

Measuring Hot Flashes: Summary of a National Institutes of Health Workshop

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Vasomotor symptoms, including hot flashes and night sweats, are the most frequently reported symptoms of the menopausal transition. Although prevalence rates vary substantially across populations of menopausal women, the vast majority of women in the United States will experience hot flashes at some point during menopause. Other groups of people also experience hot flashes, including breast cancer survivors and men undergoing androgen deprivation therapy.

Although estrogen and other forms of hormone therapy are effective in treating hot flashes, recent findings from the Women's Health Initiative indicate that the benefits of hormone-based therapies for hot flashes are attenuated by risks, including coronary heart disease, stroke, and pulmonary embolism.^{1,2} Moreover, hormone therapy for hot flashes is inappropriate for individuals with a history of hormone-dependent tumors. Many people have turned to complementary and alternative medicine (CAM) to manage hot flashes, with varying degrees of success. Unfortunately, the empirical base of scientifically sound clinical trials to assess the efficacy and even safety of various CAM modalities is neither extensive nor strong. Current medical advice is that hormones should be used at the lowest dosage and for the shortest period.³ However, little is known about risks and benefits of smaller doses, shorter treatment times, and different routes of administration. Thus, it is likely that scientists will be conducting clinical research on a range of treatments to reduce hot flashes.

The current status of knowledge about hot flashes and their treatment suggests several opportunities for the National Institutes of Health (NIH) to address this public health issue and prepare for future research. Early in 2005, the NIH will convene a State of the Science meeting to review current knowledge about existing therapies for

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Dr Li provided services as a science writer/consultant under contract to the National Center for Complementary and Alternative Medicine while the manuscript was being prepared.

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managing the menopausal transition and associated symptoms, including hot flashes. In the meantime, in preparation for future clinical trials of potential treatments, the quality of existing measures of an important primary outcome, namely hot flashes, should be considered. Many studies of hot flashes rely on self-reported measures of symptom frequency and severity by using questionnaires or diaries. However, with a few notable exceptions, most instruments used to collect these subjective data have not been validated. Moreover, these measures may be "unstable"—subject to the effects of memory and recall biases in the case of retrospective reporting as well as the effects of mood, emotion, and expectations.⁴ Furthermore, many trials of therapies for hot flashes report substantial placebo effects. Sternal skin conductance monitors have been used to collect objective data on hot flash frequency in laboratory and ambulatory settings. Although laboratory studies have found a high correlation between sternal skin conductance measures and self-reported hot flashes, the correlation between these measures is lower in ambulatory studies because of underreporting of subjective hot flashes.^{4,5} Current monitors have physical limitations that prohibit long-term use in ambulatory settings.

For editorial comment, see page 735.

If we seek to undertake further clinical trials of interventions for hot flashes, especially ones that may be relatively weak compared with estrogen, we can either conduct large studies to accommodate the limitations of subjective primary end points currently in use or develop more sensitive and reliable outcome measures for use in smaller studies, which would be more economical in terms of time and resources.

On January 20, 2004, the National Center for Complementary and Alternative Medicine, in collaboration with the Office of Research on Women's Health, the National Institute of Biomedical Imaging and Bioengineering, the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Child Health and Human Development, the National Institute on Aging, the Office of Extramural Research, and the Office of Behavioral and Social Sciences Research, convened a work-

shop to assess the current state of hot flash measures and to consider barriers and opportunities to improve these measures.

Scientists representing a broad range of disciplines (eg, bioengineering, physiology, epidemiology, endocrinology, obstetrics/gynecology, oncology, sociology, and psychology) participated in the discussions: Dr Nancy E. Avis, Wake Forest University School of Medicine, Winston-Salem, NC; Dr Marc R. Blackman, National Center for Complementary and Alternative Medicine, Bethesda, Md; Dr Janet S. Carpenter, Indiana University School of Nursing, Indianapolis; Dr Lorraine Dennerstein, University of Melbourne, Melbourne, Australia; Dr Lorraine A. Fitzpatrick, Mayo Foundation, Rochester, Minn; Dr Robert R. Freedman, Wayne State University School of Medicine, Detroit, Mich; Dr Ellen B. Gold, University of California at Davis; Dr Charles L. Loprinzi, Mayo Foundation; Dr Michael R. Newman, Michigan Technological University, Houghton; Dr Katherine M. Newton, Group Health Cooperative, Seattle, Wash; Dr Nanette Santoro, Albert Einstein College of Medicine, Bronx, NY; Dr Jerome S. Schultz, University of Pittsburgh, Pittsburgh, Pennsylvania; Dr Belinda Seto, National Institute of Biomedical Imaging and Bioengineering, Bethesda, Md; Dr James W. Simpkins, University of North Texas, Fort Worth; Dr Rebecca C. Thurston, Harvard University School of Public Health, Boston, Mass; Dr John G. Webster, University of Wisconsin-Madison; and Dr Jon-Kar Zubieta, University of Michigan, Ann Arbor.

The workshop's deliberations and conclusions are summarized subsequently. The full workshop discussion and findings are available at www.nccam.nih.gov/hotflashworkshop.

MEETING HIGHLIGHTS

A considerable amount of scientific literature describes the endocrinologic and physiologic changes that occur during hot flashes. However, our understanding of the mechanism of action and factors that trigger hot flashes is incomplete. Briefly, a hot flash is a sensation of heat and flushing that occurs suddenly. It is associated with vasodilation and a decrease in core body temperature (Tc) and is often accompanied by sweating, chills, palpitations, increased metabolism, elevated heart rate, and a sensation of anxiety.⁶ Small but statistically significant elevations in Tc often precede menopausal hot flashes recorded in controlled laboratory conditions.⁷ However, an increase in Tc alone does not explain a hot flash. It is hypothesized that an increase in Tc will produce a hot flash only in people with an extremely narrow thermal neutral zone. In normal conditions, when the Tc decreases beyond the lower limit of the thermal neutral zone, shivering is induced. When the Tc is elevated

higher than the upper limit of the thermal neutral zone, sweating and peripheral vasodilation ensue. If the hypothalamus senses the Tc increasing, the body will dissipate heat through vasodilation and sweating. If the body gets too cold, vasoconstriction occurs and shivering increases the Tc. Research by Freedman and Krell⁸ found that the thermoregulatory zone for symptomatic menopausal women essentially drops to 0°C, whereas among asymptomatic women, it is about 0.4°C, similar to that found among younger women and men.

The endocrinologic correlates of hot flashes are complex. Decreases in estrogen level correlate with hot flashes, and treatment with estrogen effectively stops hot flashes. However, estrogen levels alone cannot explain the phenomenon of hot flashes. Estradiol profiles in symptomatic and asymptomatic menopausal women are very similar.^{6,9-14} Similarly, hot flashes can occur in the last trimester of pregnancy when estrogen levels are high.⁶ Thus, a decline in estradiol is necessary but insufficient to explain the occurrence of hot flashes in women.

A similar pattern is seen with gonadotropins. The luteinizing hormone (LH) levels in women with and without hot flashes are the same.⁶ However, the relationship between LH pulses and hot flashes appears to be temporal. Nevertheless, women with gonadotropin-releasing hormone deficiency or those who underwent hypophysectomy had no circulating LH level but reported hot flashes; thus, questions are raised about the relationship between LH and hot flashes.^{15,16} Numerous studies have shown that hot flashes are preceded by several biochemical changes, such as increased levels of LH, corticotropin, and growth hormone, and increased serum cortisol levels afterward, although the importance of these changes is not entirely clear.^{6,7,17}

More recently, catecholamines were implicated in the onset of hot flashes. Norepinephrine is known to be important for thermoregulation.⁶ Administering norepinephrine into the preoptic hypothalamus causes peripheral vasodilation, heat loss, and decrease in Tc. There is evidence that gonadal steroids modulate central noradrenergic activity. Some elegant studies have shown that the brain metabolizes norepinephrine (3-methoxy-4-hydroxyphenylglycol) at higher rates in symptomatic women than in asymptomatic women.⁷ This may implicate norepinephrine in the triggering of hot flashes.

Overall, the workshop participants concluded that more research is needed on the mechanism of hot flashes and whether and how hormones might affect onset. Also, better tools, including measures of specific hormones, may be needed to accomplish this goal.

Understanding whether and when a hot flash occurs relies on subjective self-reported data and/or objective data

captured by monitors, such as sternal skin conductance monitors. Existing objective measures can capture data on frequency, but they cannot provide information on intensity, duration, or interference with activities or quality of life. Thus, both objective and subjective measures of hot flashes are needed.

An ideal objective measure for hot flashes should correlate well with self-reported data, be specific to hot flashes, and be usable under ambulatory conditions.⁵ A review of the objective published hot flash data shows that only sternal skin conductance monitors fulfill these criteria. The bioengineers participating in the workshop described a range of sensor technologies that are either in use or in development that might be adapted for measuring hot flashes. However, until additional physiologic or endocrinologic factors are found to be consistently related to hot flashes, participants concluded that near-term efforts should be focused on improving tools to measure sternal skin conductance to make them more amenable for use in long-term ambulatory studies.

The methods for collecting self-reported data rely on questionnaires or diaries. Several different scales, items, and diaries have been used in various studies of hot flashes, but few have been validated. Moreover, comparisons of objective and subjective measures indicate substantial problems of underreporting in self-reported data of hot flash frequency. Whether women do not perceive the hot flash or do not report it is unclear. Several items and scales are used to capture data on hot flash intensity. Items recommended by the Food and Drug Administration define 3 levels of severity for vasomotor symptoms: mild—sensation of heat without sweating; moderate—sensation of heat with sweating, able to continue activity; and severe—sensation of heat with sweating that causes cessation of activity. This measure combines assessments of heat, sweat, and functioning. However, it is unclear whether sweating is the characteristic that women always use to assess severity. For example, the fear of sweating during a public presentation rather than actual sweating might cause a woman to rate a hot flash as severe. Thus, context and other factors, such as mood, are likely to impinge on measures of severity. Overall, the workshop participants concluded that additional work is needed to fine-tune self-reported data collection, including work to validate instruments and diaries.

Placebo effects can be substantial in studies of hot flashes. Although many studies report such an effect, there is little if any research on how or why the placebo effect occurs. Interpretation of diminishing symptoms that occur during the pretrial period (the so-called Hawthorne effect) or in the treatment and placebo arms is complicated by the fact that the number of hot flashes would be expected to

decrease as women experience menopause, even in the absence of treatment. Interesting issues and questions were raised at the workshop concerning the role of μ -opioid receptors in the brain regarding expectancy of relief from pain and the capacity of μ -opioid receptor binding to be modulated by estradiol. Clearly, improving our understanding of central nervous system processes involved in triggering hot flashes and in mediating placebo effects could have important implications for future treatments of hot flashes.

Animal models have the potential to provide extremely useful information on a variety of human health problems and conditions, including hot flashes. Participants at the workshop reviewed animal data on vasomotor changes in rodent, sheep, and nonhuman primate models. The opiate withdrawal model in rats is the best-characterized animal model for hot flashes. It is replicable, sensitive to known drug therapies for hot flashes, and cost-effective. The animal model involving hypoglycemia-induced hot flashes is less well characterized but is replicable and cost-effective. Animal models could be important for the study of several issues associated with hot flashes, such as the role that the hypothalamus plays in hot flashes and screening compounds proposed for treatment of hot flashes. Although primate models afford interesting scientific opportunities, expense and insufficient numbers of naturally menopausal primates without comorbidities present important limitations.

SUMMARY

The etiology and mechanism of hot flashes remain incompletely understood. Future studies of hormonal and neurologic systems may provide promising leads to improve our understanding of the basic phenomenon and perhaps also shed light on the placebo effect. However, this is likely a complex undertaking. Critical to this effort is the ability to reliably identify when a hot flash has occurred. The leading objective measure in use today—sternal skin conductance monitoring—has some limitations in ambulatory settings. However, a more severe limitation is the inability of sternal skin conductance to provide any information on duration, intensity, and interference with activities.

Ultimately, researchers desire a convenient and cost-effective sensor for monitoring hot flashes without cumbersome electrodes that might become compromised if a subject experiences extensive sweating or takes a shower and one that can capture data continuously for relatively long periods of observation. However, researchers also need well-characterized methods for collecting self-reported data. If the primary concern is helping women with hot flashes find relief, then subjective measures collected through diaries or interviews cannot be dismissed. Given

the importance of this information, it would make sense to undertake methodologic research to ensure that the best possible systems are used to collect valid and reliable information.

The factors that we want to measure with respect to hot flashes are likely to change over time as more is learned about the underlying phenomenon. This will probably be an evolutionary process, one involving decisions about what biological factors will be most useful for the task at hand, what technologies might be available or easily adaptable, which measures should be bundled together to maximize the precision of data collected with the available technology, and the analysis of the data to generate new hypotheses and perhaps the need for new measurement tools.

Investigators face several challenges when considering the design of studies of hot flashes. Substantial placebo effects and small sample sizes have produced studies with equivocal findings. The placebo effect, while remarkable in its dimensions in some studies of hot flash interventions, is not understood. Distinguishing placebo effects from the natural dissipation of symptoms over time would be extremely helpful. Similarly, the ability to induce a placebo effect to reduce the discomfort and annoyance associated with hot flashes might be helpful. The use of neuroimaging technology offers potential for greater understanding of the placebo effect.

The group concluded that better measures of hot flashes require improved knowledge in several areas:

- The physical processes underlying hot flashes, which will identify additional factors to measure and the factors that influence the perception and reporting of hot flashes
- Improved sternal skin conductance systems, with additional tools to be developed when other factors of hot flashes are identified
- The performance characteristics of questionnaires and diaries to collect self-reported data on hot flash frequency
- Improved and validated instruments for collecting data on intensity and interference with daily activities
- The mechanism(s) of action of placebo, which may also help distinguish natural attrition of symptoms from placebo effect
- Animal models to elucidate triggers and mechanisms of hot flashes and to screen potential treatments

Investigators interested in studying hot flashes face complex issues. The incomplete understanding of the basic physiology underlying hot flashes clearly calls for further work in this area. Some mechanistic studies cannot be conducted with human subjects; thus, animal models are needed. Animal models could be particularly helpful for understanding the neurobiology of hot flashes and perhaps placebo effects.

Bringing scientists together from different fields would appear to be a promising approach to moving this area forward. Scientific advances are being made increasingly at the interfaces of traditional disciplines, and approaches to science are becoming more integrative. Finding appropriate collaborators from other disciplines is not necessarily easy, and meeting a collaborator from another discipline is only the first step in building a multidisciplinary research team. Effective teams begin with compelling reasons for their existence, but further incentives must be developed to ensure full realization of their potential. The success of team science depends on individuals who are comfortable with boundary-crossing activities. Working as part of a team that is seeking solutions to complex problems requires a willingness to work in an interdisciplinary environment, to collaborate with different types of organizations, and to recognize the importance of a variety of roles in the project. It is likely that a multidisciplinary approach to hot flash research would be helpful given the number of physiologic, clinical, and behavioral factors involved. For example, psychologists and sociologists could contribute to identifying factors that may influence the placebo effect, such as pill color; developing and validating questionnaire items and diary formats; ascertaining the effect of mode of data collection on the quality of the resulting data; and determining the best ways to provide information to subjects. However, if they were part of a multidisciplinary team that included basic scientists, clinicians, and bioengineers, different questions might be asked, and better tools might be developed to collect both subjective and objective data on hot flashes.

The increasing emphasis on collaborative science is also embraced at the NIH level. Since May 2002, the NIH has been engaged in a series of activities collectively known as the "NIH Roadmap," whose goal, in keeping with the NIH mission of uncovering new knowledge about the prevention, detection, diagnosis, and treatment of disease and disability, is to accelerate both the pace of discovery in these key areas and the translation of therapies from bench to bedside.

The timing of this workshop to assess measures of hot flashes appears auspicious for several reasons. First, the issue of refining and validating self-reported measures of symptoms through the use of biomarkers and multidisciplinary research teams is consonant with an NIH Roadmap initiative. Second, the new National Institute for Biomedical Imaging and Bioengineering at the NIH offers impetus for linking biomedical, social, and behavioral scientists with bioengineers to assess and improve existing technology or develop new technologies to collect data on physiological markers specific to hot flashes.

Third, people are already purchasing and using CAM modalities or are resuming hormone therapy for relief of hot flashes, and they and their clinicians are eager for and deserve more information on the safety and efficacy of these remedies.

We acknowledge the hard work and enthusiasm of participants and meeting cosponsors at the National Institutes of Health meeting on assessing and improving measures of hot flashes.

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