induction and of instructed in-home practice. Although the hypnotic induction followed a transcript, specific imagery for relaxation and imagery for coolness were individualized on the basis of each patient's preference regarding such imagery.

Statistical Considerations

The primary end point for this study was both the frequency of hot flashes and a hot flash severity score. For the participants, the number and severity of hot flashes per day was computed for the baseline week and for the final week. In addition, the severity of hot flashes was computed. One point was given for each mild hot flash, two points for each moderate hot flash, three points for each severe hot flash, and four points for each very severe hot flash. The hot flash score was calculated by multiplying the severity average for a week times the hot flash frequency for that week.

The results of this pre-test–post-test control group design were analyzed via multivariate analysis of covariance and analysis of covariance. The hot flash severity score, the HFRDIS, the HADS anxiety sub-scale, the CES-D depression scale, and the MOS-Sleep Scale were used as pre- and post-tests in these analyses. As follow-up, these post-test scores were also analyzed via a series of two-sample t tests. Confidence intervals of 95% for the change from baseline to end-of-study were computed for all measures for both groups. All statistical tests were performed as two-tailed tests and used a level of significance of $P = .05$.

A sample size of 25 in each group was based on an 80% power to detect a difference of at least 30% from baseline to follow-up with a .05 one-sided significance level.[14]

Missing data were handled by using various imputation methods (eg, patients who completed all data, average value carried forward, last value carried forward, and minimum or maximum value carried forward) and were carried out to assess the impact of missing data on the results. The amount of missing data was minimal, and the analyses indicated that the results were consistently demonstrated.

RESULTS

Eight-six patients were screened for this study, of which 26 either did not meet eligibility criteria or did not want to participate. A total of 60 women were randomly assigned. Approximately 20% of the participants who had enrolled were either lost to follow-up (n = 3) or withdrew (n = 6); three had been assigned to the treatment group, and six had been assigned to the control group. Reasons for those who did not complete the study included: being too busy/no desire to continue for personal reasons (n = 7) and not able to be reached (n = 2).

Demographic data from the participants who were randomly assigned to each condition are presented in Appendix Table A1, online only. The baseline average number of hot flashes was well balanced for the study arms. At baseline, there was no significant difference between the participants in each condition, with the exception that there were a greater number of participants who had earned a graduate degree in the treatment group than would be expected by chance ($P = .04$), but educational levels were relatively evenly distributed between the treatment and control conditions for those who completed the study.

Table 1 lists the results of the initial analyses. The first analysis compared the final measures of hot flashes (hot flash score, HFRDIS) of hypnosis versus control group participants by using a one-way multivariate analysis of covariance. Baseline hot flash scores and the HFRDIS score were used as covariates to control for individual differences. As listed in the table, the results were statistically significant; those in the hypnosis condition reported statistically significantly lower scores on the multivariate hot flash outcome measure than did those in the control group. The effect size ($\eta_p^2 = 0.479$) is considered

Table 1. Effect of Hypnosis Intervention on Hot Flashes, Sleep, and Mood

Measure and Test	Analyses			
	F	*df*	*P*	η^2 (partial)
Hot flashes (HFRDIS)	19.804	2,43	< .001	0.479
Sleep (MOS-Sleep)	45.757	1,48	< .001	0.488
Mood (HADS-A, CES-D)	6.083	2,44	< .005	0.217

Abbreviations: HFRDIS, Hot Flash Related Daily Interference Scale; MOS-Sleep, Medical Outcomes Study Sleep Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety Subscale; CES-D, Center for Epidemiologic Studies Depression Scale.

of large magnitude when using conventional criteria[15] and suggests that the difference should be visible to the naked eye. The means and standard deviations for pre- and post-test scores by group are listed in Appendix Table A2, online only, for these and other outcome variables, which shows improvement in hot flash outcome for both measures. Those in the hypnosis group showed statistically significantly better outcomes for both the hot flash score and the interference score. These results are displayed graphically in Figure 1 and Appendix Figure A1, online only.

Table 1 also lists the results of an analysis of covariance of the effects of the hypnosis treatment on participants' sleep. Ratings on the MOS-Sleep Scale at baseline and at study end were used as the covariate and outcome, respectively. As listed in the table, the difference between groups after treatment was statistically significant and had a large effect size. In Appendix Table A2, the hypnosis group showed significant improvement compared with the control group and improvement compared with their baseline scores.

The third analysis summarized in Table 1 shows the results of the hypnosis treatment on two psychological outcomes, depression and anxiety. The HADS-A and CES-D were used as both pre- and post-test for this multivariate analysis of covariate (MANCOVA). As listed in Table 1, the two groups were indeed statistically significantly different at post-test and had a moderate effect size. Descriptive data and follow-up analyses are listed in Appendix Table A2. Participants in the hypnosis treatment showed statistically significant improvement compared with control participants for both anxiety and depression. Effect sizes for both outcomes were of moderate magnitude.

The hot flash score used in the primary analysis was made up of hot flash frequency and severity. Additional follow-up focused on the frequency of hot flashes at baseline and post-test. As in previous analyses, ANCOVA (which used hot flash frequency at pre-test as a covariate and hot flash at end point as the dependent variable) revealed a statistically significant improvement for the hypnosis group compared with the control group. Hot flash scores (frequency × average severity) decreased 68% from baseline to end point in the hypnosis arm ($P < .001$). Figure 2 shows the distribution of participants' scores at pre- and post-test by experimental condition. The figure shows the similarity in the two groups at pre-test and the consistent improvement in hot flash frequency for the hypnosis group at post-test.

To additionally investigate the effects of the hypnosis treatment on the extent that hot flashes interfered with daily life, the items from the HFRDIS (both pre- and post-test) were analyzed in a MANCOVA, with follow-up of individual items. For this scale, women rated the extent that hot flashes have interfered with 10 different aspects of their lives (ie, work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life, overall quality of life), each on a 10-point scale. The overall MANCOVA was statistically significant ($F[10,29] = 4.73$; $P < .001$) and had a large effect size ($\eta_p^2 = 0.620$); at post-test, hot flashes interfered significantly less in the lives of women in the treatment group compared with those in the control group. Follow-up analyses of each item showed that all items were statistically significantly less interfering ($P < .05$) for those in the experimental group, with the exception of an item asking about interference with sexuality ($P = .124$). Effect sizes (η_p^2) ranged from 0.061 to 0.437 and from 0.150 to 0.437 for statistically significant items.

DISCUSSION

The results from this study support our pre-study hypothesis that a hypnosis intervention does significantly reduce hot flashes. The effect size was large, and a 68% reduction in hot flash scores indicated a clinically significant reduction. Satisfaction with the hypnosis intervention was favorable, and none of the patients complained or dropped out of treatment because of any negative adverse effects. This is generally consistent with our previous impressions from case studies of hypnosis for hot flashes[7,8] and with research on hypnosis for symptom management, and it suggests that hypnosis is a well-tolerated intervention for most patients.[16-18]

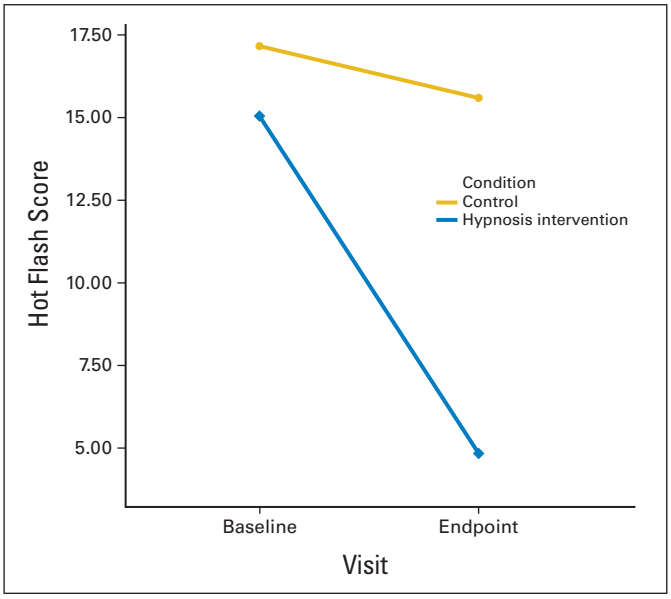

Fig 1. Hot flash scores pre- and post-test by treatment condition.

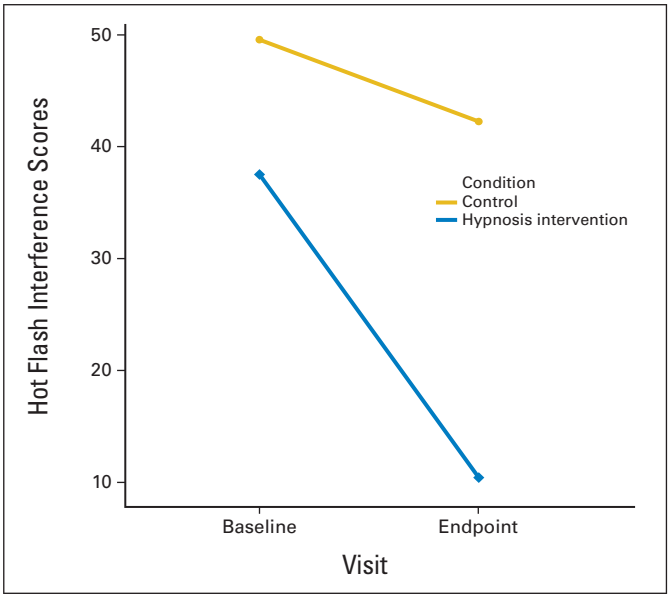

Fig 2. Hot flash interference scores at pre- and post-test by treatment condition.

Some criticism of this study is that observations were limited to 5 weeks and that it does not provide data regarding long-term follow-up. However, a ≤ 5-week time period has been used in a series of clinical trials that assessed pharmacologic therapies for alleviating hot flashes in breast cancer survivors, and it does allow comparison.[5,19-23] Our anecdotal experience has given us reason to believe that patients who continue to practice self-hypnosis continue to benefit with maintenance of reductions.[8] Subsequent studies should use a longer-term follow-up period to determine if sustained symptom relief is achieved with hypnosis.

Although it could be argued that physiologic monitoring of hot flashes is needed to validate the reduction of hot flashes, the use of self-report diaries, as used in this study, has long been established as a valid approach to obtain data on subjective phenomena, such as patient-reported symptoms.[19,20,24-26] Self-report diaries have been used in the majority of studies of interventions for hot flashes, and they provide the advantage of data about severity.[14] Nonetheless, there may be some clinical utility in using physiologic recordings in clinical trials to gain a better understanding of the mechanism of action and the physiologic impact of hypnosis on hot flashes.

It has been established previously that women with unrelieved hot flashes suffer negative emotional consequences, such as anxiety, depression, interrupted sleep, and decreased quality of life.[2,3,27] It is reasonable to hypothesize that interventions that effectively relieve hot flashes would also result in improved mood, affect, and daily activities, including sleep. Women who received the hypnosis intervention in this study did, in fact, report significant improvement on each of these secondary outcomes. Not surprisingly, on enrollment, participants reported significant interference with daily activities as a result of their hot flash experiences. HFRDIS total scores range from 0 to 100. The mean baseline HFRDIS score for the treatment group was 39.52; in contrast, the post-treatment HFRDIS scores were significantly lower than pretreatment, and the mean score was only 10.42. Therefore, this study suggests that hypnosis for hot flashes has additional side benefits that include decreased interference with daily activities and quality of life.

In terms of anxiety, the mean HADS score at baseline was below the cutoff score reported in the literature that indicates possible clinically relevant anxiety. The women who participated in the hypnosis intervention group reported significant reductions in anxiety, which supports the concept that hypnosis to treat hot flashes is also effective to alleviate even subclinical symptoms of anxiety.

However, the reason for these benefits is not entirely clear. Individuals who have negative affect (eg, anxiety, depression) may be more likely to attend to and to report physical symptoms,[28] and/or unrelieved hot flashes may result in more frustration and negative consequences.[14,27] In either case, this study suggests that the effect of hypnosis is to improve emotional and psychosocial adjustment of women who experience hot flashes.

The mechanism of action of hypnosis to reduce hot flashes is unknown, and this question was not addressed in this study. A substantial placebo effect has been observed in multiple hot flash studies.[14,19,20,22,29-33] On average, hot flash frequencies diminish by 20% to 30% with 4 weeks of placebo.[14] Also, evidence from other studies suggests that women may tend to under-report hot flashes.[34] The feeling of security that results from a mind-body intervention, such as hypnosis, may reinforce this tendency. It is generally accepted that treatments that result in hot flash score reductions of less than 40% should be considered consistent with placebo effect; therefore, interventions that result in hot flash score reductions of greater than 50% should be considered greater than would be expected from placebo.[14] These study findings indicate that hypnosis is likely to reduce hot flashes to a greater degree than placebo, by 68%. In this study, the mean number of hot flashes, regardless of severity, exceeded seven per day at baseline. Women who received the hypnosis intervention reported an average reduction of 4.39 hot flashes per day, whereas the women in the control group remained relatively unchanged. It is interesting to note that we did not observe the placebo effect for self-reported hot flashes that is typically observed in clinical trials. This outcome most likely is because the control was a no-treatment condition, which is consistent with findings that hot flashes remain stable over time if left untreated. However, given the percent reduction in hot flashes, the effectiveness of the hypnosis intervention would likely hold up against a parallel arm. A randomized clinical trial is currently underway by the authors to compare the hypnosis intervention to a placebo control and to additionally address the possible underlying mechanisms (eg, stress, serotonin).

Seasonal effects are unlikely to account for findings in this study, because the study intervention occurred during a period longer than 1 year and because the effect size was large. Another concern could be the possible use of other complementary therapies. Patients in this study were required to discontinue all other treatments for hot flashes, with the exception of vitamin E, which has had limited efficacy in relieving hot flashes.[21]

Women are interested in alternatives to traditional hormone therapy and pharmacologic interventions, and this study demonstrates the feasibility and potential effectiveness of hypnosis as an alternative treatment. However, certification in the professional use of hypnosis requires considerable training[13] and practice. Also, some patients may not be good candidates for hypnosis. For example, hypnosis should be avoided or should only be used with caution in patients with a history of severe psychopathology (eg, borderline personality disorder, schizophrenia, post-traumatic stress disorder).[35] Also, it is possible that some patients may be in the low range of hypnotizability and, as a result, may benefit less. Future studies should assess these variables. Despite these limitations, it has been our impression that most patients can benefit from hypnosis. However, long-term, randomized, placebo-controlled studies will be needed to identify the long-term effect and integrative role of hypnosis in the treatment of hot flashes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

