

National Institutes of Health State-of-the-Science Conference Statement: Management of Menopause-Related Symptoms

NIH State-of-the-Science Panel*

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The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Menopause is a natural process that occurs in women's lives as part of normal aging. Many women go through the menopausal transition with few or no symptoms, while some have significant or even disabling symptoms. Menopause is defined by the World Health Organization and the Stages of Reproductive Aging Workshop (STRAW) working group as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is recognized after 12 consecutive months without menstrual periods that are not associated with a physiologic (e.g., lactation) or pathologic cause. Menopausal transition often begins with variations in length of the menstrual cycle. The hormonal changes during the menopausal transition can span several years.

The following 3 periods or intervals were defined by experts at the STRAW working group in 2001:

1. Reproductive stage: From menarche (first menstrual period) to the beginning of the perimenopause (when cycles become variable).

2. Menopausal transition: The time of an increase in follicle-stimulating hormone and increased variability in cycle length, 2 skipped menstrual cycles with 60 or more days of amenorrhea (absence of menstruation), or both. The menopausal transition concludes with the final menstrual period (FMP) and the beginning of postmenopause.

3. Postmenopause: Begins at the time of the FMP, although it is not recognized until after 12 months of amenorrhea.

In this report, we use the term *menopausal transition* to mean the time from the late reproductive stage and entry into postmenopause. The term *perimenopause* is defined as the period immediately prior to menopause (when the biological and clinical features of approaching menopause begin) and the first year after menopause. Thus, perimenopause includes the menopausal transition and overlaps the first 12 months of postmenopause. This term is commonly encountered in the literature and in clinical practice because the proposed STRAW definitions were only published in 2001. The STRAW terminology is being validated, and results may further clarify these terms.

The focus of this report is to identify menopausal symptoms and assess treatments for them on the basis of existing scientific evidence.

We evaluate evidence that the following symptoms are, or are not, related to menopause and assess the treatments for them: hot flashes, night sweats, vaginal dryness and painful intercourse, sleep problems, mood and cognitive problems, somatic symptoms, urinary incontinence, bleeding problems, sexual dysfunction, and overall quality of life. Menopausal symptoms vary in combination, intensity, and duration, and we assess the evidence for these as well. Estrogen, either by itself or with progestins, has been the therapy of choice for decades for relieving menopause-related symptoms. Epidemiologic studies in the 1980s and 1990s suggested that estrogen-containing therapy might protect women from heart disease and other serious medical problems. The Women's Health Initiative (WHI) was a large clinical trial of postmenopausal women (age range, 50 to 79 years [mean, 63.2 years]) that was designed to see whether estrogen with or without progestin therapy could prevent chronic conditions, such as heart disease and dementia. The estrogen with progestin portion of the trial ended early because of increased incidence of breast cancer. There were increases in blood clots, stroke, and heart disease among women who received this treatment as well. These findings raised serious questions about the safety of estrogen to treat symptoms of menopause. Many women stopped hormone replacement therapy, and some searched for alternative therapies. To reflect a shift of focus from "replacement" to use of hormones for relief of symptoms, we will use the term *menopause hormonal therapy*, which

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*Panel statement from an NIH State-of-the-Science Conference held on 21–23 March 2005 at the National Institutes of Health, Bethesda, Maryland. For a list of the members of the NIH State-of-the-Science Panel, see the Appendix.

includes a range of doses and preparations of estrogen and progesterin.

Women and their health care providers need to know the safest and most effective medical and nonmedical treatments for menopausal symptoms. To address this need, the National Institute on Aging and the Office of Medical Applications of Research of the NIH sponsored a State-of-the-Science Conference on Management of Menopause-Related Symptoms on 21–23 March 2005, in Bethesda, Maryland. The conference planning committee posed 5 key questions and selected the list of symptoms for evaluation. During the first 2 days of the conference, experts presented information on the biology of the menopausal transition, the nature of the symptoms women experience, and strategies for relieving the common problems associated with the menopausal transition. After weighing all of the scientific evidence, including the data presented by both the speakers and a thorough review of the English-language literature identified in an evidence report prepared by the Oregon Evidence-based Practice Center, an independent panel prepared and presented a state-of-the-science statement answering the 5 key conference questions.

1. WHAT IS THE EVIDENCE THAT THE SYMPTOMS MORE FREQUENTLY REPORTED BY MIDDLE-AGED WOMEN ARE ATTRIBUTABLE TO OVARIAN AGING AND SENESCENCE?

Because women age as they progress from premenopause to postmenopause, it is difficult to determine which symptoms occurring during this time are due to ovarian aging specifically and which are due to general aging and/or life changes commonly experienced in midlife. Specific symptoms are discussed in this section.

Vasomotor Symptoms (Hot Flashes and Night Sweats)

The vasomotor symptoms of hot flashes—sudden sensations of intense heat with sweating and flushing typically lasting 5 to 10 minutes—and night sweats are reported with high frequency in perimenopausal women. There is strong evidence from both longitudinal and cross-sectional observational studies that the menopausal transition causes vasomotor symptoms. Hot flashes rarely occur before women enter the perimenopausal transition and occur in a higher percentage of women in the later phases of the menopausal transition. They also occur with a higher frequency and greater severity in younger women who undergo a sudden onset of menopause due to surgical removal of their ovaries or medical conditions or treatments that decrease the ability of ovaries to produce hormones. Further evidence supporting this association is provided by the large number of good-quality interventional clinical trials demonstrating improvement of vasomotor symptoms with estrogen treatment.

Vaginal Dryness and Painful Intercourse

Vaginal dryness, often leading to painful intercourse (dyspareunia), is reported by many perimenopausal and postmenopausal women. Evidence from observational studies that menopause causes vaginal dryness is strong. The percentage of women experiencing vaginal dryness increases throughout the menopausal transition and persists indefinitely in some women. Increases in vaginal dryness correlate well with the onset of the menopausal transition. Microscopic examination of vaginal cells obtained from postmenopausal women reporting vaginal dryness shows changes consistent with low estrogen levels. Furthermore, treatment of vaginal dryness with estrogen (either vaginal or systemic) results in relief of symptoms, including menopause-associated dyspareunia, for most women.

Sleep Disturbance

Sleep disturbances are common and increase with age in both men and women across the lifespan for a variety of reasons. There is moderate evidence from longitudinal cohort and cross-sectional observational studies that menopause is the cause of such disturbances in some women. The role of vasomotor symptoms in sleep disturbances remains unclear.

Mood Symptoms

From observational studies, there is limited evidence that ovarian changes associated with menopause might be a cause of depression, anxiety, and/or irritability. History of prior depression, life stress, and general health are the major predictors of mood symptoms during midlife. Because of the multiple potential causes of mood changes and the relatively high proportion of women reporting 1 or more of these symptoms, it is difficult to establish whether menopause causes any increase in the prevalence of mood symptoms during the perimenopausal years. The evidence from estrogen treatment trials is mixed, with only weak evidence of improvement in depression or anxiety relative to placebo for a small subset of moderately or highly symptomatic women treated with estrogens.

Cognitive Disturbances

There is insufficient information to conclude that there is any causal relationship between the menopausal transition and difficulty thinking, forgetfulness, or other cognitive disturbances. Existing studies are inadequate for separating aging effects from the effects of menopause.

Somatic Symptoms

The majority of studies showed no association between the prevalence of somatic symptoms, including back pain, tiredness, and stiff or painful joints, and menopausal status.

Urinary Incontinence

In a small number of longitudinal and cross-sectional studies that considered associations between menopausal status and urinary incontinence, results are mixed. Current results are inadequate to demonstrate a causal relationship.

Uterine Bleeding Problems

The menopausal transition is, by definition, associated with alteration in menstrual cycles. In addition, menorrhagia (excessive bleeding) has frequently been reported by perimenopausal women. There are no adequate long-term studies examining menorrhagia during the menopausal transition. Any such studies would need to account for the presence of fibroids and other uterine conditions.

Sexual Dysfunction

Two components of sexual dysfunction during the menopausal transition have been identified: painful intercourse resulting from vaginal atrophy and dryness, as discussed earlier, and changes in libido, arousal, and other aspects of sexuality. These latter 3 changes are strongly associated with age-related factors, such as changes in personal relationships, stressors, and socioeconomic conditions. Their association with menopausal hormone changes has not been established definitively.

Quality of Life

Currently, there is inadequate information to conclude that the menopausal transition is associated with either positive or negative effects on quality of life in a general population.

2. WHEN DO MENOPAUSAL SYMPTOMS OCCUR, HOW LONG DO THEY PERSIST AND WITH WHAT FREQUENCY AND SEVERITY, AND WHAT IS KNOWN ABOUT THE FACTORS THAT INFLUENCE THEM?

Natural History of Menopausal Symptoms

Menopausal symptoms vary among women at each stage of the menopausal transition and also vary for each woman over time as she goes through these stages. In the United States, most women experience menopause between 40 and 58 years of age, with a median age of 52 years. Factors associated with earlier menopause include lower body weight, menstrual length, nulliparity, smoking, never-use of oral contraceptives, lower socioeconomic status, and race or ethnicity. Higher body weight is associated with later onset of menopause.

Some women who transit menopause have no symptoms at all, but most experience some symptoms, often beginning several years before the FMP. Understanding the natural history of menopausal symptoms requires long-term data on numerous women from diverse backgrounds. To date, most longitudinal studies have followed women for 2 to 8 years, which is not long enough to define the natural history of menopausal symptoms during the menopausal transition and into later life. In addition, these studies were designed with 1 or a small number of follow-up assessments, and they have excluded important groups of women (e.g., those with surgical menopause and those who are receiving hormone therapy). Other major limitations of these studies are that they have mainly studied white women and have asked about current symptoms only (po-

tentially missing those that occur between interviews). Most analyses consider symptoms one at a time, yet they often occur in multiples in a woman's life. Last, the age ranges of the study cohorts miss young women with premature ovarian failure and older women (ages ≥ 65 years) who may still experience menopausal symptoms. Spontaneous premature ovarian failure cannot be considered the equivalent of an early natural menopause because other disease processes may be involved that have important clinical implications.

Prevalence of Menopausal Symptoms

The following symptoms are strongly or moderately linked to menopause: hot flashes, night sweats, vaginal dryness, and sleep disturbance. There are also moderately strong prospective observational data that mood symptoms are not increased in menopause. Evidence about other symptoms is more limited (see question 1). We list the known symptom prevalence by menopausal stage, using ranges of estimates from prior cross-sectional and longitudinal studies. The wide ranges reflect differences across studies in the ways in which symptoms are measured, frequency of assessments, and characteristics of study participants. It is important to note that women who have had sudden menopause (e.g., surgical) are likely to have symptoms at the higher end of these ranges. Long-term assessment of symptoms into the postmenopausal period is lacking because of short follow-up after the FMP. Few data exist about severity, frequency, and duration of symptom episodes.

An ongoing large-scale longitudinal study of U.S. women in the menopausal transition will yield better prevalence estimates. Data presented at this conference show that menopausal symptoms are higher in early and late perimenopause than in pre- or postmenopause, except vaginal dryness (whose prevalence continues to rise across these stages).

Vasomotor Symptoms (Hot Flashes and Night Sweats)

The estimates of prevalence of vasomotor symptoms vary from 14% to 51% in premenopause, from 35% to 50% in perimenopause, and from 30% to 80% in postmenopause. High body mass index and younger age of onset of menopause are associated with more vasomotor symptoms. After the WHI study results were published, many women in clinical settings stopped hormone therapy. In 1 study, among women who had discontinued hormonal therapy, 25% resumed therapy because of symptoms. This suggests that there may be a subgroup of women for whom symptoms are so severe that they may be willing to accept some increased risk for long-term complications.

Vaginal Dryness and Painful Intercourse

Vaginal dryness becomes increasingly more common throughout the menopausal transition. Estimates of the prevalence of vaginal dryness vary from 4% to 22% in

premenopause, from 7% to 39% in perimenopause, and from 17% to 30% in postmenopause.

Sleep Disturbance

Women seem to have more sleep disturbances as they progress through the menopausal stages. The prevalence of sleep disturbance varies from 16% to 42% in premenopause, from 39% to 47% in perimenopause, and from 35% to 60% in postmenopause. Estimates were derived from studies that included women with either surgical or natural menopause.

Mood Symptoms

In different studies, the prevalence of mood symptoms varied from 8% to 37% in the premenopause, from 11% to 21% in perimenopause, and from 8% to 38% in postmenopause (natural or surgical). According to the 1 study available to the panel that examined racial or ethnic differences, African-American women may report more mood symptoms than white women during the menopausal transition, but this estimated difference was almost negligible when socioeconomic differences were taken into account.

Other Symptoms

Estimates of the prevalence of urinary symptoms vary from 10% to 36% in premenopause, from 17% to 39% in perimenopause, and from 15% to 36% in postmenopause (natural or surgical).

No association seems to exist for increased physical symptoms or cognitive problems during the menopausal transition.

Women in the age range of menopause experience an increase in sexual dysfunction (changes in libido, arousal, and other aspects of sexuality). Although an association between sexual dysfunction and vaginal dryness is plausible, studies of the association were not available for the panel to review.

Overall, the natural history of menopausal symptoms may differ among racial or ethnic groups and for women with surgically induced menopause. Current studies may provide information on the first issue, if adjusted for socioeconomic differences. Women with surgical menopause, and some who cease hormone therapy, may experience swift onset of symptoms that can be severe.

3. WHAT IS THE EVIDENCE FOR THE BENEFITS AND HARMS OF COMMONLY USED INTERVENTIONS FOR RELIEF OF MENOPAUSE-RELATED SYMPTOMS?

A variety of treatments have been studied in randomized clinical trials (RCTs) for management of menopausal symptoms. By far, the most intensively studied treatment is estrogen, often in combination with progestin. Additional treatments that have been studied include other hormones, antidepressants, isoflavones and other phytoestrogens, botanicals, acupuncture, and behavioral interventions. However, many studies, including some RCTs, have not been designed, conducted, or analyzed in ways that can support

reliable conclusions. In this report, we did not consider studies rated as poor in the Oregon Evidence-based Practice Center review.

Estrogen (Hormone Therapy)

Vasomotor Symptoms

Estrogen, either by itself or with progestins, is the most consistently effective therapy for hot flashes and night sweats. Low-dose estrogen (i.e., doses ≤ 0.3 mg of conjugated equine estrogen, ≤ 0.5 mg of oral micronized estradiol, ≤ 25 μg of transdermal estradiol, or ≤ 2.5 μg of ethinyl estradiol) has been shown to be effective for many women, although some women require a higher dose for relief of hot flashes.

Estrogen therapy at doses equivalent to 0.625 mg of conjugated equine estrogen increases the risk for serious disease events, specifically stroke; deep venous thrombosis, pulmonary embolism, or both; and, when combined with progestin medroxyprogesterone acetate, coronary events and breast cancer. In studies in which women were treated for 5 to 7 years, increased risks for coronary and thromboembolic events started to emerge in the first year of use. Risks for stroke started to increase after 2 years of use. Risks for breast cancer started to increase after 3 to 4 years of use. Although experts theorize that long-term adverse effects associated with low-dose estrogen are lower, the precise risks and benefits are not known.

Risk-benefit analyses are important for women whose vasomotor symptoms are severe and create a burden on daily life. These women may be willing to assume greater risk for the sake of reducing these symptoms.

Urogenital Symptoms

Oral estrogen, either by itself or with progestins, and a variety of vaginal estrogen preparations are beneficial for some urogenital symptoms, such as vaginal dryness and painful intercourse. Results of studies regarding the effectiveness of transdermal estradiol for the management of these urogenital symptoms are mixed. Results from 2 large studies of oral estrogen, either alone or with progestins, showed increased risk for the development of urinary incontinence and for its worsening in women who were already experiencing it.

Other Symptoms

Estrogen has also been found to be helpful for sleep disturbances and for improved quality of life. The results from studies investigating the use of estrogen for the treatment of mood symptoms are mixed. There may be a small subset of women who experience improvement in mood symptoms with estrogen therapy.

Progestins

There is a small amount of conflicting data regarding the efficacy of progesterone alone for treatment of hot flashes. Adverse effects have not been systematically stud-

ied. Studies of the efficacy of megestrol acetate for the prevention of hot flashes have been limited to breast cancer survivors (see question 4).

Androgens (Testosterone)

Testosterone can be administered in a variety of forms, including injections, subcutaneous pellets, gels, transdermal patches, and oral testosterone in combination with estrogen. Studies comparing combination oral testosterone–estrogen with estrogen alone found improvements in libido. There were no added benefits for vaginal dryness or sleep disturbances. Studies of transdermal testosterone in women with surgical menopause also show improved sexual symptoms. Adverse effects of testosterone therapy include acne, hirsutism, and weight gain. The long-term risks of taking testosterone have not been studied in this population.

Dehydroepiandrosterone

The long-term risks, benefits, and adverse effects of dehydroepiandrosterone (DHEA) have not been studied in large RCTs. A few small prospective studies suggest a potential benefit for the treatment of hot flashes and decreased sexual arousal, although small RCTs show no benefit. However, like many other dietary supplements, the lack of a standard formulation or dose for DHEA limits the ability to generalize these findings and makes it a challenging therapy to study.

Bioidentical (and “Natural”) Hormones

Bioidentical hormones, often called “natural” hormones, are treatments with individually compounded recipes of a variety of steroids in various dosage forms, with the composition and dosages based on a person’s salivary hormone concentration. These steroids may include estrone, estradiol, estriol, DHEA, progesterone, pregnenolone, and testosterone. There is a paucity of data on the benefits and adverse effects of these compounds.

Tibolone

Tibolone is a synthetic steroid compound with relatively weak hormonal activity. It is not available in the United States but has been used in Europe for treatment of vasomotor symptoms and sexual dysfunction and prevention of osteoporosis for almost 20 years. Despite widespread use of this compound, RCTs are limited in quality and results are not definitive. The few studies that have been done suggested benefit for hot flashes and sleep disturbance. In studies comparing tibolone and estrogen, the effects were similar for hot flashes and libido; however, these were small studies.

Adverse effects of tibolone include pain, weight gain, and headache. Its association with uterine bleeding is less clearly defined. The long-term effects of tibolone, particularly with respect to breast cancer, cardiovascular disease, and the reduction of osteoporotic fractures, are still unknown.

Antidepressants

A few well-designed, short-term studies with small numbers of participants have assessed the use of antidepressants for the treatment of hot flashes. Results have been mixed. Some agents, such as paroxetine and venlafaxine, may decrease hot flashes to a moderate degree and improve quality of life for symptomatic women undergoing normal menopause, as well as for breast cancer survivors. Known adverse effects for antidepressants include diminished libido, insomnia, headache, and nausea. Long-term effects are unknown.

Other Medications

The efficacy of clonidine, gabapentin, methyldopa, and bellergal for the treatment of hot flashes and the efficacy of clonidine and gabapentin for the treatment of insomnia and mood symptoms have been studied in a few small RCTs. The only available study of gabapentin demonstrated a benefit in hot flash frequency and sleep but greater somnolence, dizziness, rash, and peripheral edema. Clonidine demonstrated efficacy in reducing hot flash frequency in studies of breast cancer survivors, but not in other groups. In this group, compared with placebo, clonidine was associated with greater difficulty sleeping. For the other drugs, most studies found no benefit for the outcomes studied.

Isoflavones and Other Phytoestrogens

A substantial number of studies of phytoestrogens and isoflavones have been conducted, motivated by epidemiologic data showing differences in levels of menopausal symptoms in countries with different levels of these nutrients in their diets. Because most of these products are not manufactured in a standardized way, they may differ in composition from trial to trial. Several studies of soy extracts suggested that they may have some mitigating effect on hot flashes. Trials of dietary soy are mixed; the majority of studies did not indicate benefit. Adverse event information provided in these studies is very limited, and long-term side effects have not been investigated.

Complementary and Alternative Approaches

The findings of the WHI have contributed to the public’s growing interest in complementary and alternative approaches for the management of vasomotor symptoms. In general, research on these approaches is scant and to date has focused primarily on botanicals, with a few studies of other approaches.

Botanicals

Only a few of the botanical products on the market have been carefully studied. Progress in investigating these supplements is hampered by methodologic challenges, including natural variability in the target botanical and other product components and variability in methods of extraction and other aspects of production.

Black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*)

mosa) is the most studied botanical product. Originally, it was thought that black cohosh had estrogenic properties, but recent work suggests that it does not. In the English-language literature, there is little evidence that black cohosh is an effective treatment for hot flashes. However, methodologic issues compromise much of the existing research, and ongoing NIH trials should provide helpful data. Black cohosh has had a good safety record over many years. Some cautions have been raised about possible adverse effects of black cohosh on the liver, but variability in a given product and use of concomitant products make it difficult to ascertain exactly what was taken when adverse events were reported.

Kava (*Piper methysticum*) has been shown to be effective in reducing anxiety, but evidence is lacking with respect to its effects on hot flashes. Furthermore, kava has been associated with damage to the liver. The U.S. Food and Drug Administration has issued a warning to patients and providers about potential harm.

Red clover leaf (*Trifolium pretense*) contains phytoestrogen compounds and is believed to work as a weak estrogen. However, studies suggest that it is not effective in reducing hot flashes.

Dong quai root (*Angelica sinensis*) is widely used for a variety of symptoms, but there is evidence that it is not effective for the treatment of hot flashes. There is an interaction with warfarin that may lead to bleeding complications.

Ginseng root (*Panax ginseng* or *Panax quinquefolius*) may be helpful with respect to quality-of-life outcomes, such as well-being, mood, and sleep, but it does not seem to affect hot flashes.

In general, the study of botanicals as treatments for hot flashes is still in its infancy. There are major methodologic problems associated with studying products that are not standardized. Basic research on dosing, factors that affect the metabolic processes of these products, and mechanisms of action is needed for this area of investigation to move forward on a solid foundation.

Overall, there is a paucity of well-designed studies of complementary and alternative approaches, including acupuncture, energy modalities, mind–body approaches, homeopathy, and manipulative and body-based practices, in addition to approaches from other healing systems, including Traditional Chinese Medicine and Indian ayurvedic medicine. Although many studies on a variety of botanicals have been published, most have important limitations that make their findings unclear.

Behavioral Interventions for Hot Flashes and Other Menopausal Symptoms

Behavioral interventions may be an important area of investigation for the treatment of menopause-related symptoms because adverse effects are rare. However, the effectiveness of such interventions has not yet been demon-

strated in large, well-controlled studies. In several small studies:

1. Exercise resulted in improved quality of life but did not affect vasomotor symptoms, vaginal dryness, or other menopause-related symptoms.
2. Health education resulted in improved knowledge about menopause and menopause-related symptoms but did not change the symptoms themselves.
3. Paced respiration (a type of slow, deep breathing that requires training) for hot flashes showed early promise in a very small group of patients.

4. WHAT ARE THE IMPORTANT CONSIDERATIONS IN MANAGING MENOPAUSE-RELATED SYMPTOMS IN WOMEN WITH CLINICAL CHARACTERISTICS OR CIRCUMSTANCES THAT MAY COMPLICATE DECISION MAKING?

Decision making for women regarding treatment of menopausal symptoms requires balancing of potential benefits against potential risks. Women at high risk for serious medical outcomes with the use of estrogen include those with a history of breast cancer; those with an elevated risk for breast, ovarian, or both types of cancer on the basis of genetic factors, family history, or both; and those who have, or are at high risk for, cardiovascular disease. Women with these risk factors may be particularly motivated to seek nonhormonal therapies to treat menopausal symptoms. A few small studies in breast cancer survivors suggest that some antidepressants (such as venlafaxine) can effectively treat vasomotor symptoms in women with breast cancer. Other treatments, including clonidine and megestrol acetate, have also shown positive effects in a few studies. These treatments have their own adverse effects (such as decreased libido, nausea, dry mouth, or constipation) that need to be weighed against the potential benefits. The long-term safety of these agents in women with breast cancer has not been studied but is of concern because of their potential estrogenic actions. Vaginal estrogen preparations to treat vaginal dryness and pain with intercourse may also be an attractive option for these women. Such topical therapies are known to increase circulating estrogen levels, but by much smaller amounts than oral estrogen therapy. Because these topical therapies have not been studied in large numbers of women for long periods of time, actual levels of risk for long-term complications, such as breast cancer occurrence or recurrence, while probably much lower than those of oral therapy, are not fully known.

Women who have had their ovaries surgically removed (causing surgically induced menopause) often experience more severe symptomatology, including hot flashes and vaginal dryness. Benefits and risks of estrogen therapy in these women are generally similar to those found in studies of other women who have had hysterectomies and are taking estrogen. Risks may be elevated, however, in women

whose oophorectomies were performed specifically to treat or prevent cancer.

In women who have undergone an oophorectomy and a hysterectomy, some studies suggest that oral or transdermal testosterone improves sexual function and psychological well-being. These studies did not demonstrate a benefit for testosterone for the treatment of vaginal dryness, sleep disturbances, or mood.

5. WHAT ARE THE FUTURE RESEARCH DIRECTIONS FOR TREATMENT OF MENOPAUSE-RELATED SYMPTOMS AND CONDITIONS?

The future research direction for the treatment of menopausal symptoms is multifaceted and can be categorized as conceptual, methodologic, care-oriented, and targeted at improving quality of care.

Conceptual

A conceptual framework is needed to link the most prevalent menopausal symptoms to genetic, neurochemical, neurobiological, and physiologic factors and reproductive surgical or medical treatments hypothesized to cause symptoms in the social and cultural context in which women experience them. Testing of the hypothesized associations in a comprehensive conceptual framework will delineate which symptoms are and are not closely associated with hormonal changes and may identify novel nonhormonal treatments targeted to specific neurochemical and biochemical pathways for the most bothersome symptoms.

Methodologic

Reliable and valid data collection instruments for the study of the most prevalent menopausal symptoms are needed, and the research community should be given incentives to use the same standardized measures across studies. These instruments need to be developed and validated in multiple languages. A standardized set of measurement tools for specific domains should be developed for use in federally funded studies and encouraged for use in all studies. Standardized approaches for the assessment of vasomotor symptoms and urogenital symptoms will greatly facilitate the comparison and pooling of results across studies.

In many of the large, well-designed clinical trials, menopausal symptoms, such as hot flashes, improved in 30% to 35% of women in the placebo groups. This high rate of resolution of symptoms may be part of the natural progression of menopausal symptoms or may be due to ancillary treatments or self-care practices, regression to the mean, or other measurement issues. Because of this very consistent finding across many trials, it is critical that all evaluations of new treatments are rigorously studied in randomized designs that include a suitable placebo or control arm. When feasible, these studies should be blinded to the participant and investigator.

Many of the reviewed studies had flawed approaches in design and analysis. More attention to optimal applica-

tion of statistical methods is crucial for both the longitudinal observational studies and clinical trials of new treatments.

To date, the vast majority of longitudinal data that describe menopausal symptoms and the effectiveness of treatments have been collected among white women. This raises critical questions about the ability to generalize findings from these studies to women from multiple ethnic and racial groups who reside in the United States. Therefore, it is critical that future observational studies and treatment trials for menopausal symptoms recruit members of ethnic and racial groups in a way that allows for precise estimates of the effects in the entire target population. In general, this will require sampling from minority groups at least in proportion to their representation in the target population. When feasible, numbers of women from minority ethnic and racial groups should be large enough to allow for reasonably precise estimates of effects within these subgroups. Systematic monitoring for adverse events needs to be implemented in all treatment trials, and both methods of monitoring and safety findings need to be included in study reports.

Symptom Management and Treatment

New research is needed that will describe the patient characteristics and self-care behaviors that are associated with fewer bothersome symptoms and better quality of life during the menopausal transition. What physical, emotional, and social characteristics predict this resilience? What assumptions do these women make about their bodies, aging, symptoms, and quality of life? Research is also needed about nonmedical treatments, including behavioral treatments, and complementary and alternative approaches to menopausal symptom management.

Longer-term follow-up studies are needed to gain a better understanding of the natural history of symptom trajectories 15 to 25 years after menopause. We also need to learn more about the minority of women who experience debilitating menopausal symptoms that affect their quality of life and functioning and who are most in need of safe treatments. The ideal observational studies would follow a diverse population of women for several decades, with few exclusion criteria; frequent follow-ups; and full symptom histories, including symptoms occurring in the time between interviews. Data describing the normal course of symptoms (namely, for women with natural menopause who take no menopause-related medications) constitute a crucial baseline for comparison with special subgroups, such as women with surgical menopause.

Little is known about major adverse events that could be associated with 3-year to 5-year exposures to low-dose estrogen and progestins for the treatment of moderate to severe menopausal symptoms. Particular attention needs to be paid to the measurement of thrombotic and cardiovascular events and breast cancer that may occur 5 to 10 years after a 3-year to 5-year exposure to low-dose hormones. A

new treatment trial of symptomatic samples of multiethnic women in the menopausal transition, with adequate representation over a range of body mass indices and designed to address the ideal dose, most appropriate duration, methods for discontinuing hormone therapy, and long-term adverse events, is needed. Because of the systemic absorption of topical application, an RCT is needed to assess the long-term safety of locally applied estrogens for vaginal dryness and dyspareunia in survivors of breast cancer. Clinical trials for the management of menopausal symptoms are also needed for women who have had prophylactic oophorectomy and thereby may experience especially severe symptoms, as noted earlier. Further investigations need to be performed to determine the efficacy and safety of testosterone monotherapy for the treatment of sexual dysfunction.

The newer classes of antidepressants, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors show some promising early results for the treatment of vasomotor symptoms, mainly among breast cancer survivors. However, adequately powered and longer (≥ 1 year) RCTs are needed to study the long-term effectiveness of medications such as venlafaxine and paroxetine and to more fully measure their adverse effects, such as decreased libido, nausea, insomnia, and headaches. In addition, smaller physiologic studies are needed to better understand which medications in these classes may decrease the effectiveness of tamoxifen and other selective estrogen receptor modulators (SERMs) that are used in breast cancer survivors.

A large barrier to identifying whether any of the dietary supplements are effective for treating menopause is the lack of standardization of the various preparations. This has led to large differences in the content of active ingredients in various preparations. A critical first step would be to establish batch-to-batch consistency and to conduct dose-ranging studies prior to conducting phase 2 and phase 3 trials to determine proof of concept and efficacy. Similarly, studies of other complementary and alternative medicine treatments need to address standardization of methods and dosages. Ultimately, clinical trials of complementary and alternative medicine therapies should assess both safety and efficacy, but it is premature to recommend these until the described steps have been accomplished.

Cross-national studies of menopause symptoms and their management are welcome additions to U.S. data. Besides self-reports, they could include objective measures of vasomotor symptoms. This would help elucidate how much differences in symptom experience are based on physiologic manifestations versus cultural differences in symptom perception, evaluation, and reporting.

Quality of Care

Tools are needed to assist health care providers and women with the estimation of absolute, as well as relative, risk of hormonal therapy during the clinical encounter so

that women have a better understanding of their personal risk profile if they decide to use hormonal therapy. Translational research is needed to enhance the knowledge of health care providers and women of the normal resolution of many symptoms among women who do not use medications. In the event that hormonal therapy is needed to manage menopausal symptoms, quality of care could be enhanced if a greater proportion of providers and patients initiated therapy at the lowest dose known to be effective rather than the dose tested in the WHI.

CONCLUSIONS

1. Menopause is the permanent cessation of menstrual periods that occurs naturally in women, usually in their early 50s. Many women have few or no symptoms; these women are not in need of medical treatment.

2. Premenopausal or perimenopausal women who have menopause induced by surgery, chemotherapy, or radiation are more likely to experience bothersome and even disabling symptoms. These women need safe and effective treatment.

3. It is difficult to differentiate those symptoms that are truly associated with menopause from those due to aging. Hot flashes, night sweats, and vaginal dryness are clearly tied to the menopausal transition, and there is some positive evidence of a menopausal link for sleep disturbance.

4. Vasomotor symptoms are reported with high frequency during the menopausal transition. Estrogen, either by itself or with progestins, is the most consistently effective therapy for these symptoms. However, the WHI has identified important risks associated with use of these therapies. Decision making for women regarding treatment for menopausal symptoms requires personal knowledge and balancing of these risks.

5. There are many potential alternatives to estrogen. However, their effectiveness and long-term safety need to be studied in rigorous clinical trials in diverse populations of women.

6. To address the charge to this panel, much more research is needed to clearly define the natural history of menopause, associated symptoms, and effectiveness and safety of treatments for bothersome symptoms. Natural histories are important for both science and policy. Knowing how many women transit menopause with few or no symptoms, and how many manage menopause largely on their own, can lead to public health information that empowers women and increases their self-reliance. Medical care and future clinical trials are best focused on women with the most severe and prolonged symptoms.

7. The state of the science in management of menopausal symptoms should be reassessed periodically.

Menopause is "medicalized" in contemporary U.S. society. There is great need to develop and disseminate information that emphasizes menopause as a normal, healthy

phase of women's lives and promotes its demedicalization. Medical care and future clinical trials are best focused on women with the most severe and prolonged symptoms. Barriers to professional care for these women should be removed.

APPENDIX

NIH State-of-the-Science Panel on Management of Menopause-Related Symptoms

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