Assessing and Improving Measures of Hot Flashes

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Introduction

Vasomotor symptoms, including hot flashes and night sweats, are the most frequently reported symptom of the menopausal transition. However, menopausal women are not the only ones who experience this symptom. Breast cancer survivors, women with chemotherapy-induced ovarian failure, oopherectomized women, women being treated for endometriosis or infertility with Lupron, and men undergoing androgen ablation therapy all report hot flashes. This translates into millions of people living with hot flashes at any point in time. While this symptom varies in its presentation, frequency, and severity, it can be very disruptive and unpleasant. Sweating, chills, and palpitations often follow a sudden wave of heat, and the quality of life can be diminished. Some women report several hot flashes a week while others experience much more frequent events, as many as 36 in a single day. The period of duration for a given hot flash varies from seconds to 10 minutes or more while occurrence of the phenomenon can persist for five years or more (Kronenberg 1990).

Estrogen or hormone therapy is effective in treating hot flashes. Yet the recent findings of the Women's Health Initiative (WHI) indicate that the benefits of taking estrogen plus progestin are outweighed by risks, including coronary heart disease, stroke, pulmonary embolism, breast cancer, and dementia. Moreover, hormone therapy for hot flashes is not appropriate for individuals with a history of hormone-dependent tumors. Many people have turned to complementary and alternative medicine (CAM) to manage this symptom, with varying degrees of success. Some CAM therapies are less potent than hormone therapies; others are less potent than placebo. And yet even partial relief may be sufficient for some people. Unfortunately, the empirical base from scientifically sound clinical trials to assess the efficacy and even safety of various CAM modalities is neither extensive nor very strong. Some people who find their hot flashes to be unmanageable are thus returning to hormone therapy. Current medical advice calls for use of hormones at the lowest dosage and for the shortest period of time. But we know little about risks and benefits for smaller doses, shorter treatment times, and different routes of administration. Thus, it is likely that the National Center for Complementary and Alternative Medicine (NCCAM) and other NIH institutes and centers (ICs) will be supporting clinical trials of a range of treatments to reduce hot flashes in the diverse populations in which they occur.

The current status of our knowledge about hot flashes and their treatment raises several questions about how NIH can move forward to address this public health problem and prepare for future research. Early in 2005, NIH will convene a State of the Science meeting to review what is known about existing therapies for the management of the menopausal transition and what is needed to improve therapy of various symptoms and syndromes, including hot flashes.

In the mean time, in preparation for future clinical trials of hot flash treatments, we began thinking about the quality of existing measures for this critical outcome. Many studies of hot flashes rely on self-reported measures of symptom frequency and severity, using questionnaires or diaries. However, with a few notable exceptions, the majority of instruments used to collect these 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 moods, emotions, and expectancies on perception and reporting. Both Hawthorne and placebo effects have been reported in several studies of hot flashes. Sternal skin conductance monitors have been used to collect objective data on hot flash frequency in laboratory and ambulatory studies. While laboratory studies have found a high correlation between sternal skin conductance measures and self-reported hot flashes, correlation between these measures is lower in ambulatory studies due to underreporting of subjective hot flashes. Unfortunately, current monitors have physical limitations that prohibit long-term use in ambulatory settings.

If we undertake clinical trials of interventions for hot flashes, especially ones that may be relatively weak compared with estrogen, we can either conduct very large studies to accommodate the limitations of subjective primary endpoints, or we can support smaller studies that use more sensitive and stable measures of hot flashes. The latter would be more economical in terms of time and resources. In addition, given the impact that many interventions can have on psychological characteristics, such as mood, and the sizable influence of psychological factors on the perception and reporting of hot flashes, utilizing both physiologic and self-reported measures of hot flashes becomes especially important to adequately ascertain intervention effects.

On January 20, 2004, NCCAM convened a workshop on assessing measurements of hot flashes in collaboration with: the Office of Research on Women's Health (ORWH); the National Institute of Biomedical Imaging and Bioengineering, (NIBIB); the National Cancer Institute (NCI); the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Child Health and Human Development (NICHD); the National Institute on Aging (NIA); the Office of Extramural Research (OER); and the Office of Behavioral and Social Sciences Research (OBSSR). (See Appendix 1 for the workshop agenda.) The objectives of this workshop included assessing our understanding of the physiological and endocrine parameters associated with hot flashes, the self-reported experience of hot flashes, the quality of existing subjective and objective measures of hot flashes, and the barriers and opportunities to improve these measures. Participation and ideas were solicited from a group of scientists representing a broad range of disciplines (e.g., bioengineering, physiology, epidemiology, endocrinology, obstetrics/gynecology, oncology, sociology, psychology), which reflects the multidisciplinary nature of the topic. Represented among the workshop participants were experts who have worked on objective measures of hot flashes (e.g., sternal skin conductance) and/or subjective measures (e.g., questionnaires and diaries), as well as a variety of sensor technologies for other physiologic parameters. Also included in this group were experts who have assessed risk factors for hot flashes and subgroups at elevated risk for them. (See Appendix 2 for a list of participants and cosponsors.)

The timing of this activity is auspicious for several reasons. Refining and validating self-reported measures of symptoms through use of biomarkers and multidisciplinary research teams is consonant with an NIH Roadmap initiative. The new National Institute for Biomedical Imaging and Bioengineering (NIBIB) at the NIH offers great potential for linking biomedical, social and behavioral scientists with bioengineers to assess and improve existing technology or develop new ones to collect data on physiological markers specific to hot flashes. Furthermore, there is considerable interest in finding new ways to decrease hot flash frequency and severity. People are already purchasing and using CAM modalities or are returning to hormone therapy for relief of hot flashes. They and their clinicians need and deserve more information on the safety and efficacy of these remedies.

The following is a summary of the presentations and discussions from the January 20 workshop, Assessing and Improving Measures of Hot Flashes. We are very grateful for the hard work and enthusiasm of participants and the contributions – both intellectual and financial – of our cosponsors.

Significance and Magnitude of the Problem

As noted above, hot flashes are a problem for women in the menopausal transition. But they also affect other populations. The presentations and discussions in this section of the agenda were focused on the following questions:

- Who is affected by hot flashes?
- What is the significance and magnitude of the problem?
- What is the variability in presence and presentation?

Epidemiology of Hot Flashes

Ellen Gold, Ph.D., University of California Davis

Rates of hot flashes reported by perimenopausal women vary widely, ranging from 40 percent in a survey of British women (Kuh et al., 1997) to 100 percent among a sample of women in Massachusetts (Leidy, 1997). (See Appendix 3.) The prevalence varies by a number of factors, such as stage in the menopausal transition, socioeconomic status, race/ethnicity, health status, menstrual/hormonal status, body mass index (BMI), and lifestyle factors, including smoking. Population differences in reporting of hot flashes are well documented (Appendix 3), although many sample sizes are small. One of the larger studies of menopause transition, which also includes significant representation of minority populations, is the Study of Women's Health Across the Nation (SWAN), a longitudinal cohort study, which just completed its tenth year and is funded by NIA, NINR, ORWH, and NCCAM.

SWAN is comprised of seven sites, each of which recruited community-based samples of women from a specific minority group in addition to the Caucasian population.[1] The overall objective of SWAN is to identify factors that affect the timing and nature (e.g., endocrine changes, symptoms) of the menopause transition and to identify the transition characteristics that are related to long-term disease risk indicators, such as changes in cardiovascular parameters and bone density.

SWAN methods consist of: (1) an initial cross-sectional screening in 1996 to1997 of 16,065 women who were between 40 to 55 years old, resided near a SWAN clinic, and belonged to the racial/ethnic group being recruited at that clinical site; and (2) a longitudinal study of 3,302 women who at baseline were between 42 and 52 years old with an intact uterus, at least one ovary, no hormone use within the past 3 months, not pregnant, participated in in-person follow-up interviews annually, and provided data on monthly menstrual calendars. In addition, a food frequency questionnaire was administered at baseline and at the fifth annual follow-up visit. During the annual visits, blood pressure, weight, height, and waist and hip circumference were measured, and an interview and a

[1] The 7 sites, including their recruited minority sample, are: Michigan (African Americans); Massachusetts General Hospital, Boston (African Americans); Rush, Chicago (African Americans); University of California Davis/Kaiser, Oakland (Chinese); UCLA (Japanese); New Jersey (Hispanic); and Pittsburgh (African Americans).

self-administered questionnaire were given. For all women, a fasting blood sample was drawn on one day during menstrual cycle days 2 to5 and assayed for serum estradiol, testosterone, follicular stimulating hormone (FSH), sex hormone-binding globulin (SHBG), dihydroepiandrosterone sulfate (DHEAS), glucose, insulin, lipoprotein, and clotting factors. In a subset of 990 women, daily diary and urine samples were collected and assayed for metabolites of estrogen, progesterone, FSH, and luteinizing hormone (LH).

At baseline, approximately half the sample was Caucasian, about 900 women were African American, and between 200 and 250 women each were Hispanic, Chinese, or Japanese. The mean age at entry was 46 years.[2] Overall, retention has been about 80 percent through follow-up year 5. By follow-up year 6, the percent of observable menopausal transitions differed by ethnic group, ranging from approximately 42 percent for Caucasians to almost 56 percent for Hispanics.

Less educated women, homemakers, and those reporting difficulty paying for basics had increased rates of reported vasomotor symptoms. Higher rates were found among African Americans, Hispanics, and Caucasians; Chinese and Japanese women reported the lowest rates. Possible reasons for these ethnic differences include: cultural stereotypes of aging and menopause; cultural differences in willingness to report symptoms; differences in diet, use of herbs, and other lifestyle factors; and genetic and/or hormonal differences.

SWAN data show that the prevalence of vasomotor symptoms increases as women move through the menopausal transition. Rates of hot flashes are higher among early perimenopausal than premenopausal women and are higher among late perimenopausal women as well as naturally and surgically menopausal women when compared with early and pre-menopausal women. This pattern of increase over the transition is similar across ethnic groups, although the rates of symptom reporting differ (Gold et al., in preparation). This pattern is consistent with the extant literature. Age appears to have an important effect on reporting of vasomotor symptoms, independent of menopausal status. Statistically significant differences in annual estradiol levels (adjusted for body mass index, smoking, and menopausal status) were found in Japanese and Chinese women having significantly lower estradiol than African Americans, Caucasians, and Hispanic women (Randolph et al., 2003). Lower estradiol levels, or perhaps lower variability in estradiol levels, may account in part for the lower prevalence of vasomotor symptoms among Chinese and Japanese women. While SWAN data show higher rates of vasomotor symptoms among overweight or obese perimenopausal women, the issue of weight or BMI and hot flashes is inconsistent across the literature. However, the effect of BMI may differ in perimenopausal and postmenopausal women since perimenopausal women have more ovarian function than postmenopausal women.

In terms of lifestyle factors, smoking has been shown in a number of studies to be associated with significantly increased reporting of hot flashes. The relationship between hot flashes and physical activity is inconsistent across studies but largely shows no effect. SWAN found variable effects of dietary phytoestrogens or supplements on hot flashes, while clinical trials of their effects have been inconsistent in their results.

[2] The mean age of the SWAN cohort at baseline is less than the mean age of menopause since investigators were collecting data throughout the menopausal transition.

Preliminary data from the Women's Healthy Eating and Living (WHEL) trial show high rates of vasomotor symptoms among breast cancer survivors (Gold et al., in preparation). The 3,088 participants in the WHEL trial were recruited at several sites. All had stage I, II, or IIIA breast cancer. Women were randomized to a plant-based dietary intervention or NCI's "5 A Day" program. After excluding women who had recurrences of breast cancer, who started or stopped tamoxifen therapy, or who started or stopped phytoestrogen supplements in the first year, hot flashes were examined in 2,040 participants. The mean age at entry was 54.0 years, slightly older than SWAN participants. Of the women who were either naturally or surgically postmenopausal, nearly 90 percent reported hot flashes. Reporting of both mild and moderate to severe vasomotor symptoms was higher for women receiving chemotherapy, and symptom reporting was higher in WHEL than in SWAN. After one year, a majority of the women reported no change in vasomotor symptom severity, while a quarter reported decreased symptom severity. Variation in rates of hot flashes appears to be related to when women experience menopause, either natural or medically or surgically induced. Vasomotor symptom reporting was higher in breast cancer survivors with higher BMI, and other risk factors for hot flashes were similar to those found among healthy women.

Hot Flashes in Prostate Cancer Survivors

Charles L. Loprinzi, M.D., Mayo Clinic

Hot flashes are a common and potentially chronic problem in men with prostate cancer who undergo androgen deprivation therapy (ADT). This is a major quality of life issue for a significant proportion of men receiving ADT.[3] Back of the envelope estimates find that more than 150,000 men in the U.S. have hot flashes associated with ADT therapy. This estimate assumes 220,000 new cases of prostate cancer each year in the U.S., 35 percent of which will receive ADT. Of men receiving ADT, 75 percent report hot flashes for an average three years. Thus, 222,000 x 0.35 x 0.75 x 3 yields 173,750 men with a history of ADT treated prostate cancer reporting hot flashes during a three-year period. Although there is a dearth of good data on men's experience with vasomotor symptoms, several clinical reviews suggest that 60 to 80 percent of men with ADT complain about hot flashes. Almost 50 percent complain about them after 5 years and approximately 40 percent after 8 years. Thus, hot flashes are a common problem in this population and can persist for years.

There are a number of treatments for hot flashes that appeared to have similar effects in men and women. Decreases of hot flash frequencies in women treated with clonidine are approximately 10-15 percent greater than that seen with placebo. In a double blind, cross over study of clonidine to reduce self-reported hot flash frequency in men, a similar effect was seen, but the difference from placebo effect was not statistically significant. Research has found virtually identical results for men and women receiving megestrol acetate for hot flashes, with approximately an 80 percent reduction in self-reported hot flash frequency compared to a 20 percent reduction with placebo. Newer antidepressants (e.g., venlafaxine, paroxetine) have also been tested and in nonrandomized pilot

[3] Stearns and coworkers report that the natural history of hot flashes in men, including variation in severity and frequency, has not been widely studied. "Almost 70 percent of men who undergo surgical orchiectomy report hot flushes. About 70 to 80 percent of men on long-term androgen suppression have hot flushes, and 30 to 40 percent of these patients report that symptoms are a major source of discomfort" (Stearns et al., 2002:1854).

studies appear to produce similar results in men and women with respect to lowering self-reported hot flash frequency.

Longitudinal Data: Factors Predicting Absent or Prolonged Hot Flashes

Lorraine Dennerstein, Ph.D., University of Melbourne (Australia)

The longitudinal phase of the Melbourne Women's Midlife Health Project began with 438 participants drawn from a baseline sample of 2,001 Australian-born Caucasian women in 1991. Participants were required to have an intact uterus and at least one ovary, a menstrual period in the last 3 months, and no history of hormone therapy use. It took about 9 years of annual follow-up for approximately 50 percent of the women to complete their menopausal transition. The period of greatest change in terms of hormones and reproductive aging coincided with the late menopausal transition phase and continued until women were one year after their final menstrual period. Beginning in the early menopausal transition period until about one year after menopause, there occurred a significant decline in estradiol and a sharp increase in FSH. The only significant changes in symptoms reported during this period were a decrease in breast soreness and increases in trouble sleeping, night sweats, dry vagina, and hot flashes (Dennerstein, et al. 2000). In this sample of women, hot flashes were the third most frequently reported symptom during the late menopausal transition, after aches/stiff joints and lack of energy. The study has found a significant relationship between hot flash reporting and lower estradiol levels (Guthrie et al., 1996; Dennerstein et al., 2000).

Bothersome hot flashes are frequently associated with the approach of the final menstrual period. Guthrie and coworkers (2003) found a prevalence rate of bothersome hot flashes of approximately 15 percent among women until two years prior to their final menstrual period. The prevalence rate then increases, reaching approximately 50 percent for women by one year after their final menstrual period. It is notable that it takes more than 4 to 7 years for the prevalence of hot flashes to return to the background level of about 15 percent.

Discussion

Dr. Nancy Avis reported results from the Massachusetts Women's Health Study (MWHS). Dr. Avis and colleagues used longitudinal data to examine premenopausal factors that predicted subsequent hot flashes (Avis et al., 1997). In the MWHS, they found a wide range for the duration of hot flashes, with some women reporting hot flashes or night sweats for as many as six years. However, other women reported going through menopause without any hot flashes. When looking at factors that predicted hot flashes, they found that women who reported more symptoms in general prior to menopause subsequently reported more hot flashes and night sweats. They also found that smoking, a long perimenopause, more negative attitudes toward menopause, and lower education were related to increased hot flash reporting. Women who were most bothered by hot flashes or night sweats had them at greater frequency, were current smokers, or were divorced. They did not find a relationship between hot flashes and exercise but noted that only a small percentage of women in the MWHS sample exercised regularly.

Objective Measures of Hot Flashes

An ideal objective measure for hot flashes should correlate well with self-reported data, be specific to hot flashes, and usable under ambulatory conditions (Freedman, 1989). The physical changes that accompany hot flashes are generally conceptualized as endocrinological and physiological in nature. This would focus measurement strategies on hormone levels, body temperature, skin conductance, and the like. However, similar hormone profiles are found in symptomatic and asymptomatic women, and changes in temperature - whether measured on skin or internally - are not specific to hot flashes. To date, only sternal skin conductance has been demonstrated to be specific to hot flashes and stable under varying conditions. The presentation and discussion of objective measures of hot flashes focused on what is currently known about the endocrinology and physiology of hot flashes and existing measurement tools and what additional information and tools would be needed for improvement.

Endocrinology of Hot Flashes

Lorraine Fitzpatrick, M.D., Mayo Clinic[4]

The scientific understanding about the pathophysiology of hot flashes is less developed than one might wish. Dr. Fitzpatrick underscored this point by showing the results of a Medline search for the time period 1966 through October 2003. That search identified 486 articles pertaining to "hot flashes," 35,993 articles pertaining to "pathophysiology menopause," and only four articles that included both terms. As a practicing clinician, she pointed out through a series of vignettes how different treatment approaches may be required depending on a woman's age and diagnosis of risk factors, including whether she is naturally menopausal or surgically menopausal, a breast cancer survivor, or has coronary artery disease. The proper treatment approach is best informed by good measurements, which will also facilitate studies to understand their origins, prevalence, frequency, and response to different treatment approaches.

The precise trigger of hot flashes is not known. Estrogen withdrawal (not just deficiency) is not solely responsible for hot flashes since there appears to be no correlation between estrogen levels and vasomotor symptoms. Additional evidence includes the observation that clonidine reduces hot flashes without changes in estrogen levels and that hot flashes can occur in the last trimester during pregnancy when estrogen levels are high (Freedman, 2000). Similarly, looking at gonadotropins, no differences in LH levels have been found in women with and without hot flashes. There appears to be a temporal relationship between LH pulses and hot flashes. However, women with GnRH deficiency or who were hypophysectomized had no circulating LH but did report hot flashes, thus raising questions about the certainty of the relationship between LH and hot flashes. Many studies have shown hot flashes to be preceded by several biochemical changes, such as increased LH, ACTH, and GH, and increased cortisone afterwards, although the significance of these changes is not entirely clear. Overall, we need to know more about whether hormones affect the onset of hot flashes, and how. Also, we may need better tools, including measures of hormones, to accomplish this goal.

[4] Since the conference, Dr. Fitzpatrick has moved from the Mayo Clinic to Amgen. Her address listed in Appendix 2 is her current address.

Opiates and other psychoactive substances have been implicated in the pathophysiology of hot flashes in some studies, but findings are not consistent (Freeman, 2000). For example, alcohol-induced hot flashes have been found to occur in patients taking chlorpropamide, which is related to opiate receptor activation. Naloxone infusion has been found to reduce hot flashes and LH pulse frequency, which suggests a possible relationship between hot flashes and LH levels. Depending on the study, B-endorphin levels have been found to decrease or increase preceding hot flashes.

More recently, catecholamines have been implicated in the onset of hot flashes. Norepinephrine is known to be important for thermoregulation (Freedman, 2000). Placing norepinephrine into the preoptic hypothalamus causes peripheral vasodilation, heat loss, and decline in core body temperature. There is evidence that gonadal steroids modulate central noradrenergic activity. And some elegant studies show that the brain metabolizes norepinephrine (MHPG) at higher rates in symptomatic women than asymptomatic women (Freedman, 1998). This may implicate a role for norepinephrine in the triggering of hot flashes.

In terms of specific catecholamines, clonidine reduces central noradrenergic activation and hot flashes, as measured by a reduction in heating time and number of hot flashes (Freedman et al., 1990). It also is associated with reduced levels of the norepinephrine brain metabolite MHPG. However, the alpha-2 antagonist, yohimbine, increases central noradrenergic activation and the number of hot flashes.

Estrogen comes from various sources in the body, and estrogen is associated with a stable thermoregulatory set point. At menopause, when estrogen levels are declining, this stability may be compromised, and hot flashes may result. However, as noted in the epidemiological presentations above, external factors can also appear to influence the occurrence of hot flashes and may have an effect – direct or indirect – on the underlying thermoregulatory mechanism. The conundrum is whether the external factors, such as socioeconomic status, are linked to hormone levels or neurotransmitters or another part of the underlying physiological processes associated with hot flashes. For example, stress, psychological factors, smoking, and alcohol may all have effects on serotonin levels.

There has been some discussion about whether norepinephrine, serotonin, and endorphins may be responsible for hot flashes. Studies have shown that estrogen withdrawal increases norepinephrine, decreases serotonin, and decreases endorphins. Estrogen withdrawal causes hypersensitivity of 2a receptors to any amount of serotonin, which might explain the hyperthermia as a result of estrogen regulation.

Core body temperature (Tc) has a circadian rhythm that also appears to affect hot flash frequency (Freedman 2000; Freedman et al., 1995). Using 24-hour ambulatory monitoring of sternal skin conductance, skin temperature and core temperature, investigators have observed that a majority of hot flashes are preceded by elevations in Tc. Core body temperature levels were generally lower in symptomatic women between midnight and 4 a.m. Therefore, there is an associated circadian shift with hot flash frequency. Similarly, there appears to be a relationship between thermoregulation and sleep. In addition to finding hot flashes to be associated with EEG-documented nighttime waking episodes, postmenopausal women with hot flashes have more stage 4 sleep. The number of hot flashes 2 hours before sleep correlates with the amount of stage 4 sleep. The percentage of time in stage 4 sleep was greater in neutral and warm conditions in symptomatic women.

There are many treatment options available to manage hot flashes, including vitamin E, evening primrose oil, soy isoflavones, dong quai, red clover, black cohosh, ginseng, yam cream, Chinese medicinal herbs, naloxone, propranolol, progestins, androgens, tibolone, alpha-adrenergic agonists, anti-dopaminergic agents, bellergal, SSRIs, SERMS, gabapentin, and others. Current research suggests that many purported treatments do not work well, if at all, and safety has not been demonstrated for all treatments. Other therapies work well but are not as efficacious as estrogen. Still others might work very well, but studies are needed to evaluate them. Successful efforts to target the development of new interventions depend on better understanding of the pathophysiology of hot flashes, which we currently lack.

Physiology of Hot Flashes

Robert Freedman, Ph.D., Wayne State University

As noted earlier, hot flashes are the most common symptom of the climacteric. The sudden sensations of intense heat with sweating and flushing typically last 5 to 10 minutes, but they have been reported to last as long as an hour, depending on how they are defined. In general, hot flashes can persist for 1 to 5 years, although they have been known to occur in 70 and 80 year old women.

Dr. Freedman presented data on 77 hot flash events reported by 12 symptomatic women. His research team measured a number of physiological parameters associated with hot flashes.[5]

1. Skin temperature was assessed at four different sites around the body. The mean skin temperature increased a few degrees centigrade during the few minutes surrounding the hot flash. In earlier work, Freedman (2000:216) reported that "Peripheral vasodilation, as evidenced by increased skin temperature, occurs during hot flashes in all body areas that have been measured. These areas include the fingers, toes, cheek, forehead, forearm, upper arm, chest, abdomen, back, calf, and thigh. Finger blood flow, and hand, calf, and forearm blood flow also increase during hot flashes." (See also Freedman, 1998.)
2. Core body temperature (Tc) was recorded with an ingested telemetry capsule. Small but significant core temperature elevations preceded 60 to 65 percent of symptomatic women who underwent ambulatory monitoring for 24 hours. Increase in Tc also preceded 76 percent of menopausal hot flashes recorded under controlled laboratory conditions (Freedman, 2000:217). (See also Freedman et al., 1995.)
3. Metabolic rate was measured by indirect calorimetry, which increased significantly during the period surrounding the hot flash. The reason for such an increase is unknown, but an increase in metabolism does not seem to explain the increased temperature associated with hot flashes (Freedman, 1998).
4. Sweating is measured by hygrometry. Measurable sweating has been found to occur during 90 percent of reported flashes, and there is a close temporal correspondence between hygrometry and sternal skin conductance monitoring of hot flashes (Freedman, 2000: 217; Freedman, 1998).

[5] Freedman noted that his samples frequently include women with severe hot flashes. His samples generally are recruited through newspaper advertisements. For example, the advertisement for a sleep and menopause study sought post-menopausal woman aged 45 to 60 experiencing frequent hot flashes (6 or more in 24 hours). One woman reported 39 hot flashes in a single day. Eligible women had a BMI under 30 (women with a BMI greater than 30 tend to have apnea), were taking no medications, and used no illicit drugs.

5. Modest increases in heart rate, by approximately 7 to15 beats/min, occur at the same time as the peripheral vasodilation and sweating (Freedman, 2000:218; Freedman, 1998).

Sternal skin conductance has been found to be the most sensitive and specific marker for hot flashes. Tataryn and colleagues (1981) found a strong correlation between sternal skin conductance and subjective reports of hot flashes. The correlations between hot flashes and other parameters measured, such as finger and tympanic temperature, were weaker. When he set a threshold level of ≥2 μmho/30 sec for sternal skin conductance measures of hot flashes, Freedman (2000:218) found a 95 percent concordance between the skin conductance and self reported hot flashes. (See also Freedman, 1989.)

Many studies have shown that estradiol (E2) levels in plasma, urine, and the vagina do not differ between symptomatic and asymptomatic women (Askel et al., 1976; Stone et al., 1975; Hutton et al., 1978; Freedman et al., 1990; Freedman et al., 1995; Freedman and Krell 1999; Freedman and Dinsay, 2000). A decline in E2 is necessary but not sufficient to explain the occurrence of hot flashes in women. The study by Hutton and coworkers (Hutton et al., 1978) collected 24-hour serial blood samples for E2 and estrone (E1) from one woman. Neither E2 nor E1 levels showed a correlation with her self-reported hot flash symptoms.

A temporal correspondence between luteinizing hormone (LH) pulses and hot flashes has been studied. However, it should be noted that women without a pituitary also report hot flashes, so LH pulses are now viewed as epiphenomenal, not causal. Although significant elevations in metabolic rate (as measured by respiratory exchange ratio) and mean skin temperature coincided with increased sternal skin conductance, Freedman has concluded that, taken together, "the present findings demonstrate that Tc elevations preceding most hot flashes are not caused by peripheral vasoconstriction or increased metabolic rate…the data are consistent with the hypothesis that hot flashes are triggered centrally by noradrenergic activation, possibly originating in the hypothalamus" (Freedman, 1998: 336). However, no one knows why Tc increases approximately 30 minutes prior to a hot flash recorded by sternal skin conductance tests.

Dr. Freedman's initial working hypothesis was that the decline in E2 levels modulated the central alpha adrenergic system that caused the release of a neurotransmitter, probably norepinephrine, which in turn triggers hot flashes. Freedman tested the effect of clonidine and yohimbine on hot flashes (Freedman et al., 1990). In a series of experiments, Freedman demonstrated that the occurrence of a hot flash incurred with body heating was delayed after women were given 1 μg/kg of clonidine. No such delay was seen in women receiving the placebo. Conversely, intravenous administration of yohimbine at a dose of 0.034 mg/kg in 13 symptomatic women stimulated a hot flash while no responses occurred in women receiving the placebo or in 8 asymptomatic women given successively higher doses of yohimbine.

Freedman drew blood to measure plasma levels of 3-methoxy-4-hydroxy-phenylglycol (MHPG), a metabolite of norepinephrine (Freedman, 1998). Levels of MHPG were assessed in 13 symptomatic women at the beginning of an objectively measured hot flash and one hour later. In addition, blood was drawn from 8 asymptomatic women at matched times. Freedman found that MHPG increases significantly during hot flashes but did not occur with controls. In replicating the finding of increased plasma MHPG levels in symptomatic women during the flashes, Freedman found no change in vanilmandelic acid (VMA), a catecholamine metabolite.

Since sweating is a heat dissipation response, scientists have posited that hot flashes and associated sweating could be triggered by Tc elevations. Under normal thermoregulatory conditions, humans have a thermal neutral zone. When Tc drops past the lower limit of the thermal neutral zone, shivering is induced. When Tc is elevated above the upper limit of the thermal neutral zone, sweating, and peripheral vasodilation ensue. If the hypothalamus senses Tc increasing, the body will dissipate heat through vasodilation and sweating. If the body gets too cold, vasoconstriction occurs and shivering will act to raise Tc. Freedman's research has found that the thermoregulatory zone for symptomatic menopausal women has essentially collapsed to 0 degrees, whereas among asymptomatic women, it was 0.4 degrees, which is similar to that found among younger women and men (Freedman and Krell, 1999).

Interestingly, Molnar (1981) and Kronenberg and colleagues (1984) did not find Tc elevations prior to hot flashes, using rectal and esophageal measures of temperature. Freedman's lab used a more rapidly responding radio-telemetry pill to record Tc in relationship to hot flashes and monitored subjects over 24 hours. Scientists have known for several centuries that body temperature has a circadian rhythm. Freedman found a significant circadian rhythm for hot flashes as measured by sternal skin conductance (Freedman et al., 1995). While there are similarities with changes in Tc over 24 hours, the pattern for hot flashes is slightly different. Similarly, there are circadian differences found when symptomatic women are compared with asymptomatic women. Tc declines at night among symptomatic women, which can be related to night sweats that lower Tc. In aggregate, the data show a small but significant increase in Tc before hot flashes, followed by a drop in Tc. The drop in Tc is approximately three times greater than the rise in Tc that precedes the hot flash. Ambient temperature was stable, so it was not a contributing factor in this study of Tc. These findings were replicated in a laboratory-based sleep study. For 8 symptomatic women, Tc increased significantly prior to hot flash; there was no rise in rectal temperature, but skin conductance data showed a characteristic rise followed by a decline.

Freedman's theory on hot flashes is therefore based not on Tc elevation but on the thermoregulatory system. The thermal neutral zone is significantly narrowed in symptomatic women. Increase in Tc acting within a very narrow - if not nonexistent - zone is believed to trigger hot flashes in women when they hit the "upper" threshold. Scientists are still working to understand how that zone becomes so narrow. Elevated levels of brain norepinephrine are believed to narrow the zone, as seen in studies of rats, rabbits, and guinea pigs. No such studies have been conducted in humans. Similarly, there are few data on MHPG in animals. It appears that clonidine widens the zone and yohimbine narrows it in humans. Selective serotonin reuptake inhibitors may play a role in modulating hot flashes, but the mechanism of action is unknown. Dr. Freedman posited that increased levels of 5HT in synapses leads to widening of the thermoregulatory zone in humans, as has been seen in rats.

More research is needed to understand the mechanisms and chains of events underlying hot flashes. It is difficult to tease out the interaction between hormonal changes and aging processes. Indeed, it is difficult to say which hormones trigger hot flashes.

The literature contains several studies that have collected sternal skin conductance data under ambulatory conditions. One of the first studies was a clinical trial of the effectiveness of paced respiration and progressive muscle relaxation to decrease hot flashes. Alpha wave EEG feedback

was used as the control, since it is plausible but physiologically not effective. Data for the 24-hour period before and after treatment show hot flash frequency declined by about half for women receiving only the paced breathing intervention (Freedman and Woodward, 1992). There was no change in hot flash frequency detected for those who also received the progressive muscle relaxation exercises or the alpha wave placebo.

In the next presentation, Dr. Janet Carpenter presented information on other studies that collected sternal skin conductance data under ambulatory conditions. However, it is clear that this objective measure of hot flashes is extremely useful in studies seeking to understand the basic physiology of hot flashes as well as the impact of proposed therapies. If we improve our understanding of the basic physiology of hot flashes, it may be possible to measure other related physiologic parameters in the future.

Comparison of Objective Measures to Self-Reported Data in Ambulatory Studies

Janet S. Carpenter, Ph.D., R.N., Indiana University

Dr. Carpenter began her presentation by noting the importance of both self-reported and sternal skin conductance data. Self-reported data are the only way to get information on severity of hot flashes and their interference with daily activities. However, self-reported data can be influenced by personality, mood, and intervention expectancy or placebo effects (Carpenter et al., 1999: 214). She has therefore used sternal skin conductance measures in her own research on hot flashes.

Accuracy and precision in measuring hot flashes are important for several reasons, including the ability to:

- Temporally relate hot flashes to other phenomena;
- Quantify strength of relationship with other phenomena;
- Examine physiological mechanisms;
- Document physiological versus perceived response to an intervention;
- Quantify intervention effect sizes;
- Compare effect sizes across studies.

Dr. Carpenter described the Biolog system for sternal skin conductance measures that she has used in conjunction with self-reported diaries to assess objective and subjective reports of hot flash frequency and impact on daily activities (Carpenter et al., 1999:210). The Biolog system is a lightweight, automated, ambulatory monitor that is worn around the waist or over the shoulder to sample skin conductance level (SCL) every second through leads that are attached to the sternum. The leads contain a potassium-based gel that is custom made by Dr. Carpenter's research team. The Biolog system stores up to 2 MB data internally and is capable of downloading to a PC via an interface box. Moreover, data analysis is possible using customized software. Additional options of the Biolog include the following features:

- The hot flash signal appears when SCL raises to the $\geq$2µmho threshold in 30 seconds.
- The machine can be programmed to produce a beep when this threshold is hit or to remain silent.
- Special battery and memory capabilities can now capture and store data for 7 days, which is helpful for capturing daily variability.

- Additional monitoring channels are available for measures of temperature, heart rate, EKG, and others.

Self-reported data on hot flash frequency can also be collected on the Biolog system. To indicate a perceived hot flash, a woman must press two red buttons simultaneously and hold them down for 3 seconds until she hears a beep to confirm that the event has been recorded. In the literature, this is referred to as event marking. The two-button procedure and three second threshold were developed to avoid inadvertent event marks or false events.

Dr. Carpenter then discussed the adequacy of the Biolog system for measuring symptom frequency. She has compared diary records, event-marked hot flashes, and Biolog recorded hot flashes based on sternal skin conductance. In comparisons of frequency, Carpenter discussed findings from a sample of breast cancer survivors (BCS). She cautioned that this sample may not be representative of populations of other women and may not be the best group for understanding physiological measures of hot flashes.[6] She found a substantial level of underreporting in self-reported measures of hot flashes (diary and event marked events) compared with objective sternal skin conductance measures during a single 24-hour period.

In her reporting on the use of sternal skin conductance monitoring in ambulatory studies, Dr. Carpenter noted "none of the participants reported problems with lead attachment. Leads were securely attached on all participants at the end of the 24-hour monitoring session, even in the presence of heavy perspiration among BCSs who were taking tamoxifen" (Carpenter, et al. 1999: 211). About one-third of subjects reported difficulties using the diary and the event marker during daily activities and during sleep. A much smaller proportion reported the monitor to be heavy or constrictive and feeling itchy where leads were attached to the skin. One participant reported some difficulty sleeping while wearing the monitor (Carpenter et al., 1999:212). This feedback suggested that there is a need to improve the Biolog system for use during both waking hours and sleep. In response, the maker of the Biolog (UFI, Morro Bay, CA) substantially reduced the size. The original monitor that was used in 1999 measured 5 x 7 x 1.5 inches and weighed 22 ounces. The newer monitor that has been used in subsequent research conducted by Dr. Carpenter measures 1.3 x 2.8 x 5 inches and weighs 8 ounces.

Specificity for self-reported measures is much better than sensitivity since the majority of women's time is spent in a non-flashing state. And under some conditions, there is good correlation between subjective and objective measures. Laboratory studies find up to a 100 percent concordance between objective and subjective measures, which is to say that every hot flash reported by the woman was validated by sternal skin conductance data. However, outside the laboratory, concordance decreases. Comparing diary data to sternal skin conductance data, Dr. Carpenter has found that approximately half (43 percent to 65 percent) of all objectively recorded hot flashes are not reported by women, raising questions about the accuracy of diary data on hot flash frequency. Accuracy, she noted, is not just a nighttime problem. Incomplete self-reports are found during waking hours as well. Dr. Carpenter has also found that comparisons between event markers, which date and time stamp data,

[6] It was noted that the circadian rhythm of hot flashes appears to be different in breast cancer survivors. Animal studies also indicate that chemotherapy and certain cancer treatments can alter thermoregulation. Self-reported data from cancer patients may also be different in that they have likely experienced a number of diagnostic procedures, medical treatments, and this may have heightened awareness of physical status or a different motivation structure for reporting health events. These factors may affect how vasomotor symptoms are perceived and reported.

operating in a similar fashion as electronic PDA diary devices, and sternal skin conductance data show similar rates of concordance (43 to 46 percent). Thus, from her data, these types of electronic diary devices are not necessarily more advantageous than paper diaries.

In comparing objective measures with event marks, correlation does not appear to be higher for events that are rated as higher intensity/bother (distress). One might assume that hot flashes recorded by sternal skin conductance but not reported by women may be milder events, but this has not been established empirically, primarily due to the lack of self-reported data on approximately half of all objective hot flashes recorded. Moreover, correlation between objective and subjective measures of flash duration is not good. Women described their hot flashes as subsiding much more quickly than recorded by the instrument. Thus, sternal skin conductance measures do not appear suitable for collecting data on duration, severity, and bother (distress) associated with hot flashes. The area under the curve produced by sternal skin conductance monitors does not differ when comparing hot flashes rated by women as severe or mild.

Dr. Carpenter examined the variability in objective data on hot flash frequency. Baseline within-person variability was calculated by subtracting the lowest frequency reported from the highest frequency in a specific time period, dividing by the mean frequency, and multiplying by 100. Using this formula, Dr. Carpenter found a mean variability of 46 percent, with a standard deviation of 44 percent. It is not clear why such variability occurs. This variability seems to be as great or greater than previously reported placebo effects but comparable to previously reported intervention effects (Sloan et al., 2001). This level of variability presents significant problems in assessing intervention effectiveness.

Dr. Carpenter described a randomized, cross over, placebo-controlled study of magnet therapy for hot flashes (Carpenter et al., 2002). Data from this study showed a significant decrease in objective measures of hot flash frequency in the placebo group. Another ongoing intervention study using both subjective and objective measures may show placebo effects, as well.

In summary, the clear strengths of the Biolog system are its physical characteristics (small size, lightweight, portability), ability to capture data on hot flash frequency during waking hours and sleep, and ease of data analysis. Few subjects report problems using the monitor. However, leads can become detached, and there have been cases where the monitor has been turned off inadvertently, which results in uninterpretable data even if the machine is turned back on. Moreover, if dropped, the monitors must be sent back to the manufacturer to be recalibrated, but they can often recover data collected prior to being dropped. The costs for these systems may be problematic for large-scale studies. Costs include the monitor itself, software, gel, chemicals, electrodes, and training for personnel to make up gel and clean and load electrodes, connect and disconnect participants, download, and analyze data. Analysis time has decreased with new software capability. It used to take 4 to 6 hours to analyze one 24-hour session; it now takes Carpenter's team less than 30 minutes to do so. Cleaning the electrodes and making the gel is a time consuming, tedious task, but is not difficult.

Discussion

Nanette Santoro, M.D., Discussant

Dr. Santoro grouped her comments into three areas. First, experimental models with controls are very helpful for understanding how and why menopausal women and subsets of men get hot flashes. It may be valuable to look to additional populations, such as young women and women with perimenopausal hot flashes, as well.

Second, both subjective and objective measures of hot flashes are needed. Self-reports are especially important for other areas, such as pain management, and will be important for some aspects of hot flashes as well, particularly because women's perceptions of hot flashes affect their quality of life and treatment-seeking behavior. Being able to capture change in hot flash distress and perceived severity/bother, even in the absence of change in frequency, might be a victory in itself.

Third, it is important to make sense of the clinical experience. Some people have learned to adapt to their hot flashes even without verbalizing their discomfort (for example, a woman who starts to layer her clothing, perhaps avoiding turtlenecks and switching to camisoles). The impact of hormones appears to differ across women. Some women, particularly those with more severe symptoms, may represent the women who tolerate small changes in estrogen poorly and, thus, need pharmacologic help. Patients being treated with SSRIs report diminished levels of aggravation. In populations reporting drug abuse, there could be a misattribution of hot flash symptoms to drug withdrawal, which in turn could lead to increased drug use. Clonidine has been used to treat hot flashes and is also used to treat heroin withdrawal. This points to a possible connection among mood disturbances, drug abuse, and brain responses.

A fundamental issue is understanding what is being reported. Individuals may be equating a hot flash with the rush of heat, but it is not clear that everyone is referring to the same sensations. Some women are probably reporting hot skin, others sweating, or discomfort. The FDA guidelines differentiating between mild, moderate, severe, and very severe hot flashes are based on assessments of sensation of heat with perspiration. However, these measures are not based on empirical data. In some cases, the levels assigned by women subjectively appear to be generally consistent. Women seem to reliably describe their hot flashes as mild, moderate, or severe (Frick, 1998). In other cases, individual variability in sensitivity was pronounced when self reported data were compared to objective markers. Some women registering very strong physiological symptoms rated their symptoms as mild. Differences by population characteristics may also affect sensitivity to vasomotor symptoms. For example, some studies have shown that negative affect in cancer patients is correlated with symptom reporting. In general, breast cancer survivors report more frequent, severe, and bothersome hot flashes. Those with severe hot flashes also report greater negative affect (Carpenter et al., 2002). Abrupt menopause tends to produce more aggravation with symptoms. We need to clearly differentiate what is being measured, and it seems certain that subjective severity must be paired with objective measures of frequency to complete the picture.

It is also important to consider whether reporting of severity of symptoms depends on context. A hot flash event in a very public setting may be reported as much more severe than one that occurs in the privacy of one's own home. Without social and contextual data, it is difficult to interpret reporting of severity or intensity. Reports of severity or distress (bother) may depend on the extent to which a person is focused on the problem.

As evidence the importance of context in which measurement occurs, Dr. Carpenter reported 34 to 36 percent concordance between objective measures of hot flashes and diary entry during a 24 hour

ambulatory monitoring (Carpenter, unpublished data). A similar study that relied on in-patients in a laboratory found a concordance rate of 65 percent, with 17 to 18 percent false-positive rates in both studies. The higher concordance in the laboratory setting may be related to the controlled environment, the same ambient temperature, lack of movement or exercise, the lack of distraction away from internal sensations, increased adherence to reporting of perceived hot flashes, and awareness of the fact that they were being studied for their hot flashes.

Dr. Thurston added that her ambulatory study produced similar correlations between objective and subjective measures as those described by Dr. Carpenter (Thurston et al., 2004). However, these rates of hot flash reporting can vary sizably across both women and situations. Psychological factors, including stable individual differences as well as more transient psychological states, can affect whether or not a hot flash is perceived (Thurston et al., 2004). Therefore, it is possible that intervention studies that affect psychological factors, such as SSRIs, may influence the perception of the hot flash more than the actual flash. It is impossible to disentangle these two processes with sole reliance on self-reported data, and the use of dual measurements may be important to understand the mechanism by which these interventions are operating.

Freedman noted that emotional flushing is distinct from hot flashes. The sternal site was selected for measuring hot flashes because it is insensitive in most cases to emotional response (which usually triggers sweating in the soles of the feet and the palms of the hands). It is also a suitable place for attaching electrodes. Changes in sternal skin conductance have been observed when women exercise; however, the pattern produced on the data recording instrument by exercise is very different from the pattern produced by a hot flash.

Investigators have found false positive self-reports (Thurston et al., 2004). That is, a woman reports a hot flash but the sternal skin conductance monitor does not register one. Other sensations may be misperceived as hot flashes. Some breast cancer survivors, as well as naturally menopausal women, complain about losing the ability to discriminate between a hot flash and just being hot. This may be related to becoming desensitized from the chronic condition of having hot flashes. And, certainly, there are other activities and states that may produce heat or sweating. As noted earlier, the converse of false positive self-reports is more common. That is, a much larger proportion of women fail to report hot flashes that are picked up by sternal skin conductance, indicating that over-reporting is not a large problem. However, it is unclear if study participants don't perceive the missed events or if they are perceived but not recorded. Participants in ambulatory studies have commented that they were not rigorous about noting all events in their diaries or hitting the event marker for each symptom, but often this occurred because they are too busy doing other things. Similar rates of missed events are seen in women using event buttons on sternal skin conductance monitors and paper and pencil diaries (Thurston et al., 2004).

Additional discussion centered on sleep disturbances and hot flashes. Women may or may not misattribute their wakefulness or sleep disturbances to night sweats. The data are not entirely clear on this point. However, it was noted that sleep architecture changes with age. Thus, it is unclear if changes in sleep patterns reported by menopausal women are related to vasomotor symptoms or normal aging. Similarly, Dr. Thurston noted that sleep disturbance can be related to other factors, such as depression, anxiety, and daily stress Thurston et al., 2004). Dr. Dennerstein hypothesized that melatonin shifts through the menopausal transition could affect sleep.

Dr. Dennerstein added that data from her longitudinal study indicate a decline in negative mood through the menopausal transition. Wellbeing improves even though more hot flashes are reported (Dennerstein et al., 2002).

Promising Sensor Technologies

Two different types of technology appear to be of prime interest for hot flash research: (1) small, cheap, easily produced for ambulatory studies; and (2) more complex, perhaps more expensive, to help explicate the basic underlying processes related to hot flashes. The engineers discussed different types of technologies currently available and promising technologies that might be explored for future measures of hot flashes.

Introduction

John Webster, Ph.D., University of Wisconsin

There are several ways to categorize biologic measurement systems, such as invasive versus noninvasive, ambulatory versus laboratory based, and the like. Some systems are clearly more preferable to subjects than others. (The group noted that subjects willing to undergo many study procedures almost always avoided rectal temperature probes.) Studies of hot flashes have collected data on physiological measurements in several ways, each of which has its strengths, limitations, and possibilities for improvement:

- Sternal skin conductance system - simple, inexpensive, presently pocket-sized, could be miniaturized.
- Respiratory exchange ratio - complicated, expensive, relatively large equipment.
- Skin temperature - simple, inexpensive, slow response to change, could be miniaturized.
- Core body temperature - radiotelemetry pill, currently available.
- Sweat rate (mg/(cm2·min)) – complicated.
- Self reported data - button presses to record events.

Current measures capture the frequency or occurrence of hot flashes but do not capture information on intensity, duration, or interference with daily activities or impact on quality of life. The current methods are based on symptom detection, but there may be other indicators that would be useful (e.g., chemical composition of sweat, hormone levels, circulating metabolites of brain norepinephrine).

Extremities and skin can become warm for a variety of reasons, hot flashes being only one such cause. Thus, skin and optical measures (e.g., tools to detect skin color changes by spectrophotometry, laser Doppler skin blood flow, fluorescence, and luminescence) may not provide good measures since they are not specific to hot flashes.

Chemical measures that might be added at greater difficulty and expense and might include:

- Endocrine profiles
- Sweat composition
- Lactate
- pH
- PO_2

- CO_2
- Antibody sensors
- Electrophoretic measurement of glucose

Bioengineering holds great promise for improving measures. Indeed, measurements for other physiologic parameters have already experienced significant breakthroughs. Table 1 summarizes the available measures and notes their usefulness overall and usefulness in ambulatory studies.

Table 1: Hot Flash Measurement Tools

Measurement	Method	Usefulness	Availability	Comments
Acquiring data	Sensors	Yes, if specific	Currently available	Need right sensor
Processing	Electronics	Minimize interference	Currently available	Filtering
Storing	Computers	24 h of data	Currently available	Very small
Presenting	Numbers or graphs	If desired	Could be put on Palm Pilot or similar device	Can present to patient or investigator
Holter monitor	Used for ECG	24 h of data	Currently available	Could measure anything
Telemetry	Like a telephone	If needed in real time	Currently available	Swallow able temperature pill
Sternal skin conductance	Electrodes and recorder	Yes	Currently available	Fast response, specific
Color	Spectrophtometry	Unknown	Could be	Detects flush
Chemical analysis	Selective electrode	Unknown	Sensor chip	Skin sweat
Acceleration	Strain gage	Unknown	Sensor chip	Activity
Humidity	Electrical conductance	Unknown	Sensor chip	Skin sweat

Potential Sensor Technologies for Hot Flash Research

Jerome Schultz, Ph.D., University of California, Riverside
Michael Neuman, M.D., Ph.D., Michigan Technological University

In addition to the categories of biologic measurements noted above, measurement systems can focus on a number of parameters, including (1) physical, such as temperature and conductivity, (2) physiological, such as blood flow and skin color, and (3) biochemical, such as of metabolites and hormones.

Some measurements are made with sensors, and there are literally hundreds, if not thousands, of sensors that are currently available. Increasingly, sensor technology relies on micro sensors, which can capture data on multiple systems, such as pulse, blood pressure, body temperature, and blood oxygen. Such monitors of physiologic status are of interest to the military to monitor the health

status of troops, athletes to monitor performance, and individuals to monitor their health status. Other examples of sensors include those developed to measure skin hydration by opto-thermal decay lifetime; chip-based micro spectrophotometer and multispectral analysis of skin surface; the Microvascular Perfusion Smartshirt with breadboard connections woven into cloth for mounting sensor elements; physiological monitoring by acoustic signal processing; Cyranose, which is comprised of individual thin-film carbon-black polymer composite chemiresistors that are "trained" to detect specific characteristics using analytical and statistical techniques.

Biosensors must combine a sensor with a transducer to get a signal. There are hundreds of different biomolecules that can be used to detect certain substances. There have been only two noninvasive sensors for biochemical monitoring: a pulse oximeter that measures the amount of oxygen in the blood, and a hematocrit measurement system for bilirubin in infants. The noninvasive hematocrit measurement system for bilirubin is based on principle component analysis of curves that change with pH, oxygen, red blood cell counts, and the like. The challenge is to develop a sensor that can succeed both scientifically and commercially. As one example, Spectrx measures glucose through continuous sampling of extremely small amounts of interstitial fluid. The device is practical and competitive, and relies on a finger-pricking device. A hormone sensor could apply the same logic, with subcutaneous placement of a biosensor with external monitoring. Skin surface temperature, skin electrical conductivity, photoplethysmographic pulse, and skin color can be easily sensed. Some of the noninvasive measurement systems pose a few more difficulties in their development but may be more acceptable to subjects. It is conceivable that sensors could be miniaturized to take multiple and simultaneous measures over periods of time.

Dr. Schultz concluded by mentioning two existing systems that might be applicable to the study of hot flashes. Psychologists developed skin thermal conductivity, which is related to perfusion. The sensor for this technology is slightly warmer than the skin, and the instrument essentially measures heat transfer, which is proportional to perfusion of that tissue. This is not too complicated to build and might be interesting to investigate as a potentially useful tool to capture data on hot flashes. Transcutaneous arterial oxygen (TAO) tension was a popular device among neonatologists in the 1980s. This technology already exists, the sensors are simple, and it can be integrated into several measurement devices.

Dr. Neuman shared his experience from the Collaborative Home Infant Monitoring (CHIME) study that might be relevant for ambulatory and home monitoring of hot flashes. He emphasized the need to keep the monitoring simple. Subject training and support (telephone, home, or clinic visits) must be provided in the use of the instrument, and steps must be taken to encourage compliance. He also added that equipment malfunction must also be anticipated. Desirable features of ambulatory monitoring instrumentation include its ease of application and removal, proper placement, and low maintenance; its small size, which would be unobtrusive to daily activities; reliability; and automated data collection capabilities.

Discussion

A practical question was raised about what data regulatory bodies, such as the Food and Drug Administration (FDA), require of clinical studies. It was pointed out that that FDA does not treat dietary supplements and behavioral interventions in the same way as pharmaceuticals. Currently self-report data is standard for clinical studies of hot flash therapies submitted to the FDA for approval. In February 2003, the FDA issued new guidelines for measuring outcomes of interventions

for hot flashes, requiring that therapies be tested in women with 7 or 8 hot flashes per day and those trials last 12 weeks or more. Because many more hot flashes are picked up by sternal skin conductance than are reported by women, interest in this measurement may increase, as it is sometimes difficult to recruit women with sufficiently frequent hot flashes.

Participants suggested a number of logical next steps to improve the objective measurement of hot flashes:

- Improve existing sternal skin conductance systems, making them smaller, cheaper, and easier to use.
- Identify other physiologic parameters that are specific to hot flashes but stable under other conditions and identify promising technologies that might be adapted to collect the relevant data.
- Determine if preliminary data from chip humidity sensors might be useful in capturing data on sweating.
- Improve self-reported items on severity of hot flashes.
- Improve our understanding of the basic processes underlying hot flashes.

Several people noted the current incomplete understanding of hot flashes and the need for refined tools. There is a kind of circular conundrum embedded in this issue. If we had better measurement tools, we may be able to increase our understanding of hot flashes. If we knew more about hot flashes, we might be able to decide which physiologic parameters warranted improved measurement tools. For example, the temporal relationship between propagation of what is happening in the skin and severity does not seem to hold. Approximately 30 seconds prior to a hot flash, skin perfusion is observed as blood flow increases. Blood flow changes faster than temperature, so changes in temperature may lag. However, there are additional problems with temperature since increases are not always related to a hot flash.

Participants also noted time constraints on measurement, experimental design, and subject participation. For example, in studies that use sophisticated imaging technology, subjects can only be monitored for approximately 30 minutes. In that amount of time and under those conditions, it is very difficult to guarantee that a hot flash will occur naturally, and it is difficult to monitor changes in other physiologic parameters, such as hormones. It would be very interesting to collect data on hormones, such as LH and estradiol, to more clearly define what is happening in the central nervous system during a hot flash. Similarly, it would be important to collect data on enzymes and catecholamine metabolism that can affect estradiol levels in the brain.

The SWAN study collects daily urine specimens that might be useful to examine variability in estrogen and metabolites. But there may be important subpopulation issues that need to be heeded. For example, estradiol may play a role in hot flashes, depending on whether a woman experienced a natural menopause or not. One investigator is now gathering data on estradiol and progesterone from blood specimens obtained with self-administered finger pricks that results in dried blood placed on a collection card, which is then sent to a central laboratory for analysis. One participant encouraged thinking broadly beyond estrogen to ovarian activity.

Other subpopulation differences that drive the presence or absence of hot flash symptoms may be related to genetics. It could be useful to start genotyping symptomatic and asymptomatic individuals. SNPs can be obtained from skin samples pulled from prepared adhesives; data from buccal smears or

cheek swab specimens have also been very useful. It is possible that estradiol and catecholomine responses have a genetic component. The SWAN and the Melbourne studies are both collecting DNA samples. SWAN also has a serum repository and daily urine samples. However, it should be noted that similar patterns of hot flash occurrence between mothers and daughters has not been demonstrated.

In summary, what we want to measure with respect to hot flashes is likely to change over time as more is learned about the underlying phenomenon of hot flashes. There is a current need for measures that are easier to use in ambulatory studies, and there is a desire to continue to refine and optimize performance characteristics of sternal skin conductance. The more that can be learned about the error structure in self-reported measures, the more useful those measures will be. It would be useful to integrate the improvement of objective and subjective measures. This is likely to be an evolutionary process, one involving decisions about what biological parameters 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, how to analyze the data to generate new hypotheses, and how to determine and prioritize the need for new measurement tools.

Self-Reported Data on Hot Flashes

Several people noted the lack of standard, well-characterized instruments to collect self-reported data on hot flashes. In the past, this has led to researchers generating their own measures in an ad hoc fashion. We need to know much more about the psychometric properties of existing instruments and their correspondence with objective measures if we hope to improve the quality of self-reported data.

Validity of Self-Reported Measures of Vasomotor Symptoms

Katherine Newton, Ph.D., Group Health Cooperative

The methods for collecting self-reported data of vasomotor symptoms are not complex. However, questions remain about the quality of data they produce. Dr. Newton began her presentation by asking the following questions concerning questionnaires and diaries used to collect these data. (1) Which instruments are most frequently used? (2) Which have received the best evaluation? (3) Are there ongoing or future activities to improve them?

Menopause Questionnaires

Dr. Newton briefly reviewed a number of menopause questionnaires, which are largely checklists of symptoms that could fall into several domains, such as vasomotor symptoms (sweats, flashes), vaginal dryness, somatic symptoms, psychological/mood, urinary problems, sleep, sexuality/libido, memory/concentration, and quality of life. Factor analysis consistently reveals that vasomotor symptoms are one factor related to menopause. Dr. Newton focused on the following four questionnaires that are used most often to inform the vasomotor domain.

The Kupperman/Blatt Index is frequently used in studies of interventions of hot flashes. It was developed in the U.S. in the 1950s, and originally it relied on physician ratings. However, now it calls for self-reported data from women and includes items on 11 menopausal symptoms, each of which is rated for severity on a 4-point scale (none to severe). Many other scales are compared with

the Kupperman/Blatt Index, since it is widely used, has face and context validity, and is responsive to change. However, there has been no formal evaluation of the Index, and it has been criticized for ill-defined terms, lack of reliability and validity assessments, lack of statistical justification for weights, absence of factor analyses to justify summary scores, and an absence of questions concerning vaginal dryness and libido (Adler, 1998). Although widely used, the Kupperman/Blatt Index requires further evaluation.

The Women's Health Questionnaire (WHQ) was developed in the United Kingdom in the 1980s for women between the ages of 45 to 65 years. It was intended to be primarily a quality-of-life instrument. It relies on self-reported information and is now available in 27 country-specific languages. It includes 36 items with 4-point response categories (definitely to not at all). Researchers can use this questionnaire once they have obtained permission, and the questionnaire is free to non-profit organizations. It has been used in studies resulting in 19 publications. It has been validated against the depressed mood subscale in the General Health Questionnaire (0.86) as well as the SF-36 mental health (-0.7) and vitality (-.65) scales. It shows high internal reliability (Cronbach alpha 0.7 to 0.84), high test-retest reliability (0.78 to 0.96), and is sensitive to change. It is also one of the few instruments that have undergone evaluation for psychometric properties. Perhaps most importantly, the WHQ allows for cross-cultural comparisons of the menopausal experience.

The MENQOL was developed for use among postmenopausal Canadian women between the ages of 47 and 62 years. It includes 29 yes/no items and is self-administered. Severity is rated using a 6-point scale (not at all bothered to extremely bothered). It is not widely used, despite quite extensive validation efforts.

The Menopause Rating Scale (MRS) was developed in Germany in 1996. It was tested in a sample of 306 mid-life German women, between the ages of 40 and 60 years. It was primarily intended to measure quality of life. The instrument is comprised of items on 11 symptoms and rates severity on a 4-point scale. The symptoms pertain to psychological, somatic, and urogenital systems. Domains have been determined using factor analysis. The instrument is available in 9 languages and relies on self-reported information. It has been tested for cross-cultural equivalence. The MRS does not appear to be widely used, although no formal permission is required to use it. Subsets of data from the MRS correlate well with Kupperman quartiles ($r = 0.91$), the SF-36 psychological ($r = -0.73$), and 14-day test-retest reliability test ($r = 0.82$).

All of the menopause questionnaires discussed above have been developed in Caucasian women. They are appealing in that they capture a variety of domains and characteristics in a single questionnaire. This is a decided advantage for large population-based studies. They are easy to administer. Standardization facilitates cross-study comparisons of data. The disadvantages are that no one domain is measured in depth, and measurement of vasomotor symptoms is minimal.

One basic question to be asked is whether or not we need a menopause-specific questionnaire. Most domains can be evaluated with existing and very well characterized questionnaires, such as those for depression, anxiety, and sleep disturbances. The domains that appear to be specific to menopause (although not unique to this population) are vasomotor symptoms and vaginal dryness. It may be more practical to simply add items on vasomotor symptoms to the other outstanding instruments.

Self-Reported Instruments for Vasomotor Symptoms

Daily Diaries

"Daily diaries are useful for collecting data on chronic conditions with recurring symptoms, such as asthma and headache, and on common recurring events, such as menstrual cycle phases and associated symptoms in pre- and peri-menopausal women. Diaries are also useful for recording events in clinical trials… Daily recording decreases recall errors and generally is preferable to a single retrospective measurement for such conditions" (Johannes, et al., 2000: 200). A hot flash diary is intended to record every hot flash. Some also collect information on severity of hot flashes (mild, moderate, severe), degree of bothersomeness, and duration. A variety of diaries have been used, and the methods employed are sometimes poorly described.

Electronic diaries can generate audit logs with date and time stamps for data entry. Electronic questionnaires can build in skip patterns and check for errors or inconsistent responses. This can lead to fewer missing data and eliminate separate data entry tasks, thus sidestepping transcription errors. Thus, electronic diaries may hold promise for improving data quality when compared with paper and pencil modes. The use of personal digital assistants (PDAs), like palm pilots or similar devices, have the advantages of being portable, allow instantaneous recording, prompts, reminders, definitions, and regular data downloading. Disadvantages to using PDAs include the need for programming or other technology, the expense, instrument malfunction or breakage, and perhaps computer anxiety. There has been no published literature on the use of this technology for recording vasomotor symptoms.

Sometimes diaries ask subjects to summarize events for a day, which would decrease the reporting load to once a day. This is the method developed by Loprinzi and Sloan to measure vasomotor symptoms in cancer patients (Sloan et al., 2001; Finck et al., 1998). Subjects were asked to summarize daily the number and severity (mild/moderate/severe/very severe) of hot flashes and to check any of a number of listed symptoms (such as appetite loss, sleeplessness, nausea, abnormal sweating, etc.) that they experienced over this time period. A score is computed by multiplying frequency times severity. The results of these calculated scores parallel data on hot flash frequency. Men and women reported similar results. The Loprinzi and Sloan daily diary method for data collection on hot flashes has been tested primarily on cancer survivors. It would be useful to see how this instrument performs in studies of other populations, such as women undergoing natural menopause or surgically induced menopause. Such measures are generally thought to be less precise than prospective diaries since they may be influenced by the most recent hot flash experienced, as well as other memory processes.

Distant Recall

Other studies have asked subjects to report vasomotor symptoms for a longer recall period, such as the last week or the last month. There is little literature on recall of hot flashes and how subjects perceive them months or years later. However, it is likely that the longer the recall period, the less precise the data will be. Moreover, cognitive psychologists would argue that it is hard to remember non-emotional events that happen frequently.

Scales

Dr. Carpenter's Hot Flash-Related Daily Interference Scale (HFRDIS) is a 10-item scale measuring the degree to which hot flashes interfere with 9 daily activities: work, social activities, leisure, sleep, mood, concentration, relations with others, sexuality, and overall quality of life (Carpenter et al., 2002:107). It has been validated in breast cancer survivors and has demonstrated convergent validity

with hot flash severity and bother (from hot flash diaries, r = 0.51 to 0.81). It has also demonstrated construct validity (positive correlation with mood disturbance and negative affect; negative correlation with vigor and positive affect). And it is sensitive to change in number of hot flashes over time. Its use has been limited, although it can be easily added to clinical or research-related hot flash assessment protocols. Dr. Carpenter is using the HFRDIS in an intervention study to see if it will be sensitive to intervention effects and can serve as a proxy for or adjunct to a daily diary system to measure hot flash frequency, severity, and bother.

In summary, Dr. Newton observed that diaries of frequency, duration, and intensity of symptoms are universally used, yet only the Loprinzi group has validated their diary. However, this diary has not been validated against sternal skin conductance monitoring. Questions remain as to whether daily diaries are blunt instruments or whether they provide an essential measure of the hot flash experience. The HFRDIS instrument measures one component, interference, which models ways in which we might look at other characteristics of vasomotor symptoms. Moreover, it is not clear how much is really gained from going beyond measures of hot flash frequency. However, one might argue that the degree of bother or interference associated with hot flashes might be the primary motivator for women to seek treatment.

The following questions may be important to consider in deciding whether and how to improve self-reported measures of hot flashes.

- How should self-report vasomotor symptom instruments be validated?
- What is the gold standard for hot flash frequency? Severity? Interference? Duration?
- What are the most important characteristics of hot flashes that we should be capturing?
    - Symptoms (heat, sweating, chills, palpitations, anxiety, others?)
    - Intensity
    - Frequency
    - Duration
    - Function/interference
    - Bothersome-ness
    - Meaning of symptoms to the subject
    - Actions taken
- Do characteristics of hot flashes vary with type of menopause? By population affected?
- Which characteristics are most troublesome? Memorable?
- How do different treatments affect the characteristics of hot flashes?
- How good is recall of vasomotor symptoms?
- Can intensity ratings be standardized?

<u>Herbal Alternative (HALT) Study</u>

The Herbal Alternative (HALT) study was launched to explore whether herbal therapies could bring relief for hot flashes by decreasing negative sensations, such as sweating, even if they couldn't decrease the frequency of hot flashes. HALT involves 351 peri- and post-menopausal women between the ages of 45 and 55 years. Women included in the study must have had at least two hot flashes or night sweats per day or at least six over 2 weeks, and flashes had to be of moderate to severe intensity. The sample produced a total of 19,736 hot flashes and 3,544 night sweats from diary reports.

In pilot work, it became clear that women wanted help with assessing hot flash intensity. They needed instructions on how to rate hot flashes and the investigators needed to assure some standardization of reports across subjects. Looking at FDA definitions for intensity and adding instructions, intensity of hot flashes were defined as follows:

Intensity: Hot Flashes

- **Mild** = passing sensation of hotness without sweating
- **Moderate** = sensation of hotness with sweating, but allows for continuation of current activity
- **Severe** = sensation of intense hotness with sweating that interferes with continuation of activity

Instructions for night sweats were developed to mirror the hot flash scale but included elements of sleep interference:

Intensity: Night Sweats

- **Mild** = don't wake up, but notice them when get up or wake up for other reasons, or notice damp sheets/nightgown when wake up.
- **Moderate** = wake you up because you're hot and/or perspiring, but no action is necessary other than rearranging blankets or sheets.
- **Severe** = wake up hot/perspiring and need to take action (e.g., remove night clothes, open the window, or get out of bed).

Women were also asked to check if they had any other symptoms, which were provided on a list. This broader list of symptoms was of interest to see which therapies might affect which symptoms. It also provided information on whether specific symptoms that have been incorporated into definitions of hot flashes actually occurred in this sample.

Night sweats were more likely to be rated moderate or severe compared to hot flashes, even though the definitions were fairly similar. Anxiety and palpitations accompanied very few hot flashes or night sweats. Feeling hot and feeling sweaty were the most common symptoms associated with hot flashes and night sweats. Chills were most likely to accompany hot flashes and night sweats rated as severe.

Discussion

Rebecca Thurston, Ph.D., Harvard School of Public Health

Dr. Thurston raised a number of observations and questions.

- Hot flash measurement tools can be categorized into four categories: (1) symptom scales based upon retrospective reporting over weeks or months; (2) daily diaries completed at the end of the day; (3) daily diaries, either paper or electronic, completed at the time of the hot flash (also known as ecological momentary assessments); and (4) physiological measures of hot flashes, such as sternal skin conductance.
- Symptom scales:

    - Inadequate information is available about the psychometric properties of symptom scales.
    - Of particular concern is retrospective reporting and the quality of the resulting data. The cognitive psychology literature suggests that memory for experiences, such as hot flashes, is poor and may reflect reconstruction rather than recall (Bradburn et al., 1987; Stone et al., 2003). People tend to estimate a base rate based on a smaller unit of time and then extrapolate the frequency of a day, weeks, or more (Bradburn et al., 1987).
- Daily diaries:
    - Those completed at the end of the day are subject to the same recall problems as the symptom scales.
    - The pain literature suggests that the mood or physical state that people are in when they fill out these impact estimates influences reporting. For example, when pain patients completed symptom estimates at the end of the day, they were tired, experiencing a more negative mood, and in more pain. Therefore, they tended to inflate the number of painful episodes that they experienced throughout the day (Eich, 1985; Erskine et al., 1980; Stone and Shiffman, 2002).
- Daily diaries completed in real time:
    - These tools are likely to yield more precise estimates of hot flash frequency, intensity, and bother. They may avoid problems of distortion and biases associated with recall (Stone and Shiffman, 2002).
    - We don't know much about adherence rates for such diaries. Their superior properties would hold true only if subjects recorded events as they occurred. Competing activities may diminish adherence.
    - Electronic PDA devices have electronic date and time stamps for when the participant entered data, which may allow investigators to ascertain adherence with self-reported data entry requirements. However, electronic PDA devices are similar to the use of event markers on the Biolog, which also provides a date and time stamp for self-reported hot flashes. Dr. Carpenter's data indicates that paper diary and event markers suffer from the same problems. While the pain literature suggests that electronic devices are superior to paper diaries (Stone et al., 2003), hot flash studies differ from pain studies in important ways. Downsides of these PDA devices include cost, breakage, and data loss.
- Physiologic measures:
    - These measures can provide good information about the frequency and timing of hot flashes.
    - However, existing measures cannot provide data on duration, severity, or bother.
- Diaries plus physiologic measures:
    - A combination approach to measuring hot flashes may provide the most valid and complete assessment of hot flashes.

Dr. Nancy Avis summarized some preliminary data from SWAN, which looked at the correspondence between reports of hot flashes on an annual interview and on a monthly calendar. On the annual interview, women were asked to report on hot flashes for the past two weeks. Women also kept monthly menstrual diaries on which they reported hot flashes in the past month and past two weeks at the end of the month. Interview data were compared with diary data from the same month. Data were somewhat more consistent for yes/no reporting than for reporting frequency.

These preliminary data showed approximately 84 percent agreement between questionnaire and diary items for the occurrence of hot flashes in the past two weeks (yes/no). Sixteen percent of responses were inconsistent, with about 11.3 percent of women reporting them in the past two weeks in the interview but not in their diaries. Data looking at hot flash frequency showed 77 percent consistency between interview data and monthly diaries, with 16 percent overestimating hot flash frequencies in interviews. Responses from pre- and post-menopausal women were more consistent than those during the peri-menopausal period, suggesting that it may be more difficult to report on symptoms that fluctuate more.

General menopausal questionnaires provide only a little information about vasomotor symptoms, and Dr. Dennerstein argued that we probably need a newer and better system to capture self-reported information on hot flashes if we want to use them in concert with physiological measures. Dr. Thurston emphasized the apparent significant influence of psychological factors on hot flash reporting (Thurston et al., 2004). Subjective measures capture this subjective experience alone, which may diverge significantly from physiologic data. However, objective measures cannot capture the subjective experience. Therefore, a combination of objective and subjective measures would provide the most complete assessment of hot flashes.

Dr. Gold cautioned that it is important to first be clear about what exactly is to be measured. She also cautioned that socioeconomic differences in patterns of symptom reporting might reflect literacy issues as well, which might influence the degree of familiarity with computers and degree of comfort operating electronic devices. Dr. Freedman noted that, in his experience, PDAs break and can be cumbersome to use. One process used to collect data for FDA review required that subjects enter their password prior to entering data on each hot flash. (This was required for privacy reasons and to prove veracity of data input.) This process proved extremely cumbersome and problematic for subjects. Dr. Carpenter added that there are lots of forms that electronic diaries can take, including a watch-like mechanism where a number can be entered for severity. Such a system might be appropriate for even low-literacy populations. However, all of these measures require that the woman perceive and report the hot flash, and this type of repetitive, subjective reporting was found to be problematic in Dr. Carpenter's ambulatory studies.

Dr. Carpenter pointed out that prospective paper or electronic diaries, event marking devices, and sternal skin conductance monitoring are all types of ecological momentary assessment. Which is to say that each of these methods is designed to assess hot flashes at the moment of the occurrence in the participant's natural environment.

A concern was expressed that so many questions are asked from a pathophysiological perspective, which might affect responses. Menopause is part of a normal aging process and shouldn't be viewed as pathological. Thus, the wording of items in instruments should reflect a non-pathologic approach to this issue. There is a large literature on structuring and ordering of questions, the effect of stigma or embarrassment on responses. Dr. Fitzpatrick reported differences in response based on order of questions in her study. Symptoms near the top of the list were more likely to be checked than those further down the list. Dr. Dennerstein noted that lots of symptoms are often asked to disguise interest in vasomotor symptoms so as not to bias responses. It may be important to involve scientists with expertise in survey research and instrument construction and testing in future iterations of research to improve the collection of self-reported data.

Several people took issue with the FDA definitions for hot flash severity. Some subjects have reported that it is the perceived propensity for sweating, not actual sweating that is of greatest concern. Thus, propensity for sweating might be more highly correlated with severe hot flash ratings. It might be useful to ask about heat and sweating separately.

The Placebo Effect and Natural Decrease in Hot Flashes Over Time

One problem encountered in clinical studies of hot flash therapies is the substantial placebo effect. While many studies report such an effect, there is little if any research on how or why the placebo effect occurs. In addition, studies often find a substantial Hawthorne effect, with enrollees reporting fewer hot flashes during the run-in period before assignment to treatment arm. To further complicate this picture, we would expect the number of hot flashes to decrease as women move through menopause, even in the absence of treatment.

It would be extremely useful to understand the relative contribution of the placebo and Hawthorne effects to the overall decrease in hot flashes observed during the course of a clinical trial. It would also be useful to be able to utilize the placebo effect to provide relief to women. Moreover, it would be very helpful to be able to understand the relative contribution of the placebo effect and the natural attrition of symptoms that occurs over time. Thus, Dr. Jon-Kar Zubieta was invited to share his insights on the placebo effect. He is currently conducting research on the placebo effect associated with expected analgesia for pain,

Hot Flash Relief: Disentangling the Neurobiological Effects of Therapy from Placebo in Humans

Jon-Kar Zubieta, M.D., Ph.D., University of Michigan

Dr. Zubieta divided treatments for hot flashes into three categories: (1) hormone based therapies, such as estrogen and progesterone preparations; (2) SSRIs; and (3) complementary and alternative medicine approaches.

Hormonal preparations have been found to be two to five times more effective than placebos, reducing self-reported hot flashes by 50 to 100 percent in women and 80 percent in men given transdermal estradiol (Gerber et al., 2000). Studies of SSRI's and a range of CAM therapies have reported substantial placebo effects.

Serotonergic mechanisms seem to be important with respect to temperature control, which clearly involves the central nervous system. Over-activation of serotonergic transmission leads to hyperthermia. Depression seems to vary with hot flash severity. The effects of major depression on serotonergic receptors have been primarily observed in women.

In the premenopausal state, the hypothalamus helps to stabilize the thermoregulatory set point and monitors the hyperthermic and hypothermic responses. This results in a normal thermoregulatory response that is impinged upon by serotonergic receptors and other external factors. In perimenopausal and postmenopausal states, the thermoregulatory set point is somehow destabilized, and there is an imbalance in serotonergic receptors. This alters the thermoregulatory response and

leads to vasodilation. The thermoregulatory set point can be re-stabilized by estrogen, progestin, SSRIs, or other neuroendocrine agents. Even the passing of time appears to re-stabilize the thermoregulatory set point, re-balance the serotonergic receptors, and generate a normal thermoregulatory response. Changes in the behavior of serotonergic receptors during menopause may be associated with symptom severity and effects of drugs. These receptors are not localized to the hypothalamus but are located throughout the brain.

To help elucidate the functional neuroanatomy of the placebo effect, Dr. Zubieta presented the study of Mayberg and coworkers (2002). This study uses functional neuroimaging to examine regional metabolic and blood flow changes in depression. Changes in brain glucose metabolism were measured using positron emission tomography (PET scans) in hospitalized men with unipolar depression. In this double blind, randomized, placebo controlled study of fluoxetine, some men were assigned to the placebo arm and evaluated after 6 weeks. Clinical improvement was seen in both arms of the study, which the authors considered to be consistent with the "well-recognized effect that altering the therapeutic environment may significantly contribute to reducing clinical symptoms" (Mayberg et al., 2002:728). They found increases in glucose metabolism and decreases in limbic-paralimbic metabolism in the brains of men receiving the placebo. The brain regions found to be activated in men receiving placebo overlapped the regions activated in men receiving active drug. However, according to these investigators, "the additional subcortical and limbic metabolism decreases seen uniquely in fluoxetine responders may convey additional advantage in maintaining long-term clinical response and in relapse prevention" (Mayberg et al., 2002:728).

The literature contains other examples of research linking affective responses and placebo effects. One study of pain effect modulation through hypnosis provides direct experimental evidence in humans linking frontal-lobe limbic activity with pain relief (Rainville et al., 1997). Another neuroimaging study revealed that the brain areas that are activated during distress caused by social exclusion are also those activated during physical pain (Eisenberger et al., 2003). This finding sheds interesting light on the feeling of physical pain that accompanies emotional loss or distress.

Dr. Zubieta suggested that understanding the links between vasomotor symptoms and brain activity is likely to inform our understanding of hot flashes and placebo effects. His research has confirmed and expanded the hypothesis that the endogenous opioid system, in particular the mu-opioid system, is active in particular parts of the brain during sustained pain and plays a central role in an individual's experience of pain. The mu-opioid receptors attenuate the spread of pain messages in the brain when naturally occurring (endogenous) opioids bind to them.
Experimental evidence from animal models and human studies implicate mu opioid neurotransmission in several areas:

- Stress responses and stress-induced analgesia;
- Endogenous opioid analgesia and effects of opiate drugs;
- Regulation of amygdala and nucleus accumbens-mediated responses to salient stimuli, including drugs of abuse;
- Placebo effect;
- Regulation of GnRH and LH pulsatility.

The direction of modulation is typically suppressive of the relevant response (e.g., stress, anxiety, locomotion). Neurotransmission mediated through the mu-opioid receptor is distributed in both

affective and motivational circuits in the brain and include neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.

Although not very well studied, it is plausible that estradiol withdrawal during menopause induces a loss of hypothalamic opioid activity with corresponding changes in hypothalamic-pituitary-ovarian (HPO) axis activity and in thermoregulatory stability. Animal models of hot flashes, which are induced with opioid withdrawal, are susceptible to regulation by estradiol and alpha-2 antagonists. There are several factors that perhaps play a role in this. Mu-opioid receptors induce cyclic suppression of GnRH/LH pulses. Naloxone enhancement requires high estradiol in plasma. And the night-time LH pulse found in women of reproductive age is absent in postmenopausal women. Zubieta reported that estradiol has been shown in animal models to effect mu-opioid receptor concentrations, immunoreactivity and mRNA, and enhancement of the release of endogenous opioids in cell cultures.

In an experimental study of mu-opioid receptor regulation of sensory and affective dimensions of pain, Zubieta and coworkers (2001) found that pain activated mu-opioid receptors in areas of the brain that are associated with the body's attempt to minimize the pain experience. They found receptor activation in the amygdala, the thalamus, the hypothalamus, the frontal cortex, and the nucleus accumbens. This activation resulted in as much as a 12 percent change in mu-opioid receptor availability in the prefrontal cortex and was associated with a reduction in the amount of pain and pain-related emotions reported by subjects. There was substantial variation in mu-opioid receptor binding and release, which was modulated by estradiol. These findings are consistent with the observation that people vary both in the number of receptors they have for these anti-pain chemicals and their ability to release similar endogenous substances themselves. Such variability in the pain-response system may help to explain individual differences in reaction to pain and pain medications. Perhaps most interestingly, Zubieta found an overlap of estradiol and placebo effects on mu-opioid neurotransmission.

Examination of serotonergic and opioid neurotransmission in human subjects may provide promising leads to improve our understanding of the mechanisms underlying hot flashes and menopausal symptoms. These mechanisms may be mediating both the effects of estradiol and progesterone on thermoregulation as well as the effects of hot flash treatments. However, we must also address the possibility that expectation of relief, which is found among subjects assigned to the placebo arm in blinded studies, may also be mediated by overlapping or perhaps interacting mechanisms.

Discussion

Clearly, the placebo effect can be quite powerful. The fact that some studies have found response effect to vary by color of pill administered indicates that expectation may play an important role in the placebo effect. It might be interesting to conduct a dose response study for placebos.

The expense associated with conducting neuroimaging studies points to the need to formulate very specific hypotheses to be tested with such systems. And data from animal models might be very helpful in determining which hypotheses warrant further testing in humans using relatively expensive technologies. However, the group found the overlap in brain circuitry for placebo and treatment conditions to be intriguing and even reassuring. Overlap is also found with mood regulators and pain, registering in the areas that are regulated by estradiol. This may help modulate pain during pregnancy and the post-partum period.

Animal Models of Hot Flashes

James W. Simpkins, Ph.D., University of North Texas Health Science Center

Animal models can provide extremely useful information to help understand a variety of human health problems and conditions, including hot flashes. For example, animal studies have shown that elevations in hypothalamic norepinephrine lower the sweating threshold (Freedman and Blacker, 2002: 487). The hypothalamus clearly plays a role in hot flashes, but we know little about what actually occurs. This would be difficult to study in humans. Dr. Freedman is now trying to develop a model of hot flashes in rhesus monkeys, which, if successful, will allow for the study of hypothalamic mechanisms. It would also be useful to have animal models or other high throughput screening systems for compounds being proposed for treatment of hot flashes.

The known physiologic correlates suggest the following required characteristics of animal models for studying hot flashes relevant to humans:

- Rapid onset of skin temperature increases;
- High amplitude of skin temperature increases;
- Subsequent fall in core body temperature;
- Increase in heart rate;
- Increase in LH secretion;
- Activation originating in the central nervous system;
- Improvement with estrogen;
- Antagonized by adrenergic blockers;
- Seen in both gonadal hormone deprived males and females.

There has been little investment in animal models of hot flashes, which has had a detrimental affect on the field. Published animal models relevant for the study of human hot flashes include:

- Opiate withdrawal in rats (more than 20 publications);
- Hypoglycemia in rats (4 publications);
- Day-night skin temperature rise in rats (2 publications);
- Ovariectomy-induced rise in skin temperature (2 publications);
- Ambient temperature increase in OVX rats (2 publications);
- Ovariectomy in sheep (1 publication);
- Ovariectomy in non-human primates (1 publication).

Dr. Simkins reported on a series of data generated in the mid-1980s from an animal model based on the withdrawal of estrogen. He also conducted a literature review of symptoms associated with opiate withdrawal as reported by physicians, psychiatrists, and nurses, and compared them to symptoms described by women experiencing estrogen withdrawal during menopause (Simpkins et al., 1983; Simpkins and Katovich, 1984; Simpkins and Katovich, 1989). A phase shift of the charts show an almost perfect match, except perhaps for most severe symptoms of opiate withdrawal.

Studies of addicted rats subjected to withdrawal produce signs that mimic hot flashes related to estrogen withdrawal in humans (Simpkins et al., 1983; Katovich and Simpkins, 1986). After addicting rats to opiates, they were then given a large dose of naloxone to induce withdrawal. This produces a thermal response in the tail that dissipates over the course of an hour or so (Simpkins et al., 1983). A milder withdrawal reduces amplitude of response and is followed by a more rapid

stabilization (Katovich et al., 1984). The initial rise in temperature is followed by a decline in core body temperature. The tail temperature response activates an increase in the heart rate and an LH surge (Simpkins et al., 1983; Genesan et al., 1991). The tail temperature response also appears to be sensitive to endogenous steroids. Administration of steroids produced approximately a 50 percent reduction in response compared with animals that did not receive steroids (Katovich and Simpkins, 1989). Ovariectomized animals lead to a high amplitude tail temperature response. Chronic estrogen treatment of ovariectomized animals can markedly blunt this response (Katovich and Simpkins, 1989). If rats are given clonidine 10 minutes prior to induction of withdrawal, withdrawal symptoms are blocked by clonidine (Katovich et al., 1987a). This action appears to originate in the central nervous system (Katovich et al., 1986; Katovich et al., 1987b). In aggregate, these findings suggest that the rat model, although not perfectly reflecting the human hot flash phenomenon, may serve a useful role in the study of hot flashes.

Dr. Simpkins noted that diabetics who overdose on insulin experience symptoms similar to hot flashes. He proposed a hypoglycemia/brain neuroglucopenia model for hot flashes (Simpkins et al., 1990a; Simpkins et al., 1990b). This model posits that hot flashes occur when brain energy demand exceeds glucose availability. This can happen because of acute excess activity of the brain (which is what happens in opiate withdrawal in animals) or acute or chronic glucose deprivation (Simpkins et al., 1990a; Simpkins et al., 1990b). One of the things that estrogens do is regulate how much glucose gets in the brain. Ovariectomized animals lose 30 percent of the capacity to transport glucose into the brain (Bishop and Simpkins, 1992; Bishop and Simpkins, 1995; Shi and Simpkins, 1997; Shi et al., 1997).

In an observational study of the role of glucose-deprivation in hot flashes, subjects were given a big breakfast about two hours prior to observation. When glucose was high, there were few hot flashes; when glucose levels were declining, flashes began to occur (Katovich and Simpkins, 1989). Further study has demonstrated that maintaining higher levels of glucose in women substantially reduces hot flashes objectively measured (Dormire and Reame, 2003; Dormire, 2003).

This relationship can be modeled in animals. Very rapid onset and high amplitude in temperature change was observed for rats chronically given insulin (Katovich and Simpkins, 1989; Kimpkins and Katovich, 1990). In animals given saline, there were no changes in temperature. In insulin treated animals, hot flash incidents increased over time with continued insulin (Katovich and Simpkins, 1989; Simpkins and Katovich, 1990).

One can induce temperature responses by preventing cells from metabolizing glucose, inducing essentially a cellular hypoglycemic response (Simpkins et al., 1990a). Skin temperature response appears to be part of a counter-regulatory attempt to elevate blood glucose to get glucose to the brain. Similarly, returning to the opiate withdrawal model, increasing glucose can reduce the magnitude of the flashes (Simpkins et al., 1990b). This evidence suggests that glucose plays a role in the etiology of hot flashes.

Dr. Simpkins summarized the relationship between known animal and clinical models and whether they fit the required characteristics for modeling human hot flashes (Table 3). Not all characteristics have been assessed for all the models. He noted that old rats are very expensive and may not constitute a cost-effective model.

Table 3. Known Animal Models and Correspondence to Human Hot Flash Characteristics

	Rapid Onset	High Amplitude	Heart Rate	LH Surge	Brain Origin	Antagonism by Estrogens	Antagonism by Adrenergic Blockers	Cost Effective
Rodents								
Opiate WD	+	+	+	+	+	+	+	+
Hypoglycemia	+	+	ND	ND	+	ND	ND	+
Day-Night	+	+	ND	ND	ND	+	ND	+
Aging	+	+/-	ND	-	ND	ND	ND	-
Ovariectomy	-	-	ND	ND	ND	+	ND	+
Ovariectomy + Ambient Temp.	+	+	ND	ND	ND	+	ND	+
Large Animals								
OVX sheep -	-	ND	+/-	ND	ND	ND	-	-
OVX Primates+	+	+	+	ND	+	+	-	-
OVX Women +	+	+	+	ND	+	+	-	-
Natural Menopause	+	+	+	+	ND	+	+	-
Castration males	+	+	ND	ND	ND	+	ND	-
GnRH Agonists	+	+	ND	ND	ND	+	ND	-

For large animals, natural menopause meets all the criteria short of brain origin, which is assumed and not yet demonstrated. The main problem with large animals is the cost. High throughput assays would not be feasible for the larger animals.

Dr. Simpkins concluded that the opiate withdrawal tail temperature response in rats is the best-characterized animal model for studying hot flashes. It is highly replicable, sensitive to known drug therapies for hot flashes, cost effective and has the potential for high throughput screening of compounds. Hypoglycemic-induced hot flushes are less well characterized, but replicable, cost effective and adaptable to high throughput screening. Large animal models for hot flashes suffer from their expense and the lack of high throughput assay potential.

Discussion

Robert Freedman, Ph.D.

Freedman showed slides comparing data from animal and human models that relate to the opiate withdrawal model. Data from animal models would predict that naloxone would increase the number of hot flashes. However, citing work from Judd's laboratory, Freedman reported that naloxone

infusion did not affect naturally occurring hot flashes in a well-controlled study of 16 post-menopausal symptomatic women when skin temperature and skin resistance data were examined (DeFazio et al., 1984). In another study of naturally occurring hot flashes in post-menopausal women that compared saline and naloxone infusions, there was no significant difference in the numbers of hot flashes or LH pulses (DeFazio et al., 1984).

It is important to note that the women in these studies were not "primed." It is likely that a woman must have sufficient estrogen to precipitate a dampening effect from naloxone on numbers of hot flashes. It is also expected that if a woman is given opioids and then given naloxone, more hot flashes could be precipitated. But inducing a hot flash would describe a different phenomenon than naturally occurring hot flashes. There very well could be a difference between acute and chronic effects of drug use.

Berenson and colleagues' recent paper (2001) reports that when the day/night activity cycle is manipulated, an increase in tail temperature is observed that is not phasic like hot flashes but instead is elevated for several days. Estrogen, clonidine, and a few other drugs suppress the increase.

It was noted that insulin-induced hyperglycemia can make rats very cranky. It is not clear whether an increase in adrenalin is responsible for some of the observed effects.

In another study by an Italian group (Cignarelli et al., 1989) of symptomatic women, researchers found that blood glucose did not appear to differ before and after hot flashes measured by sternal skin conductance. This was unexpected since, according to other research, one would expect lower glucose levels to be associated with periods of hot flashes. However, latency issues may be important.

In terms of ovine studies, Freedman dismissed data from a sheep model because it did not measure temperature in the carotid rete, which he considers to be the physiologically relevant site.

Building Effective Multidisciplinary Teams

Future research to improve measures of hot flashes is likely to require multidisciplinary research teams. As part of the NIH Road Map initiatives, NIH is interested in these multidisciplinary teams. Finding appropriate collaborators from other disciplines is not necessarily easy. But meeting a collaborator from another discipline is but the first step in building a multidisciplinary research team. Dr. Belinda Seto, Deputy Director of the National Institute of Biomedical Imaging and Bioengineering, was invited to discuss how we might think about building such teams.

Building Multidisciplinary Teams at NIH

Belinda Seto, Ph.D., National Institute of Biomedical Imaging and Bioengineering

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest of the NIH research institutes and centers, signed into law on December 29, 2000 and established on April 20, 2001. The formation of NIBIB reflects NIH's support for an engineering approach to solving biomedical problems.

The mission of NIBIB is to improve health by promoting fundamental discoveries, design and development, and translation and assessment of technological capabilities in biomedical imaging and bioengineering, enabled by relevant areas of information science, physics, chemistry, mathematics, materials science, and computer sciences. The Institute is also charged with coordinating among the biomedical imaging and bioengineering programs of other agencies and NIH institutes to support imaging and engineering research with potential medical applications, and facilitating the transfer of such technologies to medical applications.

The NIH Bioengineering Consortium (or BECON) was the precursor to NIBIB, and continues to coordinate and facilitate research, training opportunities, and scientific symposia associated with biomedical engineering across NIH under the administrative auspices of NIBIB. The 2003 BECON symposium sought approaches for catalyzing and rewarding team science, as a complement to individually rewarding science, and identified five key topic areas:

- NIH Policies, Procedures, and Funding Mechanisms
- Academic Institutions' Assessment and Reward Procedures
- Credit and Ownership Issues Related to Publication of Team Science
- Models of Team Science
- Institutional Administration of Research Teams

Dr. Seto shared the principles and factors considered essential for team success that were identified at the BECON symposium recommendations as a way to help frame the discussion (Table 4). Some of the recommendations are not trivial to implement. (Additional details about BECON activities, and the full report, are available at *www.becon.nih.gov*).

Table 4. Principles and Factors for Team Success as Identified at BECON 2003

Principles for Team Success	Factors Essential for Team Success
• Individual creativity should be preserved while taking advantage of the synergy of team approaches • Each team should be based on a central problem, a motivation that brings the team together and encourages collaboration • Team members should be selected based on team needs and not necessarily location	• A management structure that integrates leadership (encompassing vision, enthusiasm, and team spirit) with communications (requiring time, effort, technology, and training) • A team-friendly environment incorporating integrity, trust, respect, and sharing • Institutional commitment including space, administrative support, and faculty investment
Team Science Would Be Enhanced If…	
NIH: • Allowed multiple key investigators on individual grants. • Allowed multiple performance sites to receive appropriate indirect cost recovery. • Developed improved funding mechanisms for team science. • Gave more attention to the special review needs of team science.	
Academic Institutions • Developed measures of team contributor value other than PI status and authorship.	

- Created career paths for those who provide the infrastructure for the team.
- Streamlined the administration of team science.

Journals:

- Specified co-authors' contributions.
- Identified guarantors of article content.
- Established data and materials sharing policies.

Effective teams begin with compelling reasons for their existence, but further incentives must be built into the system to ensure full realization of their potential. The success of team science depends upon individuals who are comfortable with boundary-crossing activities. Working as part of a team that seeks 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. Although understanding complex systems is something that engineers are trained to do, they are likely to be more successful in the biomedical arena if they can work in concert with clinicians and health researchers. NIBIB continues to seek broad public input about new and ongoing multidisciplinary or interdisciplinary collaborations that can be formed to further the NIBIB mission and improve the health of the public. Educational programs that prepare students for these environments are essential, as are programs to improve the quality of mentoring for those who are participants and for those who must support and evaluate team performance.

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. In keeping with the NIH mission of uncovering new knowledge about the prevention, detection, diagnosis, and treatment of disease and disability, the goal of the Road Map is to accelerate both the pace of discovery in these key areas and the translation of therapies from bench to bedside. There is no doubt as to the NIH commitment to the Roadmap, as it has set aside $128 million this year for Roadmap activities, and the total will grow to over $2 billion by 2009. In the course of developing the NIH Roadmap, it has become clear that scientific advances are being made at the interfaces of traditional disciplines, and that approaches to science are becoming more integrative. This requires a cooperative effort, typically in the form of investigators from diverse research backgrounds working collectively across traditional disciplinary boundaries to answer scientific questions and achieve specific end points. This also requires a workforce capable of crossing disciplinary boundaries and leading and participating in integrative and team approaches to complex biomedical and health problems. Building research teams for the future has therefore emerged as one of the major themes in Roadmap implementation. (Additional information about the NIH Roadmap can be found on the NIH Web site at: http://nihroadmap.nih.gov.)

NIH recognizes the value and enormous contributions that existing interdisciplinary approaches have made and are making to our understanding of health, disease, and disability. However, the Roadmap is focused on developing new interdisciplinary approaches and therefore the necessary interdisciplinary workforce. NIH also recognizes that multidisciplinary approaches may be a necessary step in the evolution of interdisciplinary research training and currently offers many opportunities and mechanisms to support multidisciplinary research training.[7]

[7] NIH has clarified the distinction between a multidisciplinary and an interdisciplinary approach. A multidisciplinary approach brings experts from diverse disciplines to address collectively a common complex problem, each from his or her unique perspective. An interdisciplinary approach results from the melding of two or more disciplines to create a new

As part of the Roadmap, NIH is announcing a series of initiatives that will provide investigators with the training to effectively lead and engage in integrative and team approaches to complex biomedical and health problems. These initiatives fall into three categories: programs for long-term interdisciplinary research training; short-term courses and research experiences; and curriculum development. Collectively, the initiatives provide opportunities for integration of disciplines at all stages of investigators' careers, facilitate communication among the disciplines, and support the development of infrastructure to accomplish the building of the workforce for the research teams for the future. (See *http://nihroadmap.nih.gov/interdisciplinary/index.asp* for more details about specific interdisciplinary initiatives.)

Another aspect of team science is collaboration between public and private sectors. As part of this focus, NIH will be designating a public-private sector liaison and encouraging high-level, science-driven partnership meetings. Public-private partnerships are natural for NIBIB because of its emphasis on technology.

Future Directions

Dr. Heather Miller solicited the group's reactions to a number of themes mentioned throughout the day-long meeting: the complementary nature of objective and subjective measures of vasomotor symptoms, the placebo effect, the applicability of animal models to the study of hot flashes, and multidisciplinary team building.

The participants reiterated the conclusion that the etiology of hot flashes is still far from being completely understood. Clinicians need to know more about the underlying triggers and physiological mechanisms to be able to provide better treatment options for their patients. Bringing scientists together from different fields would appear to be a promising approach to moving the field forward. It is possible the assays being used are not sufficiently sensitive, or we may need other new tools to explore the temporal relationship of critical events or even to define those events. There could be a genetic predisposition to hot flashes, and environmental stimuli or behavioral factors may be important in the triggering of hot flashes or their relief. In short, the group generated more questions than answers on this topic.

Workshop participants reached a general consensus that a biological or physiological measure of a correlate for hot flashes is extremely desirable. Understanding the temporal sequence of events that constitute a hot flash will be critical for researchers to be able to reliably identify when a hot flash actually has occurred and the factors that trigger it. The leading measures in use today, sternal skin conductance and body temperature, are limited by their inability to measure intensity or bother. If one is primarily concerned about helping hot flash sufferers find relief, then subjective reports from diaries or interviews cannot be dismissed, as they are currently the only way to obtain qualitative assessments. Because objective measures generally capture more hot flashes than self-reports in ambulatory settings, the physical measures may be attractive for studies that require the participation of women with relatively frequent hot flashes. In aggregate, these measures are crucial to

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(interdisciplinary) science, e.g., biophysics, biostatistics, bioinformatics, bioengineering, social neuroscience, and psychoneuroimmunology.

understanding how interventions work, whether through physiologic change or in subjective experience of the hot flash or a combination of both. Interventions may affect psychological factors that in turn can affect perceptions of hot flashes and reporting them. Ultimately, we would like an innocuous sensor to monitor hot flashes that would not require cumbersome electrodes that might become compromised if subjects experience extensive sweating or take a shower. And we'd like to capture data for longer periods of observation, perhaps through some type of cost-effective transducer that can record data continuously.

The placebo effect has been remarkable in some studies of hot flash interventions, yet it is not well-understood and is difficult to study. It would be very useful to be able to distinguish placebo effects from the natural dissipation of symptoms over time. Objective measures of hot flashes, such as sternal skin conductance monitoring, may be very useful in this endeavor.

Investigators face several challenges when considering the design of hot flash studies. Large placebo effects and small sample sizes have produced a literature with equivocal findings. We need either more precise and stable measures or larger sample sizes. Given limitations in budgets and the expense of clinical trials, it makes sense to think about improving measures. Investigators also need to consider how long clinical studies should run to evaluate safety and efficacy and the implications that increased monitoring time might have. Choice of appropriate treatment comparison groups is also an issue that needs further consideration. For example, it is doubtful that an IRB will allow a study to keep breast cancer survivors on placebo for 3 or more months if effective treatments are available. Study designers must also consider the Hawthorne effect in determining the optimal baseline period before initiating the intervention. In pilot studies that offer only active treatment, the anticipatory reduction in hot flashes may exaggerate the placebo effect. However such effects would likely dissipate over time, which underscore the importance of requiring longer durations of pilot studies before making more substantial investments in randomized clinical trials.

Dr. Zubieta's studies highlight the potential of imaging technology in studies exploring placebo effects. Only a few centers have the personnel and equipment to perform these studies well. However, there may be many other opportunities to improve the fundamental understanding of the placebo effect. We already know that the context in which data are collected matters. Although not studied specifically for hot flashes, all the following factors have been shown to have an impact on patient responses: the color of the pill, instructions given to patients that "prime" the outcome, and whether or not the scientist wears a white lab coat. The input of social psychologists could be helpful to identify factors that may influence the placebo effect, to create and test questionnaire items, to ascertain effect of mode of data collection on the quality of the resulting data, and to understand how best to provide information to subjects. Others noted that some CAM treatments were more complicated to study because of their distinct characteristics that make it difficult to create appropriate placebos and to blind the study. In such cases, it may be helpful to debrief patients to ascertain whether they recognized the treatment being tested.

Mechanistic data that cannot be obtained from human studies may be obtained from animal models. The group found that animal models would be particularly helpful to understand the neurobiology of hot flashes and placebo effects. Most of the existing animal data on hot flashes have come from rodent models. To date, there has not been much research conducted on primates. Studying naturally occurring menopause in monkeys may provide very useful data, but there are few healthy older monkeys available for such research.

In summary, the group concluded that improving measures of hot flashes requires improved knowledge in several areas, including:

- The physical processes underlying hot flashes, which will also identify additional parameters 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 parameters 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 the 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.

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Appendix 1

AGENDA

WORKSHOP ON IMPROVING MEASURES OF HOT FLASHES

Co-Sponsored by ORWH, OER, NICHD, NCI, NIA, OBSSR, NHLBI, NIBIB, and NCCAM

Building 31, Conference Room 7, NIH

January 20, 2004

8:00 AM Introduction and Welcome
Stephen Straus, Director, NCCAM
Vivian Pinn, Director, ORWH
Heather Miller and NIH Co-Sponsors

8:15 AM Significance and Magnitude of the Problem
Ellen Gold – Presenter, Epidemiology of hot flashes
Charles Loprinzi – Presenter, Magnitude of the problem in men
Lorraine Dennerstein – Presenter, Longitudinal data:
Factors predicting absence or severe, prolonged hot flashes

9:15 AM Hot Flashes and Some Objective Measures
Lorraine Fitzpatrick – Presenter, Endocrinology of hot flashes
Robert Freedman - Presenter, Physiology of hot flashes
Janet Carpenter – Presenter, Comparison of objective measures
in ambulatory studies to self reported data

Nanette Santoro – Discussant

11:15 PM Promising Sensor Technologies
John Webster – Presenter, Introduction
Jerome Schultz – Presenter, Promising technologies
Michael Neuman – Presenter, Promising technologies

12:30 PM Lunch

1:30 PM Self-reported Data on Hot Flashes
Katherine Newton - Presenter

Rebecca Thurston - Discussant

2:30 PM The Placebo Effect and Natural Decrease in Hot Flashes Over Time
Jon-Kar Zubieta – Presenter

3:15 PM Animal Models of Hot Flashes
James Simpkins – Presenter
Robert Freedman – Discussant

4:00 PM Building Effective Multidisciplinary Teams
Belinda Seto - Presenter

4:30 PM What Scientific Problems and Opportunities Do We See?
Open discussion
Heather Miller and NIH Co-Sponsors

5:00 PM Adjourn

Appendix 2

WORKSHOP ON IMPROVING MEASURES OF HOT FLASHES

Co-Sponsored by ORWH, OER, NICHD, NCI, NIA, OBSSR, NHLBI, NIBIB, and NCCAM

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Appendix 3

Population Differences in Reporting Hot Flashes

Ellen B. Gold, PhD
January 20, 2004

Reference	Sample Size	Age of Sample (years)	Race/ Ethnicity of Sample	Menopause Status Of Sample	Prevalence of Hot Flashes
Keenan NL et al, 2003	2,602	45+	86% white	16% Pre 40% Hyster 44% Nat post	51.0% 64.5% 65.5%
Dennerstein L et al., 2000	172	45-55, at baseline	[Australian]	Pre (n=172) Early peri (148) Late peri (106) Post (72)	10% 15% 42% 42%
Gold EB et al., 2000	16,065	40-55	29.5% Afr Amer 46.5% white 4.4% Chinese 13.8% Hispanic 5.7% Japanese	Pre (19% with HF) – post (49% with HF)	45.6% AfrA 31.2% Cau 20.5% Chin 35.4% Hisp 17.6% Japn
Berg JA et al., 1999	165	35-56	Filipina Amer	Pre Peri Post	66.5% 72.3% 61.2%
Wilbur JE et al., 1998	153	35-69	55.6% white 44.4% black	Pre – post	41% overall
Kuh DL et al., 1997	1,498	47	[British]	43.9% Pre 24.0% Peri 5.4% Post 14.3% Hyster	18% 40% 60% 40%
Leidy LE, 1997	155	40-60		57.4% Pre 5.2% Peri 25.8% Nat Post 9.7% Hyster	34.2% 100% 92.5% --
Langenberg P et al., 1997	1,299 [under-going hyster]	36% <40 47% 40-9 10% 50-9 7.3% 60+	66.3% white 31.6% black 2.1% other	84.2% Pre/peri 10.6% Post	47% 35%
Lee KA et al., 1996	266	40-60	90% white 5.3% Asian 2.7% Afr Amer 1.5% Hispanic	41.0% Pre 14.6% Peri 44.4% Post	19-44% (by age) “awakened by hot flashes”
Skarsgard C et al., 1996	1,108	55-56	[Swedish]		81.8% ever

Reference	Sample Size	Age of Sample (years)	Race/Ethnicity of Sample	Menopause Sataus of Sample	Prevalence of Hot Flashes
Abraham S et al., 1994	60	46-63	[Australian]	Post	77%
O'Connor VM et al., 1995	462	45-54	[Australian]	69% Pre – Nat Post 31% Hyster	25% overall
Haines CJ et al., 1994	79	35+ (under-going laparo-tomy)	Chinese		5% pre-op 24% post-op
Ismael NN, 1994	400	40-60	13% Chinese 70% Malaysian 16% Indian	51% Pre 15% Peri 34% Post	19% ever 57% ever 38% ever
McCarthy T, 1994	366	40-55	86% Chinese 6% Malaysian 8% Other	56.0% Pre 14.5% Peri 28.7% Post	38% overall
Ramoso-Jalbuena J, 1994	500	40-50	98% Malaysian Filipinas	61% Pre 4% Peri 35% Post	63% overall
Samil RS and Wishnuwardhani SD, 1994	346	55% 40-4 30% 45-9 16% 50+	Indonesian		22% overall
Schwingl PJ et al., 1994	334	30-98	24% black 76% white	Post	69% 71%
Avis et al., 1993		45-55	348 Japanese 272 Canadian 2127 U.S. 394 Japanese 369 Canadian 2444 U.S.	Peri Post	15.8% 45.2% 37.3% 16.8% 45.5% 42.6%
Hammar M et al., 1990	634	52-54	[Swedish]	Post	59% (severe to moderate)
Otolorin EO et al., 1989	36	40+	[Nigerian]	53% Pre/Peri 47% Post	25% 70%
Goodman MJ et al., 1977	708	35-60	51% Japanese 49% Caucasian	54% Pre 46% Post	10%J; 16%C 24%J; 28%C