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Hot Flashes: The Ongoing Search for Effective Interventions

Kunal C. Kadakia, MD,

Division of Internal Medicine, Mayo Clinic, Rochester, MN

Charles L. Loprinzi, MD, and

Division of Medical Oncology, Mayo Clinic, Rochester, MN

Debra L. Barton, RN, PhD

Division of Medical Oncology, Mayo Clinic, Rochester, MN

Hot flashes and night sweats (vasomotor symptoms) are the most recognizable adverse symptoms through and following the menopausal transition. They affect 40-85% of all women, being more frequent and severe in breast cancer survivors^{1, 2}. Vasomotor symptoms negatively impact sleep, energy, sexuality, and overall quality of life^{3, 4}. Severe hot flashes can also lead to nonadherence to life prolonging endocrine therapies such as aromatase inhibitors and tamoxifen in breast cancer survivors⁵. Although it is well known that estrogen largely alleviates vasomotor symptoms, concerns regarding its use in women, with or without breast cancer, has led to extensive research efforts to find well tolerated and effective nonhormonal interventions.

Over the last few decades, multiple randomized controlled trials have demonstrated an approximately 50-60% reduction in hot flashes with selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors (e.g. citalopram, venlafaxine, desvenlafaxine, and escitalopram), antiepileptics (gabapentin and pregabalin), and clonidine^{6, 7}. However, many women find the side effects of these agents restrictive; as a consequence, a growing body of research has been dedicated to mind-body interventions⁸. These interventions include yoga, hypnosis, relaxation-training/paced respiration, acupuncture, mindfulness-based stress reduction (MBSR), and cognitive behavioral therapy (CBT).

The trial by Ayers and colleagues⁹ reported in this issue of *Menopause* examined the effectiveness of CBT on vasomotor symptoms. The trial involved 140 women with a mean age of 53 years and a mean of 63 hot flashes and night sweats (HF/NS) per week. Two interventions were assessed: group CBT (N=48) and a guided self-help CBT (N=47) program. The group CBT included 2-hour sessions occurring weekly for 4 weeks while the guided self-help CBT included a self-help book and two contacts with a psychologist over a 4 week period. There was a significant reduction in HF/NS problem rating, by ~50%, in each intervention group compared to ~15% and ~20% in the no-treatment control group at 6 and 26 weeks, respectively. However, there was no statistical difference between any groups, with regards to total HF/NS frequency or HF frequency, at either time point. It is not known if the treatment groups reported adherence to the intervention techniques provided after the 4 week treatment phase. As such, it remains unclear if the difference noted in HF/NS problem rating at 26 weeks was clearly associated with the intervention. The intervention groups did show improvement in mood, emotional and physical functioning, and quality of life. Although the details of the CBT sessions are not clarified in the current article, the authors do indicate that the CBT intervention was multifaceted and included

components of psychoeducation, relaxation, cognitive/behavioral strategies for sleep, paced breathing, and stress management. Details have been published in previous works^{10, 11}.

The authors of this paper have a legacy of previous manuscripts describing the psychological component of hot flashes. In fact, a previous small study demonstrated that distressing or problematic hot flashes were predicted by depression, anxiety, and low self image, but not frequency of hot flashes¹². Therefore, women with equal numbers, and perhaps severity, of hot flashes may have very different emotional responses to their hot flashes; some desiring treatment, considering the symptoms bothersome, and others, not. Some theoretical frameworks for symptoms posit that all symptoms have a psychosocial component¹³. This psychosocial component plays a role in the distress or bother related to the symptom as well as to the person's desire to "do something about it". Cognitive behavioral therapy has a long and well documented history of efficacy related to distress, sleep, and psychological aspects of coping with many of life's challenges^{14, 15}. Therefore, the use of this strategy as an adjunct to ameliorating the negative impact of symptoms, such as hot flashes, is a logical progression in effective care. Interestingly, consistent with the authors' previous paper¹², the CBT intervention in this paper reduced at least two of the predictors for bothersome hot flashes, depression and anxiety. The third factor, self-esteem, does not appear to have been measured in the current trial.

There are important limitations of this trial, highlighting some of the inherent methodological challenges faced by behavioral researchers. Most notably, the absence of an appropriate active control group does not allow a measurement of the well-known placebo effect seen in other hot flash studies¹⁶, a limitation that was acknowledged by the authors. The lack of an active control group has confounded other recent trials assessing yoga¹⁷, paced breathing¹⁸, hypnosis¹⁹, and MBSR²⁰. Ideal control groups, in studies evaluating mind-body interventions, control for aspects of group effects, time, and attention²¹.

Also, variable methods of measuring the vasomotor experience during clinical trials have been scrutinized. Often, the primary outcome of interest in HF intervention trials is HF frequency or HF score (frequency $\times$ severity); which are ideally obtained in real time, either by a diary¹⁶ or an event monitor²², so that all hot flashes experienced by the participant are captured. Similar to the current trial, other studies assessing acupuncture²³ and MBSR²⁰ have also utilized HF problem ratings as the primary outcome of interest (i.e. hot flash interference on surrogates of quality of life). The methodology utilized to obtain HF frequency and severity in the current trial, weekly recollection versus a prospective daily diary, might have influenced the lack of differences observed in total HF/NS frequency and HF frequency between groups, particularly since previous studies utilizing paced breathing and other similar strategies for hot flashes have demonstrated reductions of nearly 50%, more than what is found in the current trial²⁴. Notwithstanding, both HF problem rating and HF score appear to be valid markers of the vasomotor symptom experience, albeit different aspects of that experience, and future studies should incorporate both clinical endpoints.

Another controversial issue in the literature is the use of "physiologic" or "objective" measurements of hot flashes by means of sternal skin conductance [SSC] monitoring. Although these devices have a very high correlation between patient report and SCC detection in the controlled laboratory setting²⁵, their accuracy in the ambulatory setting is highly variable and needs further validation²⁶. Despite general reductions in HF frequency observed by SSC monitoring in all groups, the current trial found a high degree of variability, resulting in inconclusive data. While research is ongoing regarding the validity of SSC in the nonlaboratory clinical research setting, more investigation is clearly needed to improve the sensitivity and specificity of these devices before they can be considered valid markers of hot flashes in the ambulatory setting²⁷.

Why might mind-body interventions influence hot flashes? Although not fully elucidated, vasomotor symptoms are believed to be related, in part, to disruption of complex neuroendocrine pathways regulating the thermoneutral zone in the hypothalamus. Current theories suggest that decreases in estrogen lead to increases in central noradrenergic activation (i.e. sympathetic activity) resulting in a thermoneutral zone which is shifted downward and is narrower²⁸. This suggests that increased sympathetic activity modulates thermoregulation and mind-body interventions such as relaxation-training/paced respiration and MBSR might decrease sympathetic tone. Other data suggest that anxiety and negative thoughts effect the subjective perception of hot flashes^{29, 30}. Therefore, future studies utilizing multicomponent interventions should clearly match study components to relevant outcomes. It is unlikely that a CBT intervention that only addresses negative thoughts would decrease the frequency of hot flashes. Rather, evidence would support that an intervention utilizing relaxation-training/paced respiration to influence sympathetic tone, cognitive/behavioral strategies for stress and negative thoughts, and behavioral strategies for sleep would impact the actual number and psychological experience of hot flashes and improve sleep parameters.

Postmenopausal women and breast cancer survivors experience psychological, spiritual, sleep, and cognitive dysfunction beyond what could be attributable to vasomotor symptoms alone^{31, 32}. Therefore, a multifaceted intervention that can address multiple symptoms without untoward side effects is truly a patient-centric strategy. Future studies should evaluate critical versus noncritical components of behavioral strategies in addition to aspects of time commitment and adherence.

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