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A Pooled Analysis of Three Studies of Non-Pharmacological Interventions for Menopausal Hot Flashes

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Abstract

OBJECTIVE: To conduct a pooled analysis of three published trials of non-pharmacological interventions for menopausal hot flashes in order to compare the effectiveness of interventions.

METHODS: Data from three randomized controlled trials of interventions for hot flashes (two acupuncture trials, one yoga trial) were pooled. All three studies recruited perimenopausal or postmenopausal women experiencing 4 hot flashes per day on average. The primary outcome for all three studies was frequency of hot flashes as measured by the Daily Diary of Hot Flashes. Study 1 participants were randomly assigned to 8 weeks of acupuncture treatments (active intervention), sham acupuncture (attention control), or usual care. Study 2 participants were randomly assigned to 10 weeks of yoga classes, health and wellness education classes (attention control), or waitlist control. Study 3 randomly assigned participants to 6 months of acupuncture or waitlist control. To standardize the time frame for these analyses, only the first 8 weeks of intervention from all three studies were used.

RESULTS: The three active interventions and the two attention control groups had statistically similar trends in the percentage reduction of hot flashes over 8 weeks, ranging from 31% to 41%. These five groups did not differ significantly from each other, but all showed significantly greater reduction in hot flash frequency compared to the three usual care/waitlist groups.

CONCLUSION: Acupuncture, yoga, and health and wellness education classes all demonstrated statistically similar effectiveness in reduction of hot flash frequency compared to controls.

Keywords

menopause; acupuncture; vasomotor symptoms; hot flashes; yoga; control groups

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Vasomotor symptoms (VMS), which include hot flashes and night sweats, are the most common and troubling symptoms associated with menopause.^{1, 2} Although some women report experiencing the menopausal transition without any VMS,³ others experience frequent and severe symptoms that interfere with daily activities and quality of life.^{4–8} Recent estimates suggest that frequent menopausal VMS can continue for a median of 7.4 years and may last at least 14 years.⁹ VMS are the chief menopause-related problems for which US women seek medical attention.^{10, 11}

Estrogen therapy, alone or in combination with progesterone, is currently the most effective treatment of VMS. Hormone therapy (HT), however, is associated with a number of risks^{12–16} and many women seek alternatives such as other pharmaceutical agents, herbal or dietary remedies, or behavioral therapies.^{17–20} Unfortunately, many of these agents also have side effects and/or have not been shown to be effective.^{19, 21–24}

We have conducted three separate randomized trials of non-pharmacological interventions for the treatment of menopausal VMS.^{25–27} All three studies recruited peri and postmenopausal women experiencing 4 hot flashes per day. The primary outcome for all three studies was the percent reduction in hot flashes as recorded on daily dairies. Study 1 found that women randomized to 8 weeks of either true or sham acupuncture had a decrease of 40% from baseline in mean frequency of hot flashes.²⁵ Both the true and sham acupuncture groups were significantly different from usual care, but not from each other. Study 2 compared 10 weeks of yoga with an attention control group of health and wellness education classes (HWE), and a waitlist control group. There was a significant decline in hot flash frequency for all groups, but the yoga and HWE groups followed similar patterns of 66% and 63% reduction of hot flashes from baseline and had a significantly greater decrease than the waitlist group.²⁶ Study 3 was an effectiveness trial of acupuncture compared with a waitlist control where women randomized to acupuncture could receive up to 20 treatments within 6 months.²⁷ At 8 weeks, the acupuncture group had a 33.9% reduction in VMS frequency compared to a 3.3% reduction in the waitlist control group.²⁷

Although results of these studies have previously been published, we were interested in statistically comparing the effectiveness of the different interventions (including active controls) with each other. Given that all three studies used the same outcome measure and had similar eligibility criteria, we are able to combine these data into a single dataset to statistically compare the effectiveness of the five interventions and to control for any differences in sample characteristics. As suggested in a recent Editorial,²⁸ such pooled analyses provide the opportunity to compare effects of different interventions. The objective of the present paper is to present findings from this pooled analysis comparing the reduction in VMS frequency among the three active interventions (two acupuncture groups, yoga), two attention control groups (sham acupuncture, HWE), and three passive controls groups (usual care and waitlist). The sham acupuncture and HWE classes will hereafter be referred to as attention control groups, and the waitlist and usual care groups will be referred to as passive control groups.

METHODS

Descriptions of all three studies have been previously published and are summarized in Table 1. For all studies, women were recruited through newspaper advertisements, radio announcements, and hospital postings. Initial eligibility was determined by telephone screener. Potentially eligible women were scheduled for an initial clinic visit where they completed self-administered baseline questionnaires and received instructions on keeping a 2-week hot flash diary, which they mailed back to verify eligibility. For all studies, women were required to report an average of 4 hot flashes per day to be eligible. All studies were approved by the Institutional Review Boards at all sites, and all participants provided written informed consent.

The primary outcome in all studies was frequency of hot flashes as measured by the Daily Diary of Hot Flashes (DDHF).²⁹ Baseline VMS frequency was calculated using the last fourteen days of diaries available prior to randomization. Intervention phases differed among the three studies; for the purpose of these analyses, we used data from only the first 8 weeks of intervention for all studies to correspond to the study with the shortest treatment phase.

Study 1: Acupuncture vs. Attention Control (Sham Acupuncture) vs Passive Control (Usual Care)

This study was a 2-site clinical trial using a 3-arm prospective, randomized single-blind, sham-control design and usual care only control (N=56).²⁵ Women who were current or previous hormonal therapy (HT) users were not eligible. Eligible women were randomized to one of the three groups stratified by clinical center. Participants assigned to acupuncture (both true and sham) were seen twice a week for 8 weeks (a total of 16, 30 minute treatment sessions) by a trained acupuncturist. All participants were instructed not to take hormonal medications or initiate other treatments for their hot flashes during the study.

Acupuncture.—This group received needling at sites based on a “standardized individual” approach which combined standardized core acupuncture points supplemented with customized points based on a woman’s presentation.

Attention control group (sham acupuncture).—This group received shallow needling at bodily locations not corresponding to traditional acupuncture points that were thought to have minimal effects on hot flashes.

Passive control group (usual care).—This group did not receive any form of acupuncture needling. One clinical site was able to provide two acupuncture treatments to this group after two months.

Study 2: Yoga vs. Attention Control (Health and Wellness Education) vs. Passive Control (Waitlist)

This 3-arm randomized study consisted of three groups: yoga, health and wellness education (HWE) classes, and a usual care control group (N=54).²⁶ Women who had HT use in the previous three months were not eligible. All study participants agreed not to take hormonal medications or initiate other treatments for their hot flashes during the study.

Yoga.—The study intervention consisted of 10 weekly, 90-minute classes of Integral Yoga which places a major emphasis on stress reduction and decreased likelihood of increasing heat. Each class included the same basic elements: (1) breathing (pranayama)/centering meditation; (2) physical postures (asanas); and (3) deep relaxation (Savasana). In addition to the group classes, participants were asked to practice yoga at home for 15 minutes 3 times per week using a videorecording produced for this study.

Attention Control group (HWE).—This control group was designed to control for time, attention, and social aspects of the yoga intervention. It was designed to be “believable” for menopausal women without being efficacious for reducing hot flashes. Classes consisted of 10 weekly, 90-minute didactic classes on different topics: menopause, stress management (with no breathing component) (2 sessions), bone health, cardiovascular health, nutrition, financial planning, skin care, aging and long-term health planning, and cancer prevention/screening. Women were given materials to read at home to match the time spent in home yoga practice.

Passive Control Group (Waitlist).—Participants in this group did not participate in any classes for 10 weeks. They were provided with up to four yoga or HWE classes after 10 weeks.

Study 3: Acupuncture vs. Passive Control (Waitlist)

In this pragmatic 2-site, 2-arm clinical trial, participants were randomized to either a 6-month course of up to 20 acupuncture treatments, or a waitlist group.²⁷ The study did not include a sham acupuncture group as the purpose of the study was to better understand acupuncture as practiced in the real world. This study did not exclude HT users as we were interested in whether current HT use would be related to the effectiveness of acupuncture. However, only two participants were taking HT.

Acupuncture.—Study acupuncturists ascribed a Traditional Chinese Medicine diagnosis to each participant and were allowed to individualize treatment. The frequency of treatments was determined by the acupuncturist and study participant. Study acupuncturists were permitted to change acupuncture point selection and other aspects of treatment if clinically indicated at each treatment session. No restrictions were placed on duration of each treatment, or on the application of other treatment modalities such as moxibustion or manual or electrical stimulation of acupuncture needles at selected acupuncture point locations.

Passive Control Group (Waitlist).—Participants in this group did not receive any form of acupuncture needling during the first 6 months of study participation. After 6 months, they were provided up to 20 acupuncture treatments in the next 6 months.

Statistical Analysis

We computed basic descriptive data on key covariates: age (in years) at study enrollment, menopausal status (postmenopausal vs not postmenopausal), and race (white vs non-white).

Our outcome variable of interest was percentage change in weekly average number of daily hot flashes. For each of the 8 weeks following baseline, we computed an average number of daily hot flashes over the 7 days of that week. We then divided this weekly average by the average number of daily hot flashes reported during the baseline week to get a fractional proportion of baseline hot flashes. We subtracted this fraction from 1.0, and converted to percent to obtain percent reduction in average daily hot flashes from baseline week.

We first sought to determine whether we could combine the three passive control groups across studies into a single reference group based on the rationale that participants in these groups did not receive any type of study intervention. Prior to our main analyses, we statistically confirmed that there were no differences in the three passive control groups in terms of average overall reduction in hot flashes or in the pattern of reduction over the 8 weeks ($p=0.98$ for main effect of group and 0.60 for group*week interaction, in repeated measures mixed model containing three passive control groups only). We therefore combined these three passive control groups in our two main repeated measures models of interest.

Our first model tested the null hypothesis of no significant differences in level of hot flash reduction among the three active treatments and two attention control groups (collectively referred to as “intervention” groups, below). We compared the five groups in a single model controlling for the covariates of age (in years) at study enrollment, menopausal status, and race. Week was treated as an ordinal variable (taking on the values 1–8) after confirming monotonic trends in average hot flash reductions in all groups over time. We also included an interaction term between intervention group and week.

Our second model sought to determine if there was a significant difference between the five intervention groups and the three passive control groups. After confirming in our first model that there were no significant differences among the five intervention groups, we combined these five groups into one group and compared them to the group containing the three passive control recipients. Similar to the above, we controlled for the covariates of age at study enrollment, menopausal status, and race, and we again considered week as an ordinal variable. We again included the interaction term between group (combined intervention or combined passive control) and week.

All analyses were performed in SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Participants in the three studies differed significantly ($p<0.0001$) on mean age at enrollment, with Study 1 having the youngest participants, on average, and Study 3 having the oldest (Table 2). The studies also differed significantly ($p=0.008$) in racial/ethnic composition: Study 1 had the highest percentage of white participants (85%), while Study 2 had a relatively low percentage of whites (60%). There were no significant differences among the three studies in percent postmenopausal or mean number of daily hot flashes reported at enrollment.

Results of the first repeated measures analysis examining differences among the five intervention groups are reported in Table 3 and shown in Figure 1. As seen in Table 3, there were no significant differences among these five groups in either the average level of percent change in number of hot flashes (p-value for group effect = 0.99) or change in number of hot flashes over time (p-value for group*time interaction = 0.95).

Our second analysis compared the five intervention groups to the combined passive control group. Given the previous finding that there was no significant difference among the five intervention groups, we combined these groups into one group ("intervention group") and compared this group to the group comprising the three passive control groups ("control group.") As shown in Table 4, there was a significant group*time interaction in this model (p=0.02) with the intervention group showing significantly more decline over time than the control group. On average, and after adjustment for the included covariates, the intervention groups declined approximately 28% more by week 8 relative to the average among the control groups. Figure 1 illustrates this interaction using the unadjusted numbers: on average, women in the groups who received active treatment or attention control interventions reported 35–40% fewer hot flashes at the end of the 8 weeks compared to baseline, while those in the combined passive control groups reported close to 10% fewer hot flashes on average at the end of 8 weeks. This (unstandardized) effect size estimate at week 8 of a 28% difference between intervention and control was significantly different from 0 (in a contrast statement) at $p < 0.0001$. As can be seen in Figure 1, lines for the five active groups lie upon each other, and all lie distinctly below the line for the passive control groups.

DISCUSSION

This pooled analysis of three studies of non-pharmacological interventions for menopausal hot flashes shows that the active treatments (acupuncture and yoga) and attention control intervention groups (sham acupuncture and HWE classes) have statistically similar effects on the percentage reduction of hot flashes over 8 weeks, and that all five intervention groups are significantly better than the passive control groups. Yoga and acupuncture did not differ in their effectiveness in reducing hot flashes, and the two attention control groups did not differ from the two active interventions in effectiveness.

The acupuncture results support previous research showing a significant effect of acupuncture for reducing the frequency of VMS when compared to no treatment.^{25, 27, 30–35} Results of yoga studies are a bit more mixed, although most of studies do not measure frequency of hot flashes.³⁶ More recently, the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) trial (a randomized controlled trial comparing yoga, exercise, and omega-3 supplements) found that study participants in the yoga group had a 35% reduction in hot flash frequency,³⁷ which is equivalent to our results in the pooled analysis.

Importantly, this pooled analysis showed that the attention control groups were equally effective as the interventions of interest in reducing hot flash frequency. There are several potential explanations for this finding: 1) the two attention control groups were actually

active treatments; 2) the non-specific effects of patient-provider interactions (attention) or other components of the control groups (ie, shallow needling at non-acupuncture points or participation in an educational program) are sufficient to reduce hot flashes; and/or 3) expectations of treatment effectiveness accounted for these results. Sham acupuncture is currently thought to have physiological effects and is not truly a placebo comparator, which would support the first explanation.³⁸ Two reviews of acupuncture for menopausal hot flashes concluded that sham acupuncture could induce a treatment effect comparable to true acupuncture in the reduction of hot flash frequency.^{31, 35}

Although it is somewhat less likely that the HWE classes served as an active intervention since none of these classes addressed management of hot flashes, we cannot rule out this explanation. Results for HWE classes (and sham acupuncture) might also argue that the non-specific effects of the classes and sham acupuncture contributed to the beneficial effects. Other studies have also found that such attention control groups can be as beneficial as the treatment group.^{39–41} In a systematic review of control condition designs for psychotherapy for depression, Mohr and colleagues found that studies with active control groups had much smaller effect sizes than those that had a usual care or waitlist control,⁴² suggesting that non-specific effects of such interventions can be effective.

Other studies have found that expectations of treatment effectiveness are important,^{43–46} but there are two arguments against the role of expectations in our results. First, Study 1 participants did not know if they were getting true or sham acupuncture, but Study 3 participants knew that they were getting true acupuncture. However, results were very similar for both groups. In addition, for both Studies 2 and 3, we asked participants at baseline to rate their expectations that the interventions would reduce the frequency of their hot flashes. Acupuncture received the highest rating (7.9 on a 10 pt. scale), whereas the mean rating for health and wellness was considerably lower (5.9). If expectations explained our findings, we would anticipate these mean expectation ratings to be similar.

Results of this pooled analysis point to the importance of including passive control groups in study designs. Had these groups not been included in our studies, we would not have known if the interventions had any benefit over and above the passage of time, and would have drawn very different conclusions. As discussed by others, the results of randomized controlled trials can depend as much on the selection and justification of the control group(s) as the experimental intervention.^{42, 47}

A limitation of these analyses, which would apply to any pooled analyses, is that the study populations across the three studies are not perfectly matched. Even though we controlled for differences in education, age, and race, there may be unknown differences not accounted for. As previously noted, eligibility criteria around HT use differed among the three trials. However, given that each trial was randomized and that only two women among all of the women in all three trials were on HT at randomization, we believe it is unlikely that these differences in HT eligibility criteria affected results. There were also minor differences in treatment protocols between the two acupuncture studies and the passive controls varied slightly across studies. Further, it is not possible to rule out a general placebo effect such that

women in all five intervention groups benefited simply by being in a study, or that longer follow-up would show somewhat different results.

This pooled analysis takes advantage of comparing three separate studies of interventions for menopausal hot flashes that all used the same eligibility criteria and primary outcome measure. Results showing that all interventions were equally effective have clinical significance for advising women bothered by hot flashes and searching for non-hormonal treatments.

CONCLUSION

Our pooled analysis of three randomized controlled trials demonstrates the effectiveness of acupuncture, yoga, and health and wellness education classes in the management of menopausal hot flashes compared with passive controls. Our analyses also provide evidence that attention control interventions may complicate the interpretation of comparisons between presumably active “treatment” interventions and interventions intended to be “inactive” or “inert,” but which still result in improvement in participants. We believe our findings illustrate the importance of including a control arm without any intervention in behavioral intervention trials.

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Figure 1.
Estimated percent change in VMS frequency by group and weeks from randomization, controlling for baseline VMS frequency, season of randomization, site, prior use of acupuncture, use of hormone therapy, and menopause status.

TABLE 1.

Trial designs

Trial	Total Enrollment	Design	Eligibility	VMS Eligibility	Exclusion Criteria	Intervention Length
1 Avis ²⁵	56	3-arms: acupuncture, sham acupuncture (attention control), usual care (passive control)	Age 42–55 Perimenopausal or postmenopausal	4 VMS/day	Use of hormone therapy, a selective estrogen receptor modulator, aromatase inhibitor, clonidine, Bellerigal, antidepressant, or gabapentin (past 12 wks) Had received chemotherapy Significant psychiatric disorder Used acupuncture for any reason in past 4 wks Previous treatment for acupuncture for VMS Untreated thyroid disease Bleeding or clotting problem other than heavy periods Currently on prescribed medications that increase the risk of bleeding.	8 wks.
2 Avis ²⁶	54	3-arms: yoga, health and wellness education classes, (attention control) waitlist (passive control)	Age 45–58 Late perimenopausal or postmenopausal	4 VMS/day	Hormone therapy (past 12 wks) Hormone-modulating therapies (past 6 mos) History of cancer (past 5 yrs) Prior use of yoga for VMS Yoga or acupuncture (past 3 mos) Untreated thyroid disease Initiation of herbal or nutritional remedies (past 4 wks) Initiation of psychoactive medications (past 3 mos)	10 wks.
3 Avis ²⁷	209	2-arms: acupuncture, waitlist (passive control)	Age 45–60 Perimenopausal or postmenopausal	4 VMS/day	Initiation or change in dose of any tx for HF (past 4 wks) Initiation or change in dose of antidepressant (past 3 mos) Received acupuncture for any indication (past 4 wks) Received acupuncture from one of the study acupuncturists (prior 6 mos) Self-reported health status as poor or fair Diagnosis of hemophilia	8 wks.

VMS, vasomotor symptoms

TABLE 2.

Baseline descriptive data from three studies

	Study 1 (n = 56)	Study 2 (n = 54)	Study 3 (n = 209)	p-value
Mean age at baseline (SD)	51.2 (2.9)	52.9 (2.9)	53.8 (3.5)	<0.0001
Mean number of daily hot flashes at baseline (SD)	9.4 (5.1)	9.3 (4.7)	9.5 (5.0)	0.97
White, No. (%)	48 (86)	32 (60)	157 (75.9)	0.008
Post-menopausal, No. (%)	48 (86)	41 (84)	172 (83.1)	0.90

SD, standard deviation

TABLE 3.

Results of repeated measures model examining effects of group and week on percent reduction in average number of weekly hot flashes among 5 intervention groups

Variable	Parameter estimate	SE	p value
Age in years	−0.005	0.007	0.50
Race			
White	0.027	0.05	0.60
Nonwhite	(ref)		
Menopause status			
Perimenopausal	0.02	0.06	0.69
Postmenopausal	(ref)		
Week	0.02	0.003	<0.0001
Group			0.99
Study 1 acupuncture	0.04	0.10	
Study 1 active control (sham)	−0.02	0.10	
Study 2 yoga	0.02	0.10	
Study 2 active control (HWE)	−0.03	0.10	
Study 3 acupuncture	(ref)		
Group x week interaction			0.95
Study 1 acupuncture x week	−0.003	0.01	
Study 1 active control (sham) x week	0.002	0.01	
Study 2 yoga x week	−0.0001	0.01	
Study 2 active control (HWE) x week	0.008	0.01	
Study 3 acupuncture x week	(ref)		

TABLE 4.

Results of repeated measures model examining effects of combined intervention (vs combined passive group) and week on percent reduction in average number of weekly hot flashes

Variable	Parameter estimate	SE	p value
Age in years	−0.006	0.006	0.25
Race			
White	0.01	0.04	0.81
Nonwhite	(ref)		
Menopause status			
Perimenopausal	0.06	0.05	0.25
Postmenopausal	(ref)		
Week	0.006	0.004	0.15
Group			0.0001
Combined intervention	0.19	0.05	
Combined passive control	(ref)		
Week x group interaction			0.02
Combined intervention	0.01	0.005	
Combined passive control x week	(ref)		