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

March 21–23, 2005

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsored by:

- National Institute on Aging, NIH
- Office of Medical Applications of Research, NIH

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- Office of Research on Women's Health, NIH
- National Center for Complementary and Alternative Medicine, NIH
- National Cancer Institute, NIH
- National Heart, Lung, and Blood Institute, NIH
- National Institute of Child Health and Human Development, NIH
- National Institute of Mental Health, NIH
- U.S. Food and Drug Administration
- Office on Women's Health, U.S. Department of Health and Human Services

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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V. Strategies and Issues for Managing Menopause-Related Symptoms in Diverse Populations

Introduction

Background

Women going through the menopause transition may experience a variety of symptoms, ranging from hot flashes, night sweats, and problems sleeping to loss of sexual desire, depression, vaginal dryness, and urinary and bleeding complaints. As many as two-thirds of all women may experience vasomotor symptoms, such as hot flashes and night sweats, in the years around the menopause transition. For some, the resulting discomfort greatly diminishes their quality of life.

For many decades, menopausal hormone therapy (MHT) using estrogen (or, in a woman with a uterus, a combination of estrogen and progestin) has been the therapy of choice for relieving menopause-related symptoms. But recently, several large clinical trials have found mixed results—a greater chance of serious health problems, such as blood clots, stroke, heart disease, or breast cancer, and benefits like fewer hip fractures in certain groups of women using MHT. It is not clear how these findings apply to women with symptoms because these clinical trials were not designed to study such women, but rather to test whether MHT could prevent chronic diseases or conditions of aging, such as heart disease or cognitive decline. Nevertheless, many women and their doctors are concerned about the use of MHT for their menopausal symptoms and interested in learning about alternatives.

Research has identified a number of hormonal and nonhormonal approaches that show promise for managing menopause-related symptoms. A careful examination of these strategies for symptom management is urgently needed to provide women and their health care providers with options that will best control their symptoms and restore their quality of life.

Conference Process

To address this need, the National Institute on Aging and the Office of Medical Applications of Research, of the NIH, will sponsor a State-of-the-Science Conference on Management of Menopause-Related Symptoms, March 21–23, 2005, in Bethesda, MD. During the first 2 days of the conference, experts will present information on the biology of the menopause transition, the nature of the symptoms women experience, and strategies for relieving the common problems associated with the menopause transition.

After weighing all of the scientific evidence, an independent panel will prepare and present a state-of-the-science statement answering the key conference questions:

- What is the evidence that the symptoms more frequently reported by middle-aged women are attributable to ovarian aging and senescence?

- When do the menopausal symptoms appear, how long do they persist and with what frequency and severity, and what is known about the factors that influence them?

- What is the evidence for the benefits and harms of commonly used interventions for relief of menopause-related symptoms?

- What are the important considerations in managing menopause-related symptoms in women with clinical characteristics or circumstances that may complicate decisionmaking?

- What are the future research directions for treatment of menopause-related symptoms and conditions?

On the final day of the conference, the panel chairperson will read the draft statement to the conference audience and invite comments and questions.

General Information

Conference sessions will be held in the Natcher Conference Center, NIH, Bethesda, Maryland.

The conference may be viewed live via Webcast at http://videocast.nih.gov/. Webcast sessions will also be available after the conference.

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

The telephone number for the message center at the Natcher Conference Center is 301–594–7302.

Conference Sponsors

The primary sponsors of the conference are:

- National Institute on Aging, NIH
- Office of Medical Applications of Research, NIH

The co-sponsors of the conference are:

- Office of Research on Women's Health, NIH
- National Center for Complementary and Alternative Medicine, NIH
- National Cancer Institute, NIH
- National Heart, Lung, and Blood Institute, NIH
- National Institute of Child Health and Human Development, NIH
- National Institute of Mental Health, NIH

- U.S. Food and Drug Administration
- Office on Women's Health, U.S. Department of Health and Human Services

The Agency for Healthcare Research and Quality (AHRQ) provided additional support to the conference development.

Financial Disclosure

Each speaker presenting at this conference has been asked to disclose any financial interests or other relationships pertaining to this subject area. Please refer to the material in your participant packet for details.

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

AGENDA

Monday, March 21, 2005

8:00 a.m. Opening Remarks
Richard Hodes, M.D.
Director
National Institute on Aging
National Institutes of Health

8:10 a.m. **Vivian W. Pinn, M.D.**
Associate Director for Research on Women's Health
Director
Office of Research on Women's Health
National Institutes of Health

8:15 a.m. **Stephen Straus, M.D.**
Director
National Center for Complementary and Alternative Medicine
National Institutes of Health

8:20 a.m. Charge to the Panel
Susan Rossi, Ph.D., M.P.H.
Deputy Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:30 a.m. Conference Overview and Panel Activities
Carol M. Mangione, M.D., M.S.P.H.
Conference and Panel Chairperson
Director
Resource Center for Minority Aging Research
Professor of Medicine
David Geffen School of Medicine at University of California, Los Angeles

I. Menopause-Related Symptoms: Definitions, Overview, and Association With Physiologic and Hormonal Changes

8:45 a.m. Defining the Menopause Transition
Sherry S. Sherman, Ph.D.
Program Director
Clinical Aging and Reproductive Hormone Research
National Institute on Aging
National Institutes of Health

Monday, March 21, 2005 (continued)

I. Menopause-Related Symptoms: Definitions, Overview, and Association With Physiologic and Hormonal Changes (continued)

9:00 a.m. The Menopausal Transition
Nanette F. Santoro, M.D.
Professor and Director
Division of Reproductive Endocrinology
Albert Einstein College of Medicine

9:20 a.m. Symptoms During the Perimenopause: Prevalence, Security, Trajectory, and Significance in Women's Lives
Nancy Fugate Woods, Ph.D., R.N., F.A.A.N.
Dean
School of Nursing
University of Washington

9:40 a.m. Symptoms and Health-Related Quality of Life and the Menopausal Transition
Karen A. Matthews, Ph.D.
Professor of Psychiatry, Psychology, and Epidemiology
Director
Pittsburgh Mind-Body Center
University of Pittsburgh

10:00 a.m. Discussion
Participants with questions or comments for the speakers should proceed to the microphones and wait to be recognized by the panel chair. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted at the registration desk. Please be aware that all statements made at the microphone or submitted later are in the public domain.

II. Menopause-Related Symptoms: Predictors, Risk Factors, and Characteristics (Time of Appearance, Severity, Frequency, and Persistence)

10:20 a.m. A Universal Menopausal Syndrome?
Nancy Avis, Ph.D.
Professor and Section Head
Section on Social Sciences and Health Policy
Department of Public Health Sciences
Wake Forest University School of Medicine

Monday, March 21, 2005 (continued)

II. Menopause-Related Symptoms: Predictors, Risk Factors, and Characteristics (Time of Appearance, Severity, Frequency, and Persistence) (continued)

10:40 a.m. Perimenopause: Urogenital and Bleeding Issues
Bradley J. Van Voorhis, M.D.
The F.K. "Ted" Chapler Professor of Reproductive Endocrinology
Director
Division of Reproductive Endocrinology and Infertility
University of Iowa Hospitals and Clinics

11:00 a.m. Mood, Depression, and Reproductive Hormones in the Menopause Transition
Peter J. Schmidt, M.D.
Chief
Unit on Reproductive Endocrine Studies
Behavioral Endocrinology Branch
National Institute of Mental Health
National Institutes of Health

11:20 a.m. Sexuality
Lorraine Dennerstein, A.O., M.B.B.S., Ph.D., D.P.M., FRANZCP
Director
Office for Gender and Health
Department of Psychiatry
University of Melbourne

11:40 a.m. Symptoms During the Menopausal Transition: Evidence From Cohort Studies
Elizabeth Haney, M.D.
Assistant Professor of Medicine
Oregon Evidence-based Practice Center
Oregon Health & Science University

Noon Discussion

12:30 p.m. Lunch
Panel Executive Session

Monday, March 21, 2005 (continued)

III. Treatments for Symptoms During the Menopausal Transition: Benefits and Harms of Commonly Used Interventions

1:30 p.m. Background/History: Estrogens and Progestins (Formulations, Doses, Routes of Administration, and Schedule): Trends in Use and FDA Issues
Marcia L. Stefanick, Ph.D.
Professor of Medicine and Professor of Obstetrics and Gynecology
Stanford Prevention Research Center
Stanford University School of Medicine

1:50 p.m. Symptom Relief Versus Unwanted Effects: Role of Estrogen-Progestin Dosage and Regimen
Bruce Ettinger, M.D.
Clinical Professor of Medicine
University of California, San Francisco

2:10 p.m. Estrogens With and Without Progestin: Benefits and Risks of Short-Term Use
Andrea Z. LaCroix, Ph.D.
Professor of Epidemiology
University of Washington
Co-Principal Investigator
Women's Health Initiative Clinical Coordinating Center
Fred Hutchinson Cancer Research Center

2:30 p.m. Therapeutic Effects of Progestins, Androgens, and Tibolone for Menopausal Symptoms
James H. Liu, M.D.
Arthur H. Bill Professor and Chairman
Department of Obstetrics and Gynecology and Department of Reproductive Biology
Case Western Reserve University

2:50 p.m. Diagnosis and Management of Mood Disorder During the Menopause Transition
Lee S. Cohen, M.D.
Director
Perinatal and Reproductive Psychiatry Program
Massachusetts General Hospital

Monday, March 21, 2005 (continued)

III. Treatments for Symptoms During the Menopausal Transition: Benefits and Harms of Commonly Used Interventions (continued)

3:10 p.m. Hormonal Treatment of Menopause-Related Symptoms: Evidence From Randomized Controlled Trials
Heidi D. Nelson, M.D., M.P.H., F.A.C.P.
Associate Professor of Medicine and Medical Informatics and Clinical Epidemiology
Oregon Evidence-based Practice Center
Oregon Health & Science University

3:30 p.m. Discussion

IV. Alternative and Complementary Strategies for Managing Symptoms

4:00 p.m. Menopause: Review of Botanical Dietary Supplement Research
Tieraona Low Dog, M.D.
Clinical Assistant Professor
Department of Medicine
Director of Botanical Studies
University of Arizona College of Medicine

4:30 p.m. Other Complementary and Alternative Medicine Modalities: Acupuncture, Magnets, Reflexology, and Homeopathy
Janet S. Carpenter, Ph.D., R.N.
Associate Professor
Department of Adult Health
Indiana University School of Nursing

4:50 p.m. Discussion

5:15 p.m. Adjournment

Tuesday, March 22, 2005

IV. Alternative and Complementary Strategies for Managing Symptoms (continued)

8:00 a.m. Centrally Active, Nonhormonal Hot Flash Therapies
Charles L. Loprinzi, M.D.
Professor
Department of Oncology
Mayo Clinic College of Medicine

Tuesday, March 22, 2005 (continued)

IV. Alternative and Complementary Strategies for Managing Symptoms (continued)

8:20 a.m. Hot Flashes: Behavioral Treatments, Mechanisms, and Relationship With Sleep
Robert R. Freedman, Ph.D.
Professor of Psychiatry and Professor of Obstetrics and Gynecology
Wayne State University School of Medicine

8:50 a.m. Nonhormonal Treatment of Menopause-Related Symptoms: Evidence From Randomized Controlled Trials
Heidi D. Nelson, M.D., M.P.H., F.A.C.P.
Associate Professor of Medicine and Medical Informatics and Clinical Epidemiology
Oregon Evidence-based Practice Center
Oregon Health & Science University

9:10 a.m. Discussion

V. Strategies and Issues for Managing Menopause-Related Symptoms in Diverse Populations

9:40 a.m. Special Considerations: Bilateral Oophorectomy and Premature Menopause
Susan L. Hendrix, D.O.
Professor
Department of Obstetrics and Gynecology
Hutzel Hospital
Wayne State University School of Medicine

10:00 a.m. Breast Cancer, Menopause, and Long-Term Survivorship: Critical Issues for the Twenty-First Century
Patricia A. Ganz, M.D.
Professor
Schools of Medicine and Public Health
University of California, Los Angeles
Director
Division of Cancer Prevention and Control Research
Jonsson Comprehensive Cancer Center

10:20 a.m. Ethnic/Racial Diversity
Valerie Montgomery-Rice, M.D.
Professor and Chair
Department of Obstetrics and Gynecology
Meharry Medical College

Tuesday, March 22, 2005 (continued)

V. Strategies and Issues for Managing Menopause-Related Symptoms in Diverse Populations (continued)

10:40 a.m. Lifestyle Factors: Are They Related to Vasomotor Symptoms and Do They Modify the Effectiveness or Side Effects of Hormone Therapy?
Gail A. Greendale, M.D.
Professor
University of California, Los Angeles

11:00 a.m. The Impact of Risk Status, Pre-Existing Morbidity, and Polypharmacy on Treatment Decisions Concerning Menopausal Symptoms
Nananda F. Col, M.D., M.P.P., M.P.H., F.A.C.P.
Associate Professor of Medicine
Division of General Internal Medicine
Brown Medical School
Rhode Island Hospital

11:20 a.m. Issues Related to Discontinuation of Menopausal Hormone Therapy
Deborah Grady, M.D., M.P.H.
Professor of Epidemiology and Biostatistics and Professor of Medicine
University of California, San Francisco School of Medicine

11:40 a.m. Managing Symptoms: Where Have We Come From and Where Do We Go?
Isaac Schiff, M.D.
Chief
Vincent Obstetrics/Gynecology Services
Massachusetts General Hospital
Joe Vincent Meigs Professor of Gynecology
Department of Obstetrics and Gynecology
Harvard Medical School
Massachusetts General Hospital

Noon Discussion

12:30 p.m. Adjournment

Wednesday, March 23, 2005

9:00 a.m. Presentation of the draft State-of-the-Science Statement

9:30 a.m. Public Discussion
The panel chair will call for questions and comments from the audience on the draft consensus statement, beginning with the introduction and continuing through each subsequent section in turn. Please confine your comments to the

section under discussion. The chair will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Comments cannot be accepted after 11:30 a.m.

11:00 a.m. Panel Meets in Executive Session
Panel meets in executive session to review public comments. Conference participants are welcome to return to the main auditorium to attend the press conference at 2:00 p.m.; however, only members of the media are permitted to ask questions during the press conference.

2:00 p.m. Press Conference

3:00 p.m. Adjournment

The panel's draft statement will be posted to www.consensus.nih.gov as soon as possible after the close of proceedings and the final statement will be posted 3–4 weeks later.

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[She was unable to attend the Planning Committee Meeting but advised OMAR in the initial stage of planning.]

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Abstracts

The following are the abstracts of the proposed speaker presentations at the NIH State-of-the-Science Conference on Management of Menopause-Related Symptoms. They are designed for use by the panelists and the participants in the conference, and as a reference document for anyone interested in conference deliberations. We are grateful to the authors, who summarized their materials and made them available in a timely fashion.

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Defining the Menopause Transition

Sherry S. Sherman, Ph.D.

Natural menopause, which is defined by the World Health Organization (WHO) as the "permanent cessation of menstruation resulting from the loss of ovarian follicular activity,"[1] corresponds to a single point in time—the final menstrual period. It is the culmination, however, of some 50 years of reproductive aging—a process which unfolds as a continuum from birth through the menopause transition and ovarian senescence. The menopause transition represents a period of dynamic changes in reproductive and nonreproductive tissues and, hence, is believed to play a pivotal role in the biology and health status of the aging woman. The quest of increasing the scientific knowledge base on the menopause transition and its health-related sequelae has been the impetus for developing more sensitive and specific nomenclature in classifying menopausal status.

Efforts to establish and promote the use of a uniform set of menopause-related terminology have been ongoing since the seventies by groups such as the International Menopause Society,[2] Korpilampi Workshop participants,[3] and the WHO.[1,4] Definitions developed by the WHO in 1996 have experienced widespread use and are as follows:[1]

1. "The term *natural menopause* is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.

   Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect as a year or more after the event. An adequate independent biological marker for the event does not exist.

2. The term *perimenopause* should include the period immediately prior to menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause.

3. The term *menopausal transition* should be reserved for that period of time before the FMP when variability in the menstrual cycle is usually increased.

4. The term *premenopause* should be used to refer to the whole of the reproductive period up to the FMP.

5. The term *induced menopause* is defined as the cessation of menstruation which follows either surgical removal of both ovaries (with or without a hysterectomy) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or radiation).

6. The term *postmenopause* is defined as dating from the FMP, regardless of whether the menopause was induced or spontaneous.

7. Ideally, *premature menopause* should be defined as menopause that occurs at an age less than two standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature."

Other terminology, such as the *climacteric* (which includes the menopause transition as well as the unspecified period after the FMP), are internationally popular but have been employed primarily outside the United States.[5]

Although, the WHO definitions have been widely used in the clinical setting, it is apparent that they lack the sensitivity, specificity, and evidence base needed to operationally define a woman's reproductive status for scientific investigations of the menopause transition. To address these concerns, the Staging Reproductive Aging Workshop (STRAW) convened in 2001. The objective of this meeting was to develop a standardized and practical staging system for reproductive aging in women that could be reliably used by the research community as well as in the clinical setting. Aging changes in domains, such as menstrual cyclicity, endocrine status, pelvic anatomy, fertility, and the presentation of menopause-related symptoms, were evaluated for their potential role in specifying demarcations in the continuum of reproductive aging across the lifespan.[6]

Proposed Consensus Staging System and Revised Nomenclature

Figure 1. Proposed Consensus Staging System and Revised Nomenclature[6]

<table>
<tr><td></td><td colspan="3"></td><td colspan="2"></td><td>Final Menstrual Period (FMP)</td><td colspan="2"></td></tr>
<tr><td>Stages</td><td>-5</td><td>-4</td><td>-3</td><td>-2</td><td>-1</td><td>0</td><td>+1</td><td>+2</td></tr>
<tr><td rowspan="3">Terminology:</td><td colspan="3">Reproductive</td><td colspan="2">Menopausal Transition</td><td colspan="2">Postmenopause</td></tr>
<tr><td>Early</td><td>Peak</td><td>Late</td><td>Early</td><td>Late*</td><td colspan="2">Early*</td><td>Late</td></tr>
<tr><td colspan="5"></td><td colspan="3">Perimenopause</td></tr>
<tr><td>Duration of Stage:</td><td colspan="3">Variable</td><td colspan="2">Variable</td><td>1 yr</td><td>4 yrs</td><td>Until Demise</td></tr>
<tr><td rowspan="2">Menstrual Cycles</td><td rowspan="2">Variable to regular</td><td colspan="2">Regular</td><td rowspan="2">Variable cycle length (> 7 days different from normal)</td><td rowspan="2">≥ 2 skipped cycles and an interval of amenorrhea (≥ 60 days)</td><td rowspan="2">†Amenor 12 mos</td><td colspan="2" rowspan="2">None</td></tr>
<tr><td></td><td>Length decreases ~2 days</td></tr>
<tr><td>Endocrine</td><td colspan="2">Normal FSH</td><td>↑ FSH</td><td colspan="2">↑ FSH</td><td colspan="3">↑ FSH</td></tr>
</table>

*Stages most likely to be characterized by vasomotor symptoms; †amenor = amenorrhea

↑ = Elevated

The proposed STRAW consensus staging system is anchored by the final menstrual period (FMP) and consists of seven stages which are independent of age (see figure 1). Five stages, constituting the reproductive interval (3 stages) and the menopausal transition (2 stages), precede the FMP, which is then followed by postmenopause (2 stages). The stages are distinguished

principally by progressive changes in clinical (i.e., menstrual cycle length and regularity) and endocrine (i.e., follicle stimulating hormone levels) parameters.[7] Ongoing research investigations are focused on refining menstrual cycle and hormonal criteria for operationally defining stage 2 (entry into the menopause transition) as well as demarcating the various stages. Validation of the proposed criteria in diverse populations is necessary to establish the appropriateness, usefulness, and acceptability of the new proposed staging system in both the clinical and research settings.

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The Menopausal Transition

Nanette Santoro, M.D.

Reproductive aging in women is related largely, but not entirely, to the depletion of a fixed number of germ cells within the ovary.[1] This is a gradual, but sometimes exponential, process that appears to accelerate at certain times in a woman's life: Prenatally, there is a marked decline of almost half the existing follicle pool, and then the dwindling process (atresia) slows somewhat, until the early 40s when total remaining follicle numbers appear to be in the thousands. At this point in life, atresia seems to become rapid once again and women progress through the menopausal transition to essentially zero oocytes by a median age of 52.4 years. The limited numbers of follicles within the ovary play a negative role in terms of fertility and hormonal dynamics. The reduced follicle pool results in a loss of inhibin B production, which in turn release physiological 'restraint' on follicle stimulating hormone (FSH) secretion.[2] This rise in FSH, characteristic of the menopausal transition, can result in a spectrum of follicle function: If a responsive follicle is present, there may be overly exuberant production of sex steroids and even multiple folliculogenesis; if a partially responsive follicle is present, folliculogenesis may occur in part but not to its conclusion of ovulation and corpus luteum formation; and finally, if inadequately responsive follicles are all that are present, there may be no folliculogenesis at all and amenorrhea will ensue. It is important to remember that there are two follicle pools—those that are immediately available for growth within the current recruitable pool and those that are as yet insensitive to gonadotropin signals. Thus, a woman may have several months of inadequate folliculogenesis that is followed by several months of more normal cycling, as the recruitable follicles turn over. This mechanism may explain the enormous variability of reproductive hormonal patterns across the transition.[3–9] In addition to these ovary-based changes, there is evidence that the central nervous system does not respond normally to estrogen and fails to produce preovulatory luteinizing hormone surges effectively in women in the early menopausal transition.[4] The Study of Women's Health Across the Nation (SWAN) has allowed us to examine hormonal dynamics across entire menstrual cycles in a community-based cohort of women using daily urinary sampling. Cycles with and without evident luteal function were analyzed in women in the early stages of the transition. Age and body size were predictive of aluteal cycles and hormone excretion was overall lower in women of larger body size.[10] When annual hormone serum samples were examined in SWAN, most of the drop in estradiol and rise in FSH were noted to occur during the late transition to the postmenopause stage of the process, in near-exact agreement with Melbourne Women's Health Project.[6,11]

Clinically, it is important to appreciate that the entire reproductive system is undergoing change across the transition—not just the ovary. Reproductive hormonal fluctuations may underlie some of the common symptomatology of perimenopause.

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Symptoms During the Perimenopause: Prevalence, Severity, Trajectory, and Significance in Women's Lives

Nancy Fugate Woods, Ph.D., R.N., F.A.A.N. and Ellen Mitchell, Ph.D., R.N.

As women complete the transition to menopause, an estimated 85 percent report one or more symptoms,[1] with 30–50 percent of women reporting hot flashes.[1–3] Symptoms, such as hot flashes, sleep disruption, bleeding, and dysphoric mood, prompt nearly 10 percent of women to make visits to health care providers during perimenopause.[1] In the post-Women's Health Initiative era, symptom management has become more complex owing to recent awareness of the risks associated with hormone therapy. Women employ a range of symptom management options, including self-care strategies with uses of over-the-counter preparations, complementary and alternative therapies, and lifestyle modifications as well as prescription drugs.[1] Thus, perimenopause provides women with an opportunity to consider strategies for both symptom management and promotion of healthy aging.

The purposes of this paper are to examine published evidence from longitudinal studies of the menopausal transition addressing the following questions: (1) which symptoms do women report during perimenopause; (2) how prevalent are these symptoms and does the prevalence of symptoms change as women traverse the menopausal transition stages and become postmenopausal; (3) how severe are symptoms and for how long do they persist; (4) to what do women attribute their symptoms; and (5) how significant are these symptoms in women's lives?

Data from published longitudinal studies of the menopausal transition were examined for evidence bearing on each of these questions. Published reports from the Massachusetts Women's Health Study,[1] the Healthy Women Study,[4] Manitoba Project on Women and their Health in the Middle Years,[2] Norwegian Menopause Project,[5] Seattle Midlife Women's Health Study,[6] Melbourne Midlife Women's Health Project,[3] the Penn Ovarian Aging Study,[7] and the Study of Women's Health Across the Nation (SWAN)[8] were reviewed. Where possible the Staging Reproductive Aging Workshop criteria were used to approximate the menopausal transition stage.[9]

Midlife women report many different types of symptoms (e.g., vasomotor, vaginal dryness, sleep disturbance, dysphoric mood, cognitive change, somatic/pain, urinary, bleeding, and sexual symptoms), but these are not specific to perimenopause, as women experience these symptoms at many other points in their lives. Only vasomotor symptoms and vaginal dryness symptoms vary in prevalence significantly across menopausal transition stages and postmenopause in more than one population studied.[10–12] Reports from only a few studies of community-based populations have described the frequency and severity of symptoms, with a minority of women reporting severe symptoms.[10] The few studies that have provided data about the trajectory of symptoms indicate that many peak in frequency and severity during the later part of the menopausal transition when women are skipping periods and symptoms tend to abate after menopause.[10,13,14] Vasomotor symptoms (e.g., hot flashes and sweats) and vaginal dryness become more prevalent during the late menopausal transition stage and continue to increase in prevalence after the final menstrual period.[10,13] Difficulty sleeping seems to increase in a linear fashion over the menopausal

transition and postmenopause.[10] There are few reports focusing on cognitive symptoms,[15–17] somatic symptoms,[10,18] urinary incontinence,[19] bleeding problems,[20] and sexual symptoms[21,22] that examine their frequency and severity in relationship to the stages of the menopausal transition and postmenopause. Depressed mood shows no clear relationship to menopausal transition aside from a rise in the incidence of dysphoric mood during the late menopausal transition stage.[23–26] Of note is that there is no clear evidence about the persistence of hot flashes and other symptoms beyond the first few years after the final menstrual period, aside from estimates from the Massachusetts Women's Health Study and the Melbourne Women's Health Study.[10,13]

Although multiple factors have been linked to symptoms, including economic strain; health behaviors, such as smoking; comorbid conditions; prior episodes of depression or premenstrual symptoms; stressful life circumstances, such as abuse; and physical indicators, such as body mass index,[12,14] endogenous endocrine factors, such as estrogen, are most commonly hypothesized to be responsible for symptoms.[10,27] There are few studies of women's attributions about their symptoms (e.g., perceived memory changes) that discern whether or not women perceive their symptoms are related to menopause or some other aspect of their lives.[17] What is missing from this literature is a conceptual framework that links the experience of symptoms to biological dimensions of menopause as well as the social and cultural environments in which women traverse the menopausal transition. Such a framework could help account for the different consequences of symptoms in women's lives.

Symptoms are sensations that people perceive that differ from the ordinary, such as hot flashes. Perception and evaluation of symptoms precede response to symptoms. Symptom perception refers to noticing symptoms, such as their frequency and intensity, whereas symptom evaluation refers to judgments people make about their symptoms, such as their seriousness, treatability, causes, and consequences in their lives.[28] People use culturally based explanatory models—a set of professional, lay, or idiosyncratic categories—to ascribe meaning to their symptoms.[29] Responses to symptoms may include feelings, thoughts, or behaviors, such as self-care efforts (e.g., changing dietary intake, using herbal or over-the-counter preparations), seeking help or advice from one's social network, seeking help from a health professional that may include a prescribed medication, or choosing to do nothing about the symptoms. The processes of symptom perception, evaluation, and response occur within a social context that shapes the meanings people ascribe to symptoms as well as their responses.[28,29]

Contemporary literature on symptoms during perimenopause could be strengthened by use of a conceptual framework that bridges emphasis on the genetic, molecular, and physiologic factors hypothesized to cause symptoms and the social and cultural context in which women experience them. Concepts of symptom perception, evalution, and response could be linked to measurement strategies to assure optimal operationalization. For example, symptoms may occur and change in intensity too frequently to be measured accurately with annual questionnaires. Because many symptoms vary in intensity and frequency over time, recent studies of perimenopause have incorporated daily or frequent recording of symptoms in a prospective fashion versus relying on retrospective recall of past experiences.[6,8] Moreover, standardized lists of symptoms have been included to provide similar cues to study participants.[1–8] Studies that incorporate severity ratings of symptoms provide verbal descriptors that women can use to rate their symptoms as barely noticeable to extremely bothersome.[3,6] Attempts to relate symptoms to factors hypothesized as causal have included measures precisely timed to allow understanding of antecedent-consequent

relationships (e.g., measures of endocrine levels have been timed to day of the menstrual cycle and related to symptoms measured at the same time or shortly thereafter[6,8]). Finally, there have been several recent efforts focused on understanding the sociocultural contexts in which women experience symptoms. Efforts to understand the experiences of women from various ethnic groups, such as those reflected in the SWAN study, contribute important insights for symptom management for clinicians and researchers.[30–34]

Despite the advances in measuring symptoms, their significance for women's lives remains poorly understood. Although data do indicate that severe vasomotor symptoms that affect sleep and mood may interfere with women's well-being,[27] the impact of symptoms during perimenopause on well-being, role performance, adaptation to demands of daily living, and quality of life warrants additional study. The appraisal of the consequences of perimenopausal symptoms by women from different ethnic groups will be enhanced significantly as a result of the SWAN study.[30–34] These efforts should be coupled with in-depth studies of ethnic populations of women that attempt a deep understanding of symptoms in the context of culture and aging, as exemplified by Lock's work with Japanese women.[35]

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Symptoms and Health-Related Quality of Life and the Menopausal Transition

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The objectives of this paper are to: (1) define health-related quality of life; (2) describe the measures of quality of life that have been used in studies of the menopausal transition; (3) evaluate the effects of the menopausal transition on quality of life; and (4) identify key gaps in our knowledge about the effects of menopause on health-related quality of life.

Most women care not only about living long lives but also about living healthy lives free of disability, disease, and unpleasant symptoms that prevent the enjoyment of and involvement in meaningful relationships, work, and play. The characteristics of a healthy life are the essence of what is meant by health-related quality of life. The theoretical basis of health-related quality of life is based on a multidimensional perspective of health stemming from the World Health Organization's definition of health: "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity."[1] Health-related quality of life is defined "as the value assigned to duration of life as modified by impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy."[2] Our topic is whether the menopausal transition has adverse or positive effects on symptoms, functioning, health perceptions, and resilience or the capacity to respond to stress.

Given the breadth of the concepts captured by health-related quality of life, it is not surprising that many types of measurement tools are available. Some tools measure each of the major health-related quality of life concepts separately (e.g., separate checklists of symptoms that are summed), some attempt to combine scales into an overall health-related quality of life score weighting patient preferences for health outcomes, and some construct a profile of health status based on interrelated components of health, as an alternative to an aggregate index.

Many studies of menopause operationalize quality of life as frequency and severity of symptoms. Investigators have developed psychometrically sound menopause-specific measures of quality of life, including Toronto Menopause Specific Quality of Life Questionnaire, Greene Climacteric Scale, Women's Health Questionnaire, Menopausal Symptom List, Menopause Rating Scale, and Utian Menopause Quality of Life Score.[3,4] All yield factor-analytically derived subscales. With the exception of the Utian scale, all measure symptoms. For example, the Green Climacteric Scale yields scores for vasomotor, somatic, anxiety, and depression. The Utian scale yields subscales reflecting perceptions of well-being or functioning in four domains: (1) occupational; (2) health; (3) emotional; and (4) sexual. Other menopause studies have used profile measures of health-related quality of life that are widely used in diverse patient samples, including the SF–36[5] and Nottingham Health Profile.[6] The SF–36 yields scores of general health perceptions, physical functioning, general mental health, vitality, bodily pain, role limitations due to physical or emotional health, and social functioning. The Nottingham Profile Part I includes items in the following domains: pain, physical mobility, sleep, emotional reactions, energy, and social isolation. It should be noted that health-related quality of life is not usually measured objectively (i.e., by an outside observer or standardized physical tests). It is a subjective

measure that can be influenced by the respondents' personal attributes, the environmental setting, and recent stressful life events.

We reviewed the quality of life results from cross-sectional studies that had more than 450 women, were not based on samples of women seeking treatment, and were population-based; and from longitudinal studies in which women were initially premenopausal or perimenopausal and followed through the transition and were population-based. Note that the cross-sectional studies classified women based on retrospective histories of menses, which are subject to memory bias, and few studies directly measured ovarian aging, which is the physiological basis for changes in menstruation. We included selected studies that examine the changes in quality of life in women who had elective hysterectomies (although their ovaries may have been conserved) because of concern that surgical menopause has an adverse effect on quality of life. Other papers at this meeting review, in detail, the effects of the menopausal transition on vasomotor symptoms, depression, and sexual function. It is beyond the scope of this paper to review the data on menopause-induced risk for specific diseases or on the impact of hormone therapy (HT) from randomized clinical trials on health-related quality of life.

In cross-sectional studies, perimenopausal women report greater bodily pain and role limitations due to physical health or emotional problems, poorer perceived health, and more physical or somatic symptoms than do premenopausal women.[7–10] These studies are based on diverse populations, including women from England, Holland, Taiwan, Chile, France, Sweden, and the United States, where women of Japanese, Chinese, Hispanic, African, and European origin have participated. Several studies also suggest that women who choose to use HT during the menopause have poor health-related quality of life.[9,11] Several studies suggest that statistical controls for emotional symptoms remove the effect of menopausal status on somatic symptoms.[7,12] Stated differently, women who report high levels of anxiety, depression, and other emotional symptoms are the women who report poor quality of life during menopause. This is consistent with data showing that women at other life stages who report emotional symptoms also report a poor quality of life.

An inconsistent association is observed between hysterectomy status and number of somatic and vasomotor symptoms.[9,13] Longitudinal studies before and after surgery, including one randomized clinical trial, do suggest that hysterectomies lead to improvement in quality of life.[14]

Few longitudinal studies report effects of the perimenopause on health-related quality of life, other than the effects on emotional and vasomotor symptoms. The Melbourne Women's Mid-life Project found no effects of change in menopause status on perceived health. In fact well-being increased across the transition.[15,16] The Australian Longitudinal Study of Women's Health reported that women who changed from premenopause to perimenopause declined in physical function but not in other indicators, such as pain and vitality.[17] Interestingly, in that study, women who remained in the perimenopausal status at both evaluations 2 years apart were worse off in functioning, suggesting that the length of perimenopausal transition may impact women's quality of life.[18] Somatic symptoms did change with the menopausal transition in these studies, including aches, joint pains, and sleeping problems.[18,19] Sleeping difficulties may not be simply due to vasomotor symptoms that disturb sleep. One cross-sectional analysis of women who reported no vasomotor symptoms in the last 2 weeks showed that women who

reported sleep difficulties in the last 2 weeks were more likely to be perimenopausal than premenopausal in multivariate models adjusting for emotional symptoms, general health, activities, education, and ethnicity.[20]

Impaired sleep contributes to daytime sleepiness, cognitive difficulties, poor job performance, risk for depression, and low overall quality of life. Sleep characteristics can be measured objectively with polysomnography. In the Wisconsin Sleep Cohort Study, postmenopausal and hysterectomized women with vasomotor symptoms and HT users, as compared to premenopasual women, were at elevated risk for sleep disordered breathing, a condition of repeated breathing pauses during sleep.[21] In the same cohort, however, postmenopausal women had greater sleep efficiency (proportion of time sleeping while in bed) and deep sleep than did premenopasual women.[22] An ongoing study of in-home polysomnography in the Study of Women's Health Across the Nation will permit evaluation of subjective and objective sleep characteristics in Japanese-, African-, and European-American women.

In summary, perimenopausal status is associated with higher levels of somatic symptoms, but it is not established whether the perimenopause is related to other components of health-related quality of life. No studies have examined the change in resilience with menopause. It is likely that a subset of women are particularly vulnerable to the effects of perimenopause, with some suggestion that women who gain weight, are emotionally distressed, and experience stressful circumstances may be at high risk for a decline in health-related quality of life. Few studies have addressed the likely mechanisms accounting for the associations. Perimenopause is not a discrete hormonal event but a complex period of women's lives in which hormonal factors, family relationships, work status, and self-concept change. It is important to examine whether these changes alter quality of life and to disentangle the specific pathways related to health-related quality of life in mid-life women.

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A Universal Menopausal Syndrome?

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A variety of symptoms are frequently reported as being part of a menopausal syndrome. These include hot flushes or flashes, night sweats, menstrual irregularities, and vaginal dryness as well as other symptoms, such as depression, nervous tension, palpitations, headaches, insomnia, lack of energy, difficulty concentrating, and dizzy spells.[1] The question of whether a universal menopausal syndrome exists has been debated for some time. Some have suggested a constellation of symptoms that form a syndrome are experienced by most women due to declining levels of estrogen as they transition through menopause. The question of if, and how, symptoms co-occur is an important one for women who want to know which symptoms can be attributed to menopause and which to aging or other physical or psychosocial factors.

Several avenues of research can be examined to address the question of whether a single universally experienced menopausal syndrome exists. These include examining (1) how symptoms cluster or group together; (2) the prevalence of different symptoms over the menopausal transition; (3) consistency of symptom reporting across cultures, race, and ethnicity; and (4) consistency of risk factors for symptoms.

Symptom Groupings

A number of researchers have used factor analysis and related statistical approaches to determine how menopausal symptoms group together. These studies differ in terms of the specific symptoms studied, the number of symptoms included in the list, and the time frame for symptom reporting as well as the cut-point for determining factor loadings. Studies also differ in sample characteristics, such as age of sample, composition of sample (some excluded women taking estrogen), and whether the sample was clinic- or community-based. Studies were conducted in a variety of countries including the United States,[2–4] Canada,[2,5] Australia,[6] Great Britain,[7,8] Sweden,[9] Norway,[10] Japan,[2] and Southeast Asia.[11] Despite these differences, the results are overwhelmingly consistent in one respect; in every study, vasomotor symptoms come out separate from psychological or somatic symptoms.

Except for three studies,[3,4,11] these analyses are all based on samples of Caucasian women. In the Study of Woman's Health Across the Nation (SWAN), Avis et al.[3] conducted separate factor analyses of symptoms among Caucasian, African-American, Chinese, Japanese, and Hispanic women. In this multi-ethnic study, they found that vasomotor symptoms consistently loaded on a separate factor from other symptoms across all racial/ethnic groups.

Prevalence of Symptoms Over the Menopausal Transition

The cross-sectional portion of SWAN provides the opportunity to examine the prevalence of various symptoms by menopausal status in a multiethnic sample of women aged 40–55.

Figures 1a and 1b show the age-adjusted percentage of women who reported experiencing various symptoms in the past 2 weeks according to menopausal status.

Figure 1: Percentage of women reporting symptoms at different stages of the menopausal transition, adjusted for age: (a) hot flashes and physical symptoms and (b) psychological distress symptoms.

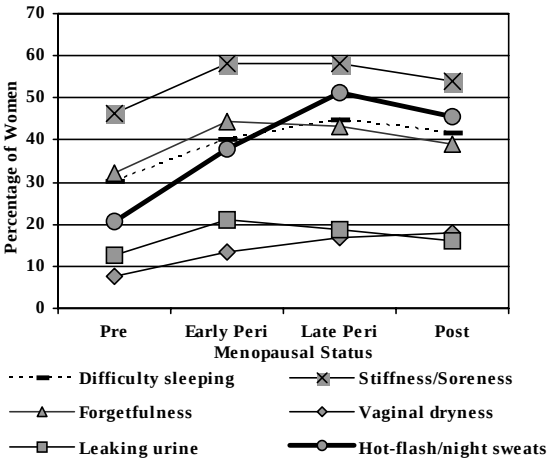

Figure 1a

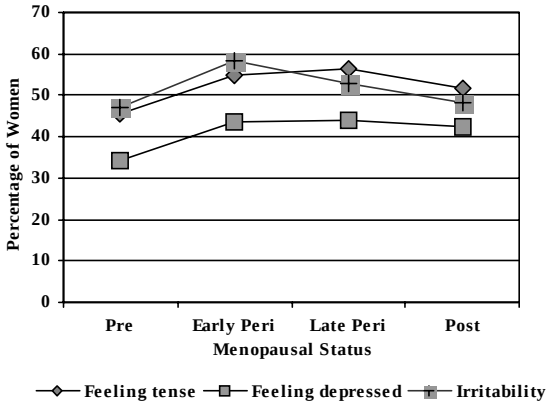

Figure 1b

Figure 1a shows hot flashes/night sweats and primarily physical symptoms, while Figure 1b shows symptoms of psychological distress. As seen in these figures, all symptoms increase in prevalence from premenopause to early perimenopause. However, the prevalence of symptoms over the transition then differs. Most notably, the reporting of hot flashes or night sweats (bolded in Figure 1a) is dramatically higher among early perimenopausal women as compared to premenopausal women and is also higher among late perimenopausal women compared to those who are early perimenopausal. No other symptom shows a corresponding pattern. Further, while the percentage of women reporting hot flashes and night sweats declines noticeably from late perimenopause to postmenopause, other symptoms (e.g., forgetfulness, stiffness and soreness, difficulty sleeping) show a much smaller decline, while others, such as vaginal dryness, show an increase in prevalence. Psychological symptoms are highest among early perimenopausal women but then slowly decline among late perimenopausal women. These different patterns of symptoms in relation to menopausal status argue against a universal syndrome.

Symptom Reporting Across Cultures

Several studies of non-Western women suggest cultural differences in menopausal symptoms. Few Indian women of the Rajput caste report any problems with menopause other than cycle changes.[12] Only a small proportion of Japanese women experience hot flashes, depressive symptoms, or irritability.[2,13] Cross-cultural/ethnic studies of menopausal symptoms

are very limited in the United States. The largest of these, SWAN, has found considerable variation of symptom reporting across race/ethnicity, even controlling for health and lifestyle factors.[3,14] Compared to Caucasian women, Chinese, Japanese, African-American, and Hispanic women reported significantly fewer symptoms in general. However, symptom reporting varies by race/ethnicity and symptom. African-American women reported more vasomotor symptoms, but Caucasian women report more psychosomatic and physical symptoms.[3,14]

Risk Factors for Symptoms

Vasomotor symptoms have been related to menopausal status, serum estrogen levels, lower socioeconomic status, smoking, less physical activity, and premenopausal attitudes towards menopause. Socioeconomic status, stress, psychosocial factors, and previous depression account for a higher likelihood of depression during menopause than menopausal status.[15] Lower socioeconomic status, age, ethnicity, smoking, and less physical activity have been associated with somatic symptoms.[14] Menopausal status is consistently related to vasomotor symptoms but inconsistently related to psychological symptoms. Other than menopausal status, there is much overlap in risk factors for different symptoms, suggesting that certain factors may be related to symptom reporting in general and there may be a subgroup of women who are more likely to report symptoms of any nature.

Conclusion

These areas of investigation all argue against a universal menopausal syndrome. The results of the factor analysis studies do not support a single syndrome consisting of menopausal, psychological, and/or somatic symptoms. The prevalence of symptom reporting across the transition also argues against a menopausal syndrome, as vasomotor symptoms follow a unique pattern from other symptoms. Cross-cultural differences suggest that symptom reporting is not universal. Finally, although there is some overlap in risk factors for symptoms, menopausal status is more consistently related to vasomotor symptoms than psychological or somatic ones. Future research should focus on how symptoms are interrelated and whether a subgroup of women can be identified who are more likely to report symptoms.

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Perimenopause: Urogenital and Bleeding Issues

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Irregular and Abnormal Bleeding Issues

Irregular and abnormal uterine bleeding are common symptoms among women in perimenopause. Indeed, the Staging Reproductive Aging Workshop (STRAW) staging system of perimenopause defines the menopausal transition as beginning when variable cycle length is noted by women.[1] Several longitudinal studies utilizing menstrual cycle calendars have demonstrated that women commonly transition from having regular cycles to more cycle irregularity before finally becoming menopausal, making irregular menstrual cycle intervals a common and even normal finding in the perimenopausal years.[2–5]

Perimenopause is known to be a time of fluctuating hormone levels. These hormonal fluctuations may explain some of the menstrual cycle variability that is noted. Data from several large studies have noted that during the perimenopausal years, menstrual cycles can either have a shorter interval or, more commonly, a longer interval. Later in the perimenopausal period, skipped cycles become more common.

Hormonal changes have been characterized, which accompany this change in menstrual regularity.[6–10] Current understanding holds that circulating inhibin-B levels drop in response to the decreased number of follicles present within the ovary. This, in turn, leads to a rise in follicle stimulating hormone levels. The ovary responds to these increased follicle stimulating hormone levels by maintaining estradiol levels at near reproductive age levels until very close to menopause at which time estradiol levels drop off significantly. With advancement through perimenopause, anovulatory cycles become more and more common and these cycles are characterized by an absence of progesterone production. This certainly contributes to cycle irregularity and particularly to the skipped cycles that characterize the late perimenopausal period.

Because of the hormonal changes that are known to occur in the perimenopausal period, exogenous hormones are used to regulate menstrual bleeding during perimenopause. A common clinical practice is to utilize birth control pills in women who do not have contraindications to birth control use, such as cigarette smoking. This practice has the advantage of improving menstrual cyclicity and regularity as well as avoiding unwanted pregnancies. Use of a low dose oral contraceptive pill has been shown to be effective in perimenopause for decreasing the amount of menstrual blood loss as well as improving menstrual cycle regularity.[11]

Women who do not tolerate an oral contraceptive pill may benefit from alternative hormone therapies during perimenopause. These alternatives include use of hormone therapy at doses generally prescribed in menopause, use of cyclic progestins, use of depot medroxyprogesterone acetate, or use of a progestin-containing intrauterine device. These alternatives have been less well-studied in perimenopausal women.

Although irregular menstrual bleeding is a very common symptom of perimenopause and can be linked to hormonal changes, it is unclear whether or not menorrhagia, the occurrence of

very heavy menstrual bleeding, is associated with normal perimenopausal hormonal changes. Indeed, cycle irregularity is a predictor of menopause where as menorrhagia or the number of days of menstrual bleeding has not been shown to be a predictor of the final menstrual period.

A common clinical finding is that menorrhagia in perimenopausal women is associated with the presence of uterine fibroids or polyps as the prevalence of these conditions peaks in women between the ages of 40–50. Pathologic changes in the uterus are found in well over 50 percent of women presenting for ultrasound evaluation of menorrhagia. Thus, it is very difficult to determine if menorrhagia is due to normal perimenopausal changes or due to the development of benign uterine lesions.

One weakness of longitudinal studies of perimenopausal women conducted thus far is the absence of correlation between menstrual bleeding complaints, hormonal levels, and pathologic changes within the uterus. Because of the well-known association between these pathologic entities with abnormal uterine bleeding, the complete correlation between hormones, bleeding cycles, and uterine anatomy is an area of importance in designing of future studies of perimenopause.

In women who are dissatisfied with medical management of menstrual bleeding problems, a surgical option is often considered. Surgical options include endometrial ablation, hysteroscopic resection of polyps or fibroids, abdominal myomectomy, or hysterectomy. More recently, uterine artery embolization has been used to treat women with uterine fibroids and abnormal bleeding. All of these surgical options are effective in controlling abnormal bleeding in selected women.

The rate of hysterectomies in the United States is known to peak between the ages of 30–54.[12] The rise in the hysterectomy rate begins well before the onset of perimenopause, with uterine fibroids being the most common indication. To what extent normal perimenopausal changes in menstrual cyclicity contribute to the decision for a hysterectomy is not known.

It is known that bilateral oophorectomies are performed in conjunction with hysterectomies in 37 percent of women under the age of 45 and 68 percent of women age 45 and older.[12] In some instances, a bilateral oophorectomy is performed because of an estrogen-dependent disease process, such as endometriosis. In other cases, it is performed as prophylaxis against future development of ovarian cancer. A bilateral oophorectomy certainly has consequences on hormonal production as both estrogen and testosterone levels will drop significantly following an oophorectomy. This, in turn, often leads to symptoms of hot flashes, vaginal dryness, and decreased libido.

Vaginal Atrophy and Dryness

Vaginal atrophy and dryness is a common symptom in perimenopause. In a longitudinal study of 438 Australian-born women observed over 7 years, vaginal dryness was noted to increase nearly five-fold as women advanced through perimenopause.[13] Vaginal dryness was a complaint in 3 percent of premenopausal women and 4 percent of women in early perimenopause. However by late perimenopause, 21 percent of women complained of vaginal dryness and this percentage

increased up to 47 percent 3 years following menopause. The link between vaginal dryness and low estrogen levels is clear, as estrogen levels drop precipitously in late perimenopause as compared to early perimenopausal women.

Therapy for vaginal atrophy in perimenopausal women has not been studied extensively. However, a recent Cochrane review of estrogen for vaginal atrophy concluded that estrogen-based hormone replacement therapy is effective in treating the symptoms of vaginal atrophy in menopausal women.[14] It is noted, however, that only a small percentage of those who benefit from estrogen therapy actually receive it. Factors that may contribute to this are a reluctance to volunteer the symptom because of embarrassment and a fear about harmful effects of hormone replacement therapy.

Although systemic forms of estrogen therapy, including oral and transdermal preparations, have shown to be effective in treating vaginal atrophy, locally-released estrogen in the form of vaginal rings, estrogen based vaginal creams, pessaries, and slow-released estradiol tablets have also been shown to be effective. The advantages of local therapy include lower systemic estradiol levels leading to reduced adverse effects, such as endometrial stimulation, uterine bleeding, and breast tenderness. Lower systemic estradiol levels may also be advantageous for women who have been previously treated for estrogen-responsive cancers.

Future studies are needed regarding the long-term safety of locally applied estrogens for vaginal dryness in perimenopause, particularly in women with a history of breast cancer.

Urinary Incontinence in the Perimenopausal Period

The prevalence of incontinence increases as women age. However, it is unclear if the hormonal changes associated with perimenopause and menopause are independent risk factors for the development of incontinence. Regardless, incontinence is a frequent complaint among women in perimenopause and menopause. Some have postulated that the drop in estrogen seen in late perimenopause and after menopause may contribute to incontinence symptoms. Estrogen appears to have a number of important roles in continence mechanisms.

The effect of estrogen on incontinence has primarily been evaluated in menopausal and not perimenopausal women. A recent review of 15 trials (374 women on estrogen and 344 women on placebo) evaluated the effects of estrogen on urinary incontinence in menopausal women.[15] Subjective impression of cure was highest among women treated with estrogen for all categories of incontinence. Thirty-six percent of women on estrogen reported a cure of their incontinence versus 21 percent on placebo (relative risk for cure 1.61, 95 percent confidence interval of 1.04–2.49). Taking all trials together, this review concluded that about 50 percent of women treated on estrogen were either cured or improved compared to only 25 percent on placebo. The overall effect seemed larger among women with urge incontinence as opposed to those with stress incontinence. It appeared that when adding progesterone to estrogen treatment, the likelihood of cure or improvement was lessened. The data are insufficient to determine long-term effects of estrogen therapy on symptoms of incontinence. This is particularly critical information since long-term use of estrogen following menopause is not currently recommended due to other side effects of this type of treatment that have been elucidated in the Women's Health Initiative study.

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Mood, Depression, and Reproductive Hormones in the Menopause Transition

Peter J. Schmidt, M.D.

Major and minor depressions are the two most prevalent forms of acute depressive illness. Major depression has an estimated lifetime prevalence of 17 percent and affects approximately twice as many women as men.[1] The prevalence of minor depression is estimated to approximate that of major depression. Major depression was identified as a leading source of disease-related disability in developed countries (second only to heart disease).[2] Minor depressions, by definition, have fewer and less severe symptoms than major depressions. Nonetheless, they are associated with disability comparable to that of major depression. In addition to the functional disability directly attributed to major and minor depressions, certain medical sequelae of depression have been identified, including increased risks for osteoporosis, metabolic disorders, and cardiovascular disease. Finally, if depression exists as a comorbid condition it may significantly increase the morbidity and mortality of several medical illnesses, including heart disease.

Despite its prevalence and associated disability, depression is underdiagnosed in the community and, therefore, also undertreated.[2] Standardized criteria for diagnosing both major and minor depressions have been defined and these diagnostic criteria are needed to distinguish depressive symptoms, which may be multidetermined, from depressive syndromes that have specific familial patterns, biological features, and treatment-response characteristics.

The majority of women do not develop depression during the menopausal transition, and, therefore, perimenopause is not uniformly associated with changes in a woman's mood. In fact, epidemiologic studies report no increased prevalence of major depression in women at midlife (age range approximately 45–55 years). Several epidemiologic studies have surveyed the presence of depressive symptoms in women at midlife and identified rates of depressive symptoms ranging from 8 to 40 percent.[3–5] However, the samples in these studies consisted of women at midlife who were in different phases of reproductive aging and, most commonly, symptoms were assessed independent of the presence of clinically meaningful depressive syndromes; these findings, therefore, are not directly translatable into prevalence figures for depressive syndromes associated with the reproductive endocrine changes characterizing perimenopause. Depressive symptoms are more frequently reported in perimenopausal compared to postmenopausal women in both community- and clinic-based studies. Similarly, community-based surveys of the prevalence of the *syndromes* of depression (i.e., major or minor depression) also suggest that the menopausal transition is a time of increased vulnerability for depression in some women. The Study of Women's Health Across the Nation (SWAN) observed that perimenopausal women reported significantly more "psychological distress" (a proxy for a persistent mood disorder) than either premenopausal or postmenopausal women.[6] Two recent studies found results similar to the SWAN data. First, Freeman et al.[7] identified an increased risk for clinically significant depression during perimenopause compared to premenopause or postmenopause. Moreover, this association remained after adjusting for several variables, including past history of depression, severe premenstrual syndrome, poor sleep, and hot flushes. We observed a 14-fold increase in the rate of onset of depression during the 24 months surrounding the final menstrual period,

relative to the 31 premenopausal years we used as a comparison time period, suggesting an increased risk of depression in women during both late perimenopause and early postmenopause relative to premenopause.[8] In all of these studies, the majority of women remained asymptomatic throughout perimenopause. Although, several factors could precipitate depression, the clustering of depressions during late perimenopause implicates hormonal events during this reproductive stage as etiologically relevant. Late perimenopause is characterized by more prolonged hypogonadism than early perimenopause, during which estradiol secretion may be increased. Thus the endocrine events of late perimenopause (estradiol withdrawal and recent onset of prolonged hypogonadism) are of particular interest in efforts to define the pathophysiology of perimenopausal depression.

The antidepressant efficacy of estradiol therapy (ET) has been examined in three recent studies of women meeting standardized diagnostic criteria for major and minor depression who were randomly assigned to enter double-blind, placebo-controlled trials.[9–11] In perimenopausal women, short-term (3–8 weeks) ET significantly decreased depression scores compared to both baseline and placebo conditions. In one study, a full or partial therapeutic response was seen in 80 percent of perimenopausal women on estradiol and in 22 percent of those on placebo,[9] consistent with the observed effect size (0.69) in a recent meta-analysis of studies examining estrogen's effects on mood.[12] The therapeutic response to estrogen was observed in both major and minor depression as well as in women with and without hot flushes. In contrast, the administration of ET under similar conditions failed to improve mood in depressed women who were 5–10 years postmenopause.[11] These data suggest that estrogen's effect on depression may be limited to perimenopausal women and is not solely a product of its ability to reduce the distress of hot flushes, which is consistent with recent community-based cross-sectional surveys.

In summary, depression is a chronic and disabling disease that disproportionately affects women. The majority of women do not develop depression during or after the menopausal transition. Nevertheless, recent prospective studies monitoring both reproductive status and mood have documented that for some women perimenopause increases the risk for the onset of depression. The role of ovarian function in these episodes of depression is suggested by both the timing of their onset relative to the last menstrual period and the antidepressant efficacy of short-term estrogen therapy.

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Sexuality

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This paper reviews the changes which occur in the different domains of women's sexual function in middle-aged women and how these relate to aging, hormonal changes related to menopause, and other psychosocial and physical factors. Clinicians have long been concerned about effects of menopause on female sexual function, as sexual complaints are amongst the most frequently reported health concerns amongst women attending menopause clinics.[1] Yet, clinical experience is based on a small proportion of self-selecting women and may not be representative of most women's experience of the menopausal transition.[2] Population-based studies provide information on the prevalence and type of changes in sexual function and relationship to menopausal hormonal changes and other possible determinants. These studies are complimentary to clinical trials which provide evidence on hormonal effects on specific parameters of sexual functioning in the groups studied.

Current definitions of female sexual dysfunction include both low sexual function and personal distress components for each of the domains of desire, arousal, orgasm, and pain.[3] Studies published prior to the development of these definitions usually do not include measures of personal distress. Only a proportion of those who have low sexual function will be distressed about it.[4] Most population-based studies of female sexual function have also failed to include validated measures of female sexual function. Measures used have included single questions addressed at particular domains of function or respondents are asked to report their sexual problems or difficulties. Other methodological limitations include low response rates, poor sampling strategies, small sample sizes, age and reproductive status of participants at baseline, documentation of hormone use or surgical or other medical interventions which may affect sexual functioning, and use of statistical techniques which address the complex interrelationships between variables.[5] Relatively few of the population-based studies of the menopausal transition have asked women about sexual functioning and even fewer of these have measured hormones.

Cross-sectional studies allow us to identify differences across age ranges, reproductive status groups, and ethnic groups. Aging and length of relationship are known to affect sexual functioning of both men and women[6,7] and these variables are often confounded. In a multinational cross-sectional study carried out concurrently in Europe and the USA (Women's International Study of Health and Sexuality) using validated measures of sexual function and sexual distress, a decline in all aspects of sexual function was evident with age. Sexually related distress, however, decreased with age so that there was no increase in sexual dysfunction with age.[8]

A number of studies have found an additional decrement in aspects of sexual function in midlife[9,10] and coinciding with mean age of menopause[11] or menopausal status where measured.[12,13] Studies which failed to find effects of menopausal status have been limited by small sample sizes,[7] wide age bands, and lack of validated measures.[14]

Very few studies have followed the same cohort prospectively across the menopausal transition. Longitudinal studies allow us to disentangle the effects of aging from those of menopausal hormonal change (which are inevitably confounded) as well as to measure the

powerful effects of psychosocial factors, including the individual's own prior level of sexual functioning and changes occurring in sexual partnerships.[15] The Melbourne Women's Midlife Health Project is a population-based sample of 438 Australian-born women who were aged 45–55 and still menstruating at baseline. The women have been followed with annual assessments and hormone measures for 13 years. A validated measure of sexual function was used (the Personal Experiences Questionnaire short form (SPEQ)), based on the McCoy Female Sexuality Questionnaire.[16–19] The scale provides domain scores for sexual desire (libido), arousal, enjoyment and orgasm (sexual responsivity), frequency of sexual activities and dyspareunia. Feelings about partners and partner problems are also measured. A total score of sexual function is calculated from the libido, sexual responsivity, and frequency of sexual activities domains. Scores of less than 7 indicate low sexual function similar to women with sexual dysfunction.[20] From early to late menopausal transition, the percentage of women with SPEQ scores indicating sexual dysfunction rose from 42 to 88 percent.[21] By the postmenopausal phase, there was a significant decline in sexual responsivity, frequency of sexual activities, libido, and the overall total score as well as a significant increase in vaginal dyspareunia and partner problems in sexual performance.[22] Increasing dyspareunia and decreasing libido and responsivity correlated with decreasing estradiol but not with androgens.[21] These results assist us in understanding the impact of the menopausal transition on women's sexuality. However, analytic techniques, which can include psychosocial factors and the effects of time, are necessary to understand the relative importance of hormonal factors. Using techniques of autocorrelation and cross-correlation together with structural equation modeling, we found the most important factors (in decreasing order of importance) influencing a woman's sexual functioning are: (1) her prior level of sexual functioning; (2) losing or gaining a sexual partner; (3) feelings towards the partner; and (4) estradiol level.[22] Endogenous testosterone (utilized as the free testosterone index) and dehydroepiandrosterone sulfate were not related to sexual function domains.[20,22] When a validated measure of distress (Female Sexual Distress Scale) was included in the 11th year of followup, we found that only 17 percent of the women (then aged 57–67) were significantly distressed.[4]

The Melbourne sample consisted of Caucasian women. It is not clear whether there will be any ethnic variation in response to declining estradiol at menopause. Using cross-sectional data from baseline (when women were prior to or early in the menopausal transition),[23] the Study of Women's Health Across the Nation reported substantial ethnic differences in sexual domains. Other studies carried out in Europe have also reported substantial differences between countries in domains of sexual functioning, such as frequency of sexual intercourse, but, nevertheless, found a similar pattern of decline in sexual responsivity with menopause across all countries.[24]

The above report has focused on changes related to the natural menopausal transition. Surgical menopause where both ovaries are removed would be predicted to have more deleterious effects on sexual function, as all ovarian estrogen and androgen will be removed.

Conclusions

There is a decline in all aspects of female sexual function with age. A further incremental decline in most aspects of sexual function occurs as women pass through the menopausal

transition. This further decline is related to falling estradiol levels. Other factors, such as prior sexual functioning and partner-related factors, have larger effects on women's sexual function than do hormonal factors. However, when relationship factors are stable, declining estradiol has noticeable effects. Not all women with low sexual function are distressed about it.

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Symptoms During the Menopausal Transition: Evidence from Cohort Studies

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Although many symptoms have been attributed to the menopausal transition, it is unclear which symptoms are actually associated. A systematic review was undertaken to describe the evidence about symptoms associated with menopause and potential factors that influence them—two of the five Key Questions specified by the Planning Committee for the National Institutes of Health State-of-the-Science Conference on Management of Menopause-Related Symptoms.

Relevant studies were identified from multiple searches of MEDLINE and PsycINFO (1966 to November 2004); and from recent systematic reviews, reference lists, editorials, Web sites, and experts. The review focused on prospective studies of cohorts of midlife women transitioning through the stages of menopause; additional cross-sectional studies provided prevalence data. Specific inclusion and exclusion criteria were developed to determine study eligibility. All eligible studies were reviewed and relevant data were extracted, entered into evidence tables, and summarized by descriptive methods. Two reviewers independently rated the quality of studies using predefined criteria. Forty-eight studies conducted among 14 cohorts and 22 studies from other populations were included.

Key Question 1. What is the evidence that the symptoms more frequently reported by middle-aged women are attributable to ovarian aging and senescence?

- Vasomotor Symptoms: Evidence from population-based cohort[1–4] and cross-sectional studies support the association between vasomotor symptoms and the menopausal stage. Studies are consistent in reporting increasing prevalence rates of vasomotor symptoms as women transition from premenopause to either perimenopause or postmenopause, affecting 50 percent or more of women. Studies suggest that vasomotor symptoms persist for several years after menopause for some women.[5]

- Vaginal Dryness: Vaginal dryness is associated with menopause and prevalence rates increase as women transition through the menopausal stages.[3] Estimates indicate that up to one third of perimenopausal and postmenopausal women experience vaginal dryness.

- Sleep Disturbance: Although results of studies are mixed, two good-quality cohort studies indicate that women have more difficulty sleeping as they transition through menopausal stages;[1,3] this may be due to vasomotor symptoms. Up to 40–50 percent of perimenopausal and postmenopausal women experience sleep disturbance—a slight increase from prevalence rates of premenopausal women.

- Mood Symptoms: The majority of studies from a large literature indicate no associations between the menopausal stage and mood symptoms, development of a mental disorder, or general mental health; two cohort studies report increased

depressive symptoms among perimenopausal and postmenopausal women.[6,7] Studies of prevalence rates have wide ranges that are similar across menopausal stages.

- Cognitive Disturbances: The few studies evaluating cognitive disturbances in menopause report no associations.

- Somatic Complaints: Most studies indicate no associations of somatic symptoms with menopause, although somatic symptoms were increased among perimenopausal women compared with premenopausal women in one cohort[8] and two cross-sectional studies.[9,10]

- Urinary Complaints: Urinary leakage increased among perimenopausal women compared with premenopausal women in one study,[1] and another reported no associations.[3,11]

- Studies of prevalence rates have wide ranges that are similar across menopausal stages.

- Uterine Bleeding Problems: No studies meeting inclusion criteria address uterine bleeding problems, most likely because currently accepted definitions of menopause rely historically on changes in uterine bleeding.

- Sexual Dysfunction: Women from two study cohorts had declines in some or all of the measured sexual parameters as they transitioned through menopausal stages.[4,12,13] Results of cross-sectional studies are mixed.

- Reduced Quality of Life: Results of available cohort and cross-sectional studies are conflicting.

Key Question 2. When do the menopausal symptoms appear, how long do they persist and with what frequency and severity, and what is known about the factors that influence them?

- Included studies do not characterize the severity and duration of specific symptoms. Frequency is described by prevalence data in Key Question 1.

- Race and Ethnicity: The influence of race and ethnicity on menopausal symptoms has not been extensively studied. Prevalence rates of vasomotor and mood symptoms vary among race and ethnic groups in the large Study of Women's Health Across the Nation cohort.[14–19]

- Age At Onset of Menopausal Transition: Available studies are inconclusive.

- Body Mass Index: Available studies are inconclusive.

- Surgical Versus Natural Menopause: Studies present mixed results regarding the impact of surgical menopause on vasomotor symptoms, vaginal dryness, and mood.

- Depression: Cohort studies indicate that baseline mood predicts mood at a later time, but mood is not influenced by menopausal stage. Prior anxiety or depression did not predict other menopausal symptoms in a cross-sectional study.[20]

- Smoking: Available studies are inconclusive.

Vasomotor symptoms and vaginal dryness are symptoms most consistently associated with the menopausal transition. Sleep disturbance, somatic complaints, urinary complaints, sexual dysfunction, mood, and quality of life are inconsistently associated. No studies provide data on cognition and uterine bleeding problems, duration and severity of specific symptoms, or conclusive data on the influence of potential influencing factors. The literature is limited by differences in how symptoms are defined and measured, variability of study populations, and incompatibility of data preventing direct comparisons between studies or pooling of results. Future research using standard and validated measures and uniform definitions for a more comprehensive array of symptoms would improve knowledge of these associations.

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Background/History: Estrogens and Progestins (Formulations, Doses, Routes of Administration, and Schedule): Trends in Use and FDA Issues

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Estrogen therapy, as oral conjugated equine estrogens (CEE) (1.25 mg/d), was approved by the U.S. Food and Drug Administration (FDA) for the treatment of menopausal symptoms, including vasomotor and vulvar and vaginal symptoms, in 1942. In the sixties, widespread estrogen use was advocated to prevent postmenopausal estrogen deficiency and with FDA support, in 1972, of the claim that estrogens were "probably effective" for select cases of osteoporosis, estrogen prescriptions reached 30 million in 1975.[1–3] As evidence emerged that unopposed estrogen use increased endometrial cancer, prescriptions declined to approximately 15 million in the early 1980s; however, prescription growth resumed as progestins were prescribed in combination with estrogen.[1–3]

Since 1942, the FDA has approved many estrogens (noting product names in parentheses), at various dosages, for treating menopausal symptoms, including oral CEE (Premarin), synthetic conjugated estrogens (Cenestin), esterified estrogens (Estratab, Menest), estropipate (Ortho-Est, Ogen), and micronized 17-beta-estradiol (Estrace), the latter of which is also approved for delivery by skin patch (Alora, Climara, Esclim, Estraderm, Vivelle, Vivelle-Dot), cream (Estrace), or vaginal ring (Estring). Other approved creams are CEE (Premarin) and dienestrol (Ortho Dienestrol) and estradiol hemihydrate is approved as a vaginal tablet (Vagifem).

Current FDA-approved progestins (which protect the uterus) include pills containing various doses of medroxyprogesterone acetate (MPA) (Provera, Amen, Cycrin), norethindrone (Micronor, Nor-QD), norethindrone acetate (Aygestin), norgestrel (Ovrette), levonorgestrel (Norplant), and progesterone USP (United States Pharmacopia), in peanut oil (Prometerium), as well as intrauterine devices containing levonorgestrel (Mirena) or progesterone (Progestasert) and a vaginal progesterone gel (Crinone).

FDA-approved combination estrogen/progestin products for treating menopausal symptoms include: (1) pills with various doses of CEE plus cyclic (Premphase) or daily (Prempro) MPA, ethinylestradiol plus norethindrone acetate (Femhrt), or 17-beta-estradiol plus norethindrone acetate (Activella) or norgestimate (Ortho-Prefest); (2) skin patches, which deliver 17-beta-estradiol plus norethindrone acetate (Combipatch) or norgestimate (Ortho-Prefest); and (3) injection of testosterone plus estradiol cypionate (Depo-Testadiol).

Current (draft) guidelines for industry,[4] for clinical evaluation of new estrogen or estrogen- progestin-containing drugs for postmenopausal hormone therapy, recommend that studies include only women who have 12 months of spontaneous amenorrhea or 6 months of amenorrhea with serum FSH levels > 40 mIU/ml or are 6 weeks post-surgical from a bilateral oophorectomy. For an indication for treating moderate to severe vasomotor symptoms, study participants should have a minimum of 7–8 moderate to severe hot flushes per day or 50–60 per week at baseline and for symptoms of vulvar and vaginal atrophy, participants should have

self-identified at least one moderate to severe symptom that is most bothersome to her and meet specific clinical criteria. Wash-out periods, ranging from 1 week for vaginal products to 6 months or longer for pellet or progestin injectable drug therapy, prior to baseline, are specified. Recommendations are also provided for monitoring, primary endpoints, and study analysis.

In 1986, the FDA regarded estrogens as "effective" therapy for osteoporosis and several estrogen products were approved for "management" and "prevention" of osteoporosis in the 1990s, with prevention defined as preserving or increasing (lumbar spine) bone mineral density in subjects without osteoporosis at baseline. Annual prescriptions for hormone therapy reached 36 million in 1992, representing about 6 million women, including 17 percent of women older than 50 years of age.[3] By 1995, these had climbed to 58 million,[3] at least in part due to the increasingly widespread belief that postmenopausal estrogen therapy prevented heart disease.

The FDA updated its Osteoporosis Guidance in 1994 to require a 2-year randomized clinical trial of bone mineral density for an indication of prevention of postmenopausal osteoporosis and a 3-year randomized clinical trial for a treatment indication, with treatment defined as fracture reduction in subjects with osteoporosis at baseline. CEE, alone or combined with MPA, was thus approved for the prevention of osteoporosis but not for treatment. This was reviewed, but not changed, following publication of the Women's Health Initiative (WHI) trial of CEE (0.625 mg/day) plus daily MPA (2.5 mg/day), which showed significant reduction in hip (and other) fracture in women who were not known to have osteoporosis at baseline.[5] In fact, to date, no estrogen or estrogen-progestin product is approved for the treatment of postmenopausal osteoporosis, and current labeling regarding prevention encourages consideration only for women at significant risk and consideration of non-estrogen medications when prescribing solely for this indication.

Most of the current concern about the safety of estrogens, particularly when combined with a progestin, can be attributed to findings of unexpected risks reported in the WHI CEE plus daily MPA trial in July 2002,[5] which resulted in the addition of a black box warning on Prempro® and Premphase® package inserts stating, "Estrogens and progestins should not be used for the prevention of cardiovascular disease" and on Premarin® inserts stating, "Estrogens with or without progestins should not be used for the prevention of cardiovascular disease." Labeling changes more specific to women with cardiovascular disease also followed the earlier, 1998 publication of the Heart and Estrogen-progestin Replacement Study (HERS),[6] which found no cardiovascular health benefit 4.1 years after women with pre-established heart disease initiated CEE plus daily MPA but also found a significant increase in heart attacks by 1 year of use.[6]

Ironically, adoption of new estrogen/progestin combinations accounted for most of the growth in annual hormone therapy prescriptions from 58 million in 1995 to 90 million in 1999, representing approximately 15 million women per year.[7] Therefore, it wasn't surprising that hormone prescriptions declined precipitously following publication of the WHI CEE plus MPA trial[5] and an extended followup of HERS,[8] with prescriptions declining by 66 percent between July 2002 and June 2003 for the specific drug studied in these two trials (Prempro®) and by 33 percent for its estrogen only counterpart (Premarin®).[7] Prescriptions for other oral estrogens and estrogen-progestin products also declined during this period, while small increases were observed for vaginal formulations and in new prescriptions for low-dose Premarin®.[7]

Following publication of the WHI CEE plus MPA trial,[5] labeling was also changed to recommend that topical vaginal estrogen products be considered when prescribing solely for treating menopausal vulvar and vaginal atrophy and that use of estrogens, alone or in combination with a progestin, be limited to the shortest duration consistent with treatment goals and risks for the individual woman and that patients be re-evaluated periodically as clinically necessary. In addition, current labeling recommends that patients be treated with the lowest effective dose and that this dose be periodically reassessed by the health care provider.

Safety concerns regarding CEE and MPA have played a role in increasing interest in "natural" or "bioidentical" hormone therapy (i.e., treatment with individually compounded recipes of certain steroids in various dosage forms), including dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol, in a compounded dosage form based on a person's salivary hormone concentrations.[9] Proponents claim that these are better tolerated than manufactured products and are safer alternatives to pharmaceutical dosage forms of estrogens and/or progestogens.[9] Unfortunately, there are few observational studies or clinical trials comparing conventional hormone therapy with bioidentical hormone therapy; therefore, there is little evidence to support an advantage of individualized hormone dosing over conventional therapies and, at present, the use of such therapy is not supported by evidence regarding pharmacokinetics, safety, and efficacy.[9] It remains, however, that millions of women are eager to identify the most effective, and safe, approach to treating menopausal symptoms.

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Symptom Relief Versus Unwanted Effects: Role of Estrogen-Progestin Dosage and Regimen

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The purpose of this review is to summarize the clinical trial data showing, on one hand, estrogen's dose-effects in relieving vasomotor symptoms and, on the other hand, estrogen's dose-effects for creating troublesome symptoms, particularly vaginal bleeding and breast tenderness. Many expert groups have suggested postmenopausal hormone therapy (HT) should be prescribed at the lowest possible dose for the shortest possible time. Despite admonitions to use lower estrogen dosage, a recent nationwide survey showed that most women continue to take standard dosage.[1] Health care providers need to learn how and when to prescribe lower dosages of HT to relieve menopausal symptoms.

Background

How are hot flash treatment efficacy clinical trials designed? What does the U.S. Food and Drug Administration (FDA) require?[2] What is the expected placebo effect? For the purpose of this review, 0.625mg conjugated equine estrogens or its equivalent is considered standard dosage while 0.3mg conjugated estrogens or its equivalent (e.g. 0.5mg oral micronized estradiol or 25µg transdermal estradiol) is considered low dosage.

Effects of Low Dose HT on Vasomotor Symptoms

In numerous placebo-controlled clinical trials, low dose estrogens have been shown to reduce hot flashes by 60–70 percent.[3–8] In these same studies, this reduction is about twice that observed with placebo but less than the 80–90 percent reductions typically observed with standard estrogen dosage. The onset of relief is typically slower with low dosages, usually more than 4 weeks to achieve clinically relevant reductions. In the United States, there are several half-strength estrogens approved for reduction of hot flashes, and the FDA-approved labeling for estrogen states that the half-strength estrogen dosage is the preferred starting dose; only if there is lack of adequate response should the dosage be increased.

Tolerability and Continuation of HT

Women with a uterus who take estrogen require progestin opposition to prevent endometrial abnormalities. Although both cyclic and continuous progestin additions remove the potential risks of endometrial hyperstimulation, progestins added to estrogen can cause troublesome symptoms. Focusing on bleeding and breast tenderness, clinical trial data show that compared to women using HT-containing standard estrogen dosages with progestin, those using low dosages of estrogens with progestin are less likely to have vaginal bleeding,[6,7,9] or breast tenderness.[7,10–12] Since discontinuation of HT is largely due to unacceptable side effects (e.g. bleeding and breast tenderness),[13] long-term continuance may be improved if lower dosages are given. In several

clinical trials, complaints of breast fullness and tenderness were less frequent among women using lower estrogen dosages as well as those exposed to less progestin.[7,10–12] Women less troubled by local breast symptoms are likely to perceive the lower dosage as being safer—this perception is quite important in their being satisfied and continuing HT.

Progestin Co-Therapy for Low Dose HT

When prescribing low-dosage estrogen, one can safely use less progestin, either less daily dosages[14] or less frequent cycles.[15,16] While there is currently no consensus in the best dose and schedule for progestin co-therapy for use with low-dosage estrogens, adverse results in the estrogen-progestin arm of the Women's Health Initiative Study have prompted providers to seek ways to reduce progestin exposure. Thus, to protect the endometrium, rather than prescribing continuous combined estrogen-progestin regimens, some are reconsidering using cyclic regimens.

Among various cyclic HT regimens currently in use, monthly addition of 5mg medroxyprogesterone for 12–14 days is most common. However, longer intervals between progestin addition are possible, particularly when using lower estrogen doses. A dosage of 10mg medroxyprogesterone every 3 months for 14 days was demonstrated to be safe (about 1 percent per year endometrial hyperplasia rate) when added to standard-dosage estrogen[15] and would be ample to protect the endometrium from low-dosage estrogen. When using low-dosage estrogen, 6-month progestin cycles also appear safe and tolerable;[16] less than half the women using this regimen have any cyclic bleeding and only 9 percent have breakthrough bleeding between 6-month cycles.

The tolerability and endometrial safety of continuous combined low-dose HT have now been extensively studied.[14,17] When using low-dosage estrogen, low-dose co-prescribed progestin (e.g. 1.5mg medroxyprogesterone acetate) is adequate to protect the endometrium from hyperplasia. Low-dose, continuous, combined regimens produce much lower incidence of breakthrough bleeding compared to standard doses.[18,19]

Finally, in unusual circumstances, unopposed low-dose estrogen may be the best clinical choice despite presence of the uterus. The annual rate of endometrial hyperplasia is about 15 percent in women exposed to standard doses of unopposed estrogen. Those receiving half-strength estrogen would be expected to show a 7–8 percent annual hyperplasia rate, yet they appear to have no greater risk of hyperplasia than those receiving placebo.[9,18] Proliferation produced by estrogen is dose-related and low dosage produces approximately one-half as much endometrial growth as standard dosage,[19] but there may be different threshold effects for proliferation and development of hyperplasia.

Selecting Women for Low Dosage HT

Low-dose estrogen is likely to become the preferred HT option because of its superior tolerability and greater potential for patient acceptance and continuation. Health care providers should now make every attempt to reduce the dose of HT to the lowest that is acceptable (i.e., controls menopausal symptoms) and that is least likely to be harmful. A trial of reducing dosage in women using long-term standard HT to half-strength estrogen dosage found that only 6.5 percent returned to standard dosage because of unacceptable vasomotor symptoms[15] Gradual

tapering of dosage can be accomplished by alternate day oral therapy or by reduction in transdermal patch strength.

Approximately 1 in 5 women who stopped HT after learning of the Women's Health Initiative results report persisting and troublesome vasomotor symptoms.[20] These women have made the choice to live with symptoms rather than return to HT. It is not known how many of them have been given counseling about low-dose HT or how many would want to resume HT if a lower dosage were offered.

Conclusions

Low-dosage estrogen can relieve vasomotor symptoms and women taking low dosages of estrogens are less likely to have unacceptable side effects, such as irregular bleeding, heavy bleeding, or breast tenderness. Now that several lower dosage formulations are approved and marketed, health care providers and their patients should consider these new options. Furthermore, it is now appropriate to plan a new generation of low-dose estrogen studies to adequately document its risks and benefits.

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Estrogen With and Without Progestin: Benefits and Risks of Short-Term Use

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Background

Estrogen therapy has long been established as an effective treatment for relief of vasomotor symptoms associated with menopause and remains the chief therapy available for that indication. Accumulated evidence over some 25 years suggested additional benefits of estrogen therapy in reducing risks of heart disease, fracture, and dementia, leading the U.S. Preventive Services Taskforce in 1996 to recommend counseling all perimenopausal and postmenopausal women about the risks and benefits of hormone therapy for long-term prevention of chronic conditions.[1] Concerns about estrogen and the risk of thromboembolic disease and breast cancer also emerged over this period. The Women's Health Initiative (WHI) Hormone Trials were designed to test the ability of conjugated equine estrogen with (E+P) and without progestin (E-alone) to prevent heart disease and fracture and to reveal whether breast cancer incidence was increased by estrogen therapy in predominantly healthy postmenopausal women aged 50–79 at entry. Both trials were stopped prematurely because of disease risks and the failure to demonstrate the overall benefit for the health of postmenopausal women.[2,3] In response to new evidence from randomized trials, the U.S. Preventive Services Taskforce modified its stance in 2002 and recommended "against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women."[4]

The primary target population for systemic estrogen therapy has since reverted to perimenopausal and postmenopausal women with moderate or severe vasomotor symptoms and focuses on using the smallest effective dose for the shortest period of time. The purpose of this review is to examine what has been learned from the WHI Hormone Trials and other studies about the short-term risks and benefits of estrogen use focusing on major disease outcomes. For this purpose, short-term use will be defined as use for up to 1, 2, and 5 years duration. E+P for women with an intact uterus will be distinguished from E-alone for hysterectomized women. Conjugated equine estrogen has the strongest evidence base, but information on other formulations will be examined when available. Whether younger age, vasomotor symptoms, past use of hormone therapy, or disease risk profiles modify the risk estimates associated with estrogen therapy will also be examined.

The WHI Hormone Trials were designed to provide definitive risk estimates after an average of 8–9 years of followup. Thus, risk estimates observed in the first few years of the trial are not expected to be statistically significant but can suggest when the emergence of risks and benefits occurs over time. Confidence intervals will be used as an indication of precision for the short-term risk estimates presented from the WHI.

Coronary Heart Disease

E+P treatment increases the risk of coronary heart disease (nonfatal myocardial infarction or coronary death). The hazard ratio for women aged 50–59 is 1.27 over an average of 5.6 years of followup and is greatest in the first year after initiation (p-value for age effect equals 0.36).[5] Cumulative risk estimates remain elevated with use up to 2 and 5 years. Risks are similar for women with and without vasomotor symptoms. Findings from the WHI Observational Study suggest that lower dose E+P treatment may be associated with less risk. In the WHI trial of E-alone, the long-term effect on coronary heart disease in hysterectomized women was neutral with an overall hazard ratio of 0.91 in women aged 50–79 and elevated risks of 1.2 in the first 2 years after initiation.[3] For women aged 50–59, the hazard ratio for E-alone was 0.56 over nearly 7 years of followup (p-value equals 0.14 for age effect).[3]

Stroke

Estrogen treatment, both E+P and E-alone, increases the risk of stroke with hazard ratios for long-term use of approximately 1.4.[3,6] This effect is apparent within the first year for E-alone and within 2 years for E+P and persists undiminished through 5 years of use. In WHI women aged 50–59, the hazard ratios for stroke were 1.46 for E+P (p-value equals 0.81 for age effect) and 1.08 for E-alone (p-value equals 0.59 for age effect).

Venous Thromboembolism and Pulmonary Embolism

Risk of deep vein thrombosis and/or pulmonary embolism are increased three- to four-fold in the year after initiating estrogen therapy, for either E-alone[3] or E+P.[7] For E+P, risks remain elevated with hazard ratios in the two- to three-fold range for use up to 2 and 5 years. In contrast, risks of deep vein thrombosis and/or pulmonary embolism for E-alone diminish slowly after the first year but remain elevated at 2 and 5 years. Evidence from some, but not all, observational studies supports a dose-response effect for estrogen and thromboembolic events: lower doses have been associated with less elevated risks compared to standard doses.[8–11] Recent observational evidence suggests that esterified estrogen may *not* be associated with an increased risk of venous thromboembolism.[8]

Breast Cancer

Risk of invasive breast cancer is increased by E+P treatment with hazard ratios of 1.24 for women aged 50–79 and 1.20 for women aged 50–59, specifically (p-value equals 0.20 for age effect).[12] Excess cases in the treatment group did not occur until the third year of treatment and cumulative increased risk is not evident before 5 years of treatment. E-alone did not increase the risk of breast cancer over nearly 7 years of treatment. The hazard ratio for women aged 50–59 was 0.72 (p-value equals 0.51 for age effect). Observational studies, such as the Million Women's Study,[13] suggest that breast cancer risks rise with increasing durations of use of E-alone.

Other Cancers

In the WHI E+P Trial, treatment appeared to reduce the incidence of invasive colorectal cancer with an overall hazard ratio of 0.56 for women aged 50–79 and an age-specific hazard ratio of 0.79 in women aged 50–59 (seven cases in the E+P group versus eight cases in the placebo group; p-value equals 0.57 for age effect).[14] Differences between the treatment groups began to emerge soon after treatment initiation. E-alone did not alter the occurrence of colorectal cancer among women with hysterectomies. Occurrence of ovarian and endometrial cancer was too rare in the WHI hormone trials to estimate short-term risks or risks in younger women, specifically.[15]

Fractures

Estrogen treatment with or without progestin reduces the risk of hip and total fractures.[16] Reduced risks of total fracture are present in all age groups of women aged 50–79 and appear to emerge after 2–3 years of use. Too few hip fractures occur among women aged 50–59 to yield reliable risk estimates. This benefit is present for women at all levels of fracture risk.

Women With Vasomotor Symptoms

In the Women's Health Initiative Hormone Trials, the risks and benefits of hormone therapy, with or without progestin, have *not* been shown to differ significantly for women with vasomotor symptoms, or younger women ages 50–59, closest to the age of menopause. However, the absolute rates of disease events rises with age and is substantially lower in younger women.

Women With Oophorectomies

In the WHI Hormone Trial of E-alone, the risks and benefits for women with a hysterectomy were similar for those with and without intact ovaries. It is not known whether these risk estimates apply to women who experience premature ovarian failure or undergo ovarian ablation before age 50. The latter group typically is prescribed long-term hormone therapy to compensate for their loss of ovarian hormones during premenopause.

Conclusions

Estrogen therapy, even when used over short durations, increases the risk of serious disease events, specifically stroke and deep vein thrombosis and/or pulmonary embolism, and when combined with progestin (medroxyprogesterone acetate), coronary events, and breast cancer. Women considering initiation of hormone therapy should be advised of these potential risks. Lower doses of conjugated equine estrogens and use of other formulations or routes of administration may not convey the same risks, but evidence is lacking on these alternatives. A high priority should be placed on the development and testing of new and safer treatments for alleviating menopause symptoms.

Table 1: Major Disease Outcomes* (Annualized Percentage) by Time Since Randomization to E+P or Placebo in the Women's Health Initiative Hormone Trial of Postmenopausal Women Aged 50–79

	Year ≤ 1			Year ≤ 2			Year ≤ 5		
	E+P	**Placebo**	**HR (95% CI)**	**E+P**	**Placebo**	**HR (95% CI)**	**E+P**	**Placebo**	**HR (95% CI)**
Number of participant years	8,448	8,054		16,827	16,046		40,486	38,555	
CHD	42 (0.50%)	23 (0.29%)	1.81 (1.09–3.01)	80 (0.48%)	51 (0.32%)	1.55 (1.09–2.20)	160 (0.40%)	110 (0.29%)	1.43 (1.12–1.82)
Stroke	16 (0.19%)	18 (0.22%)	0.88 (0.45–1.73)	43 (0.51%)	32 (0.40%)	1.31 (0.83–2.07)	122 (1.44%)	83 (1.03%)	1.40 (1.06–1.85)
DVT/PE	50 (0.59%)	12 (0.15%)	4.01 (2.13–7.52)	73 (0.43%)	23 (0.14%)	3.04 (1.90–4.85)	145 (0.36%)	59 (0.15%)	2.34 (1.73–3.17)
Breast cancer	12 (0.14%)	19 (0.24%)	0.60 (0.29–1.23)	38 (0.23%)	51 (0.32%)	0.71 (0.47–1.08)	154 (0.38%)	121 (0.31%)	1.22 (0.96–1.54)
Colorectal cancer	8 (0.09%)	12 (0.15%)	0.64 (0.26–1.56)	18 (0.11%)	22 (0.14%)	0.78 (0.42–1.46)	37 (0.09%)	60 (0.16%)	0.58 (0.39–0.88)
Hip fracture	8 (0.09%)	9 (0.11%)	0.88 (0.34–2.28)	16 (0.10%)	22 (0.14%)	0.70 (0.37–1.34)	44 (0.11%)	59 (0.15%)	0.72 (0.48–1.06)
Total fractures	153 (1.81%)	164 (2.04%)	0.89 (0.71–1.11)	275 (1.63%)	315 (1.96%)	0.83 (0.71–0.98)	641 (1.58%)	773 (2.00%)	0.78 (0.70–0.87)
Global index	124 (1.47%)	97 (1.20%)	1.24 (0.95–1.62)	259 (1.54%)	214 (1.33%)	1.17 (0.98–1.40)	693 (1.71%)	575 (1.49%)	1.16 (1.04–1.30)
Death	22 (0.26%)	17 (0.21%)	1.24 (0.66–2.34)	52 (0.31%)	47 (0.29%)	1.05 (0.71–1.55)	194 (0.48%)	184 (0.48%)	1.00 (0.82–1.23)

*Major disease outcomes are defined as coronary heart disease (CHD), stroke, deep vein thrombosis or pulmonary embolism (DVT/PE), breast cancer, colorectal cancer, hip fracture, total fractures, or death. Global index is defined for each woman as the time to first event for a monitored trial outcome (CHD, stroke, PE, breast cancer, colorectal cancer, hip fracture, or death). Number of participant years is the sum of time from randomization to the end of the specified time interval contributed by all women in that treatment group. Abbreviations: E, estrogen in the form of conjugated equine estrogen; CEE, conjugated equine estrogen; HR, hazard ratio; CI, confidence interval.

Table 2: Major Disease Outcomes* (Annualized Percentage) by Time Since Randomization to CEE or Placebo in the Women's Health Initiative Hormone Trial of Postmenopausal Women Aged 50–79

	Year ≤ 1			Year ≤ 2			Year ≤ 5		
	CEE	Placebo	HR (95% CI)	CEE	Placebo	HR (95% CI)	CEE	Placebo	HR (95% CI)
Number of participant years	5,266	5,389		10,476	10,726		25,737	26,310	
CHD	26 (0.49%)	24 (0.45%)	1.11 (0.64–1.94)	53 (0.51%)	47 (0.44%)	1.16 (0.78–1.71)	128 (0.50%)	123 (0.47%)	1.06 (0.83–1.36)
Stroke	24 (0.46%)	15 (0.28%)	1.63 (0.86–3.11)	39 (0.74%)	27 (0.50%)	1.48 (0.91–2.42)	94 (1.78%)	77 (1.43%)	1.27 (0.94–1.72)
DVT/PE	15 (0.28%)	6 (0.11%)	2.55 (0.99–6.58)	26 (0.25%)	12 (0.11%)	2.22 (1.12–4.39)	65 (0.25%)	46 (0.17%)	1.44 (0.99–2.10)
Breast cancer	9 (0.17%)	7 (0.13%)	1.32 (0.49–3.55)	20 (0.19%)	27 (0.25%)	0.77 (0.43–1.37)	66 (0.24%)	88 (0.33%)	0.72 (0.52–1.00)
Colorectal cancer	7 (0.13%)	7 (0.13%)	1.02 (0.36–2.90)	17 (0.16%)	19 (0.18%)	0.91 (0.47–1.75)	34 (0.13%)	41 (0.16%)	0.85 (0.54–1.33)
Hip fracture	1 (0.02%)	6 (0.11%)	0.17 (0.02–1.43)	6 (0.06%)	10 (0.09%)	0.62 (0.23–1.71)	21 (0.08%)	35 (0.13%)	0.61 (0.36–1.06)
Total fractures	89 (1.69%)	103 (1.91%)	0.89 (0.67–1.18)	165 (1.58%)	184 (1.72%)	0.92 (0.74–1.13)	369 (1.43%)	531 (2.02%)	0.70 (0.61–0.80)
Global index	82 (1.56%)	70 (1.30%)	1.20 (0.87–1.65)	168 (1.60%)	156 (1.45%)	1.11 (0.89–1.38)	437 (1.70%)	451 (1.71%)	0.99 (0.87–1.13)
Death	24 (0.46%)	14 (0.26%)	1.74 (0.90–3.36)	52 (0.50%)	39 (0.36%)	1.36 (0.90–2.06)	161 (0.63%)	151 (0.57%)	1.08 (0.87–1.35)

*Major disease outcomes are defined as coronary heart disease (CHD), stroke, deep vein thrombosis or pulmonary embolism (DVT/PE), breast cancer, colorectal cancer, hip fracture, total fractures, or death. Global index is defined for each woman as the time to first event for a monitored trial outcome (CHD, stroke, PE, breast cancer, colorectal cancer, hip fracture, or death). Number of participant years is the sum of time from randomization to the end of the specified time interval contributed by all women in that treatment group. Abbreviations: E, estrogen in the form of conjugated equine estrogen; CEE, conjugated equine estrogen; HR, hazard ratio; CI, confidence interval.

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Therapeutic Effects of Progestins, Androgens, and Tibolone for Menopausal Symptoms

James H. Liu, M.D.

Clinicians have long recognized that estrogen, progesterone, and androgen receptors are localized to reproductive target tissues as well as to the brain and bone. This understanding has led to the development of treatment strategies utilizing progestins, androgens, and synthetic steroids, such as tibolone, for the menopausal woman.

Traditionally, progestins, such as medroxyprogesterone acetate (MPA) and micronized progesterone, have been used to induce secretory changes in the endometrium to prevent endometrial hyperplasia. However, in a randomized controlled trial, MPA (500 mg/2 weeks)[(1)] and megestrol acetate (40 mg/d)[(1)] at high doses were also highly effective at reducing hot flushes by approximately 80–90 percent. These 21-carbon-derived progestins may be associated with side effects, such as weight gain, fluid retention, vaginal discharge, and dry mouth. Long-term use of megestrol acetate for 3 years or longer at doses of 20–160 mg have been reported to be effective in reducing vasomotor symptoms in breast and prostate cancer survivors.[(2)] Although oral micronized progesterone is less effective for treatment of vasomotor symptoms when taken at doses higher than 100 mg/d, this preparation can be associated with sedative effects. This is possibly due to formation of 5α- and 5β-reduced metabolites, allopregnanolone and pregnanolone, which have GABA-agonistic properties.[(3)] The 19-nortestosterone derived progestins, such as norethindrone commonly found in oral contraceptives, have not been studied widely for the relief of hot flushes in menopausal women. Studies in younger, hypoestrogenic women have established an effective dose range of 1.2–5 mg for treatment of hot flushes.[(4)] At these doses, there are also modest protective effects against bone loss.[(5)]

With normal aging, circulating levels of the adrenal steroid dehydro-epiandrosterone (DHEA) and its stable conjugate DHEA sulfate decline progressively to low levels. This physiological decrease can be as much as 70–80 percent[(6)] and has been attributed to a reduction in 17,20 desmolase activity within the adrenal cortex.[(7)] Although the physiological role of DHEA remains to be defined, DHEA can be conceptually considered a prohormone that is converted peripherally to androgens and estrogens. Pharmacologic administration of DHEA to menopausal women has resulted in significant increases in circulating testosterone, dihydrotestosterone, androstenedione, estrone, and estradiol.[(8)] DHEA supplementation has been studied in small groups of menopausal women. Doses of 50 mg/day or more can result in supra-physiological elevations of testosterone, estradiol, 17OH progesterone, and dihydrotestosterone.[(9)] Lower DHEA doses, such as 25 mg/d for up to 12 months, have resulted in more modest elevations of androgens and estrogens without stimulation of significant endometrial growth.[(10)] In small prospective studies, DHEA has been reported to improve insulin sensitivity,[(11)] sexual arousal,[(12)] vaginal maturation index,[(13)] and cognitive performance;[(14)] reduce vasomotor symptoms;[(10)] and increase bone density.[(13)] Collectively, these observations suggest that DHEA supplementation may provide some benefits through its conversion to androgens and estrogens with fewer virilizing side effects, but the long-term risks, benefits, and side effects need to be evaluated in larger, clinical trials.

The decline in circulating testosterone levels during the menopausal transition is relatively gradual with levels generally lower than in younger women.[15] However, with surgical menopause and the removal of ovarian function, there is a 50 percent abrupt decline in levels of testosterone and androstenedione.[16] Thus, evaluation of effects of testosterone supplementation should be addressed separately in a surgically menopausal population versus a naturally menopausal population. Androgen receptors have been localized to hypothalamus and the limbic system suggesting a role in modifying vasomotor symptoms, mood, sexual desire, and cognitive functions.

Testosterone (T) supplementation can be administered in a variety of forms, including T enanthate injections, subcutaneous pellets, gels, transdermal patches, and as oral methyltestosterone in combination with esterified estrogen. Simon and coworkers have reported that the addition of methyltestosterone to low dose esterified estrogen provided greater relief of vasomotor symptoms and was comparable to high-dose estrogen alone.[17] In a series of studies, Sherwin and Gelfand have compared the effect of T replacement alone, estradiol alone, or a combination of estradiol plus T in surgically menopausal women. These studies suggest that women receiving T alone or in combination with estradiol had significant improvements over baseline in well-being, sexual function, and energy levels.[18–21] In a pilot study of surgically menopausal women replaced with estrogen, Shifren and coworkers found that transdermal T (150 or 300 μg/d) improved overall sexual function and psychological well-being in women with hypoactive sexual desire disorder.[22] These findings have been replicated in two larger multicenter trials of over 1,000 surgically menopausal women.[23] These studies show significantly increased sexual desire and sexual activity and decreased personal distress in women with hypoactive sexual desire disorder following T treatment for 6 months. Whether transdermal T confers these same benefits in naturally menopausal women with or without estrogen replacement is currently being evaluated. Side effects at these doses of T appear to be minimal with respect to acne, alopecia, or increased facial hair. Lipid levels were not appreciably altered from baseline. At this point, only methyltestosterone in combination with esterified estrogen is available as an FDA-approved treatment modality; however, as a number of transdermal T patches and gels are being tested in phase III trials, the purported benefits and risks of testosterone supplementation will become clear. For clinicians who are using compounded T preparations, laboratory monitoring of bioavailable or free T levels, SHBG, and lipids should be considered. There is no long-term safety data for T therapy; therefore, long-term use cannot be recommended without continuing surveillance.

Tibolone (Livial) is a synthetic steroid compound with relatively weak hormonal activity. After oral administration, it is rapidly absorbed and converted by the liver into two estrogenic metabolites (3α- and 3βOH-tibolone), which bind to the estrogen receptor and a third metabolite, Δ4-isomer, which binds to the progesterone and androgen receptors. Tibolone is not available in the United States but has been used in Europe and Canada for treatment of climacteric symptoms, sexual dysfunction, and osteoporosis prevention for almost 20 years. Despite the widespread clinical experience with this compound for the treatment of climacteric symptoms, there are surprising relatively small numbers of women studied in the randomized clinical trials comparing its efficacy to estradiol or placebo.[24] In general, most studies report that tibolone provided a similar reduction of hot flushes seen with estrogen therapy. Both mood and insomnia were also improved.[25] Due to its androgenic activity, tibolone has been reported to provide beneficial effects on sexual function.[26–28] However, none of these three studies were placebo-controlled. There are more robust data indicating a bone conservation effects of tibolone.[29] Despite the lack of endometrial stimulation, treatment with tibolone is associated with more vaginal bleeding than

placebo but less than with estradiol/norethindrone acetate therapy.[30] Due perhaps to its androgenic properties, tibolone has been reported to reduce HDL-C by 34 percent and reduce triglycerides but have no impact on LDL-C or lipoprotein a.[31] In summary, tibolone appears to be effective at reducing climacteric symptoms and bone loss, but its effects on sexual function, lipids, and breast cancer are less clear and await more definitive trials.

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Diagnosis and Management of Mood Disorder During the Menopause Transition

Lee S. Cohen, M.D.

Major depressive disorder is a highly prevalent illness and is associated with significant morbidity. Women are more commonly affected than men with several studies supporting a two-fold increase in risk for new onset of major depression in females versus males.[1] Periods of reproductive hormonal change[2–4] (i.e., the premenstrual period, puerperium, and perimenopause) may constitute times of particular risk for the development of depression in women. The extent to which perimenopause specifically is associated with increased risk for depression has considerable public health consequences. Recent U.S. census data describe the significant pace of growth of the female population compared to men with approximately 1.5 million women reaching menopause each year in the United States, an estimate arrived at by using age as a proxy.[5]

The extent to which the transition to menopause is associated with a frank "perimenopausal depressive syndrome" has been the subject of some controversy. Inconsistent findings in the literature may derive from the heterogeneity of studies where subject samples have included women from a spectrum of settings, including specialized menopause clinics and other clinical facilities as well as community-based samples.[2,6,7] Most studies also fail to systematically document the diagnosis of mood disorder and menopausal status. Menopausal status has frequently been assigned in studies based on menstrual history or age and mood disturbance is described almost uniformly absent in any systematic evaluation of whether patients suffered from concurrent vasomotor symptoms. The absence of a consistent construct to better define either women transitioning to menopause or those who are, frankly, menopausal has made comparison of these studies problematic. Another difficulty has been the absence of standardized psychiatric assessments which can accurately indicate the presence of a depressive disorder. Despite these methodological limitations, overall, a significant association between a natural transition to menopause and risk for depression seems to emerge when cross-sectional and community-based studies are examined. One recent study by Freeman[6] and a followup study to the Harvard Study of Moods and Cycles,[2] a population-based prospective study of women with and without a lifetime history of major depression, have described an increased risk for clinically significant first onset of mood disturbance in perimenopausal versus premenopausal women.

If the transition to perimenopause is a period of risk for mood disturbance, then appropriate management of such depression is critical given the morbidity associated with untreated affective disorder. Multiple studies have demonstrated efficacy of both nonpharmacologic and pharmacologic treatments of depression.[8] With increased public awareness of the efficacy of antidepressants to treat depression, particularly selective serotoninergic reuptake blockers (SSRI's) and dual-action antidepressants (i.e., venlafaxine and duloxetine), it is critical to delineate populations of men and women who appear more or less responsive to treatment with these compounds.

Several studies,[9,10] though not all,[11] suggest that as women age, the proportion of those who suffer from depression and who respond to SSRI's decreases and that older *and* younger women respond in a robust fashion to dual action agents, such as venlafaxine.[10] Other investigation

suggests that a subgroup of women may be particularly sensitive to the extent to which estrogen and other gonadal steroid modulate central nervous system neurotransmission and that such patients may respond to treatment with estrogen either as monotherapy[12,13] or as an augmentation strategy[14] to treat underlying symptoms of depression. While several controlled studies have demonstrated the efficacy of transdermal estradiol in the treatment of depression in perimenopausal women, findings from the Women's Health Initiative (WHI) have kindled vigilance about the use of hormonal preparations in women, both for its primary indication (i.e., treatment of vasomotor symptoms) and, for that matter, any other potential use. It is yet to be determined if the discontinuation of hormone therapy over the last several years increases the risk for depression. If such is the case, an increase in mood disturbance among menopausal women due to declining hormone therapy prescriptions in the post-WHI era would be anticipated.

What is the ideal algorithm for managing depression in perimenopausal women? Clearly, extensive data exist regarding the efficacy of antidepressant therapy. However, the significant prevalence of treatment-emergent sexual dysfunction[15] and weight gain associated with use of these compounds are factors which need to be considered when managing depression in this population. A challenge to the field lies in the identification of the most tolerable treatments to manage depression in an aging population while taking into account the spectrum of side effects which may complicate treatment as well as associated symptoms, such as vasomotor symptoms and other psychosocial factors, which may also modulate risk for the development of mood disturbance.

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Hormonal Treatment of Menopause-Related Symptoms: Evidence From Randomized Controlled Trials

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There is uncertainty about how to effectively manage symptoms related to menopause and minimize adverse effects while doing so. A systematic review was undertaken to describe the evidence about benefits and adverse effects of therapies for symptoms related to menopause, factors that influence therapies, and future research needs—three of the five Key Questions specified by the Planning Committee for the National Institutes of Health State-of-the-Science Conference on Management of Menopause-Related Symptoms. This report summarizes commonly used hormonal interventions, including estrogens, progestins, androgens, and tibolone.

Relevant studies were identified from multiple searches of MEDLINE, PsycINFO, DARE, the Cochrane database, MANTIS, and AMED (1953 to November 2004); and from recent systematic reviews, reference lists, editorials, Web sites, and experts. The review included randomized controlled trials of midlife women transitioning through the stages of menopause and experiencing symptoms related to menopause. Specific inclusion and exclusion criteria were developed to determine study eligibility. All eligible studies were reviewed and relevant data were extracted, entered into evidence tables, and summarized by descriptive methods. Two reviewers independently rated the quality of studies using predefined criteria. Three recently conducted systematic reviews of estrogen and 53 additional trials were included.

Key Question 3. What is the evidence for the benefits and harms of commonly used interventions for relief of menopause-related symptoms?

- Estrogen, in either opposed or unopposed regimens, is the most consistently effective therapy for vasomotor symptoms,[1,2] and demonstrates benefit in most trials evaluating urogenital symptoms.[3] Some, but not all, trials evaluating sleep, mood and depression, sexual function, and quality of life outcomes also report benefit with estrogen compared to placebo.[3]

- Breast tenderness and uterine bleeding are the most commonly reported adverse outcomes in estrogen trials; others include nausea and vomiting, headache, weight change, dizziness, venous thromboembolic events, cardiovascular events, rash and pruritus, cholecystitis, and liver effects.[1–3]

- Trials of progestin indicate mixed results for treatment of vasomotor symptoms.

- Few trials of testosterone are available; one trial indicated no differences between testosterone/estrogen and estrogen alone for hot flash severity, vaginal dryness, or sleep problems.[4] Sexual symptoms were improved with testosterone/estrogen compared to estrogen alone or placebo in two other trials.[5,6]

- For women using testosterone, acne and hirsutism occur significantly more often than for women using estrogen alone.

- Based on only a few trials, tibolone demonstrated benefit for vasomotor symptoms, sleep, and somatic complaints compared to placebo[7–9] and was similar to estrogen for some, but not all, symptoms.[10–13]

- Uterine bleeding, body pain, weight gain, and headache were more common in tibolone versus placebo groups.

Key Question 4. What are the important considerations in managing menopause-related symptoms in women with clinical characteristics or circumstances that may complicate decisionmaking?

- Evidence is not available to determine if the effectiveness of therapy or adverse effects differ for women with bilateral oophorectomy, premature ovarian failure, concurrent use of SERMs or other potentially interacting agents, lifestyle and behavioral factors, recent discontinuation of menopausal hormone therapy, or very low or very high body mass index.

Key Question 5. What are the future research directions for treatment of menopause-related symptoms and conditions?

- Determination of optimally effective doses, combination regimens, durations of use, and timing of therapy.

- Evaluation of approaches to identify optimal candidates for specific therapies.

- Head-to-head and placebo comparisons of estrogen alone and combined with other types of therapies, including nondrug interventions.

- Trials demonstrating how to discontinue estrogen when symptoms subside, including the effectiveness of tapering doses and/or replacing with other therapies, including nondrug interventions.

- Better reporting of adverse effects in trials and use of standardized categories of adverse effects so data can be combined across trials.

- Improved analysis of results, including analysis by hysterectomy and oophorectomy status, stage of menopause, age, concurrent conditions and medications, and other factors.

- Enrollment of women with specific characteristics who have not previously been evaluated.

- Use of standard definitions, measures, and outcomes so results can be compared across trials.

Trials of therapy are conclusive only for estrogen and its use in treating vasomotor and urogenital symptoms, although other therapies may prove effective if further studied. Undertaking trials to treat symptoms that are not clearly associated with the menopausal transition would not be useful. Trials are limited in many ways, including use of highly selected small samples of women; short durations; inadequate reporting of loss to followup, methods of analysis, and adverse events; use of dissimilar measures and outcomes that are often not standardized or validated; unclear inclusion and exclusion criteria; and industry sponsorship. Future research addressing these deficiencies would guide patient and clinician decisionmaking.

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Menopause: Review of Botanical Dietary Supplement Research

Tieraona Low Dog, M.D.

There are a growing number of dietary supplement products in the American marketplace specifically targeting women experiencing menopause-related symptoms. Unlike pharmaceuticals, which are required to demonstrate safety and efficacy before entering the market place, we know less about the safety and efficacy of dietary supplements, which are widely available over the counter without the level of premarket testing afforded to drugs. The purpose of this review is to evaluate the safety and efficacy of dietary supplement products based on single plants (monopreparations) for the treatment of menopausal symptoms.

We identified 20 relevant studies, through searches of the Cochrane Library and MEDLINE, from the period of 1966 to October 2004, using a detailed list of search terms related to botanicals and menopausal symptoms. Included here are randomized controlled clinical studies of botanical monopreparations administered orally for a minimum of 6 weeks to women with physical and/or psychological symptoms related to menopause.

The botanical that has received the most research attention is black cohosh (*Actaea racemosa* L., *Cimicifuga racemosa* (L). Nutt.). We identified 5 placebo-controlled trials dealing with black cohosh.[1–5] These studies used different preparations of black cohosh at different doses and for varying durations of treatment. (See Table 1.) While several studies used Remifemin®, it should be noted that the formulation of that product has changed over time.

Some studies indicate that black cohosh extract may reduce some symptoms associated with menopause, but the findings vary across studies. For example, Stoll[2] reported a statistically significant ($p<.001$) reduction in Kupperman Index (KI) and Hamilton Anxiety (HAMA) scores among women assigned to black cohosh compared with those given conjugated estrogens or placebo. Wuttke and coworkers[5] found a statistically significant reduction in the Menopause Rating Scale (MRS) among women taking black cohosh or conjugated estrogen compared with those assigned to placebo. However, reduction in hot flashes (item 1 on the MRS) did not differ significantly between the black cohosh and placebo groups. In comparisons of women taking black cohosh versus placebo, Jacobsen and colleagues[4] found a decrease in sweating but not in hot flash frequency and severity among women taking black cohosh. It should be noted that the dose used in this study is lower than that used in other studies. Moreover, these findings may be confounded by a large number of women taking tamoxifen, a drug known to induce hot flashes, and not definitive since there are too few women not taking tamoxifen to support subgroup analyses. Wehmann-Willenbrock and Riedel[3] found no significant differences in KI scores between women taking black cohosh and those receiving hormone therapy. It is difficult to interpret the findings of this study because the authors did not include an inactive placebo group, describe the randomization process, define inclusion and exclusion criteria, or use a double-blind design.

The mechanism of action of black cohosh remains uncertain, but recent research suggests a nonhormonal effect. Three case reports of possible hepatotoxicity have been published, but the

purported association with black cohosh is not clear in all cases. Numerous safety reviews[6–8] conclude that black cohosh is well-tolerated and adverse events are rare with up to 6 months of use. A recent abstract[9] reporting increased metastases from breast to lung in mice given black cohosh has raised questions concerning safety for women with breast cancer. However, other studies in animals have not found an effect on mammary tumors.

Table 1: Controlled Trials of Black Cohosh

Ref.	N	Sample	Control	Treatment	Primary Outcome Measures
1	60	Perimenopausal and postmenopausal women	Conjugated estrogens (0.6 mg/d) or Diazepam (2 mg/d) for 12 weeks	40 drops Remifemin® liquid extract BID (4 mg/d 27 deoxyactein) for 12 weeks	Kupperman Index, Hamilton Anxiety Score, Global Impressions, and Self-Assessment Depression Scale
2	80	Postmenopausal women	Conjugated estrogens (0.625 mg/d) or placebo for 12 weeks	Remifemin® extract 80 mg BID for 12 weeks	Kupperman Index, Hamilton Anxiety Score
3	60	Surgically menopausal women	Estriol (1 mg/d) or conjugated estrogens (1.25 mg/d) or estradio (2mg/d) + norethisterone acetate (1 mg/d) for 6 months	Remifemin® 40 mg BID for 6 months	Kupperman Index
4	85	Female breast cancer patients, 59 on tamoxifen	Placebo for 60 days	Remifemin® 20 mg BID for 60 days	4 day hot flash diary; menopausal symptom questionnaire
5	62	Postmenopausal women	Conjugated estrogen CE (0.6 mg/d) or placebo for 12 weeks	CR BNO 1055 Menofem® (40 mg/d)	Menopause Rating Scale

There has been significant scientific interest in phytoestrogens for the treatment of menopausal symptoms, especially soy and red clover. Again, when the literature is viewed in aggregate, we find conflicting data and minimal efficacy for hot flashes.

We reviewed six published placebo controlled clinical trials evaluating the use of soy extracts for hot flashes.[10–15] We did not assess soy interventions using soy or phytoestrogen rich diets or soy protein, as this review is limited to botanical monopreparations as dietary supplements. The studies provide contradictory results. (See Table 2.) The largest study by Upmalis, et al.[15] found a reduction in severity of hot flashes and night sweats but did not detect a significant reduction in hot flash frequency for a soy extract providing 50 mg/d isoflavones when compared to placebo. Nikander, et al.[13] did not find any significant reduction in Kupperman Index, while Penotti, et al.[10] failed to detect any significant difference in hot flash frequency or severity between women receiving 72 mg/d soy isoflavones or placebo. The study by Scambia, et al.[14] showed reduction in hot flash frequency and severity but it was of short duration and failed to report Green Menopause Scale total or subscores. The trial by Faure, et al.[11] found a greater reduction in hot flash frequency in the soy group; however findings are limited by a 39 percent

drop-out in the placebo group and lack of randomization description. Han, et al.[12] noted a significant reduction in KI score in the active group; however these findings are challenged by the total lack of improvement in KI scores or hot flashes in the placebo group.

A review of the soy clinical trials is complicated by the fact that varying doses of total soy isoflavones have been used, often without including the ratio or percentage of the individual isoflavones. While soy is generally considered safe when consumed as a food, a recent study[16] raised questions about the effect of long-term use (5 years) of soy isoflavones (150 mg/d) on the uterine endometrium.

Table 2: Placebo-Controlled Trials of Soy Extracts

Ref.	N	Sample	Control	Treatment	Primary Outcome Measures
10	62	Postmenopausal women	Placebo for 6 months	1 gram tablet BID (36 mg soy isoflavones) for 6 months	Self-reported hot flash frequency (diary)
11	75	Menopausal women	Placebo for 16 weeks	2 Phytosoya® capsules BID (17.5 mg soy isoflavones) for 16 weeks	Self-reported hot flashes and night sweats (symptom card)
12	82	Postmenopausal women with breast cancer	Soy protein without isoflavones (50.3 mg) for 16 weeks	1 soy extract capsule TID (33.3 mg soy isoflavone) for 16 weeks	Kupperman Index
13	62	Postmenopausal women	Placebo for 3 months	3 phytoestrogen tablets BID (114 mg/d phytoestrogens)	Kupperman Index, Visual Analog Scale, mood
14	39	Menopausal women	Placebo for 12 weeks	SoySelect® (50 mg/d isoflavones) QD for 12 weeks	Hot flash frequency and severity, Greene Menopause Scale
15	177	Postmenopausal women	Placebo for 12 weeks	Soy extract (50 mg/d isoflavones) QD for 12 weeks	Hot flash and night sweat frequency and severity

There are a wide variety of red clover products available in the United States. We identified 5 clinical trials[17–21] on red clover (*Trifolium pratense* L.), all of which used the product Promensil®, although at different doses. One study[17] included a treatment arm using Rimostil.® (See Table 3.)

Table 3: Placebo-Controlled Trials of Red Clover

Ref.	N	Sample	Control	Treatment	Primary Outcome Measures
17	252	Postmenopausal women	Placebo for 12 weeks	Promensil® (80 mg/d isoflavones) or Rimostil® (57 mg/d isoflavones) for 12 weeks	Hot flash frequency, changes in quality of life
18	30	Postmenopausal women	Placebo for 12 weeks	Promensil® (80 mg/d isoflavones) for 12 weeks	Hot flash frequency, Greene Menopause Symptom Score
19	30	Postmenopausal women	Placebo for 16 weeks	Promensil® (40 mg/d isoflavones) for 16 weeks	Hot flash frequency and severity
20	37	Postmenopausal women	Placebo for 12 weeks	Promensil® (160 mg/d isoflavones or Promensil® (40 mg/d isoflavones) for 12 weeks	Hot flash frequency and Greene Menopause Symptom Score
21	51	Postmenopausal women	Placebo for 30 weeks	Promensil® (40 mg/d isoflavones) for 30 weeks	Hot flash frequency and Greene Menopause Symptom Score

The largest randomized, double-blind, placebo-controlled trial[17] failed to find any significant benefit for either Promensil® or Rimostil® over placebo for either hot flash frequency or quality of life measures. Two smaller studies[20,21] found no differences between treatment and placebo groups for either hot flash frequency or Greene Menopause Symptom Score. Two studies[18,19] found a statistically significant reduction in hot flash frequency among women taking Promensil® compared with women taking placebo. However, the study by van de Weijer and Barentsen[18] found no significant difference in the Greene score between treatment and placebo groups.

Kava (*Piper methysticum* G. Forster.) has been shown to have anxiolytic effects.[22] The study by Warnecke, et al.[23] (1991) found that 300 mg/d kava extract (210 mg/d kavalactones) improved KI scores and also found statistically significant improvement in HAM–A and Depression Status Inventory (DSI) in menopausal women. However, concerns about hepatotoxicity associated with this botanical have limited its use.[22]

One trial was found for each of the following botanicals used to improve menopausal symptoms: dong quai (*Angelica sinensis* L.), ginseng (*Panax ginseng* C.A. Mey), and evening primrose oil (*Oenothera biennis* L.). The ginseng study[24] included 384 postmenopausal women who were randomly assigned to either two 100 mg doses of Ginsana® (standardized to 4 percent ginsenosides) or placebo. It failed to demonstrate any significant differences between placebo and treatment group with respect to vasomotor symptoms but did find a positive effect on depression and well-being as measured by Psychological General Well-Being Index. The study of dong quai[25] included 71 postmenopausal women, randomizing them to either placebo or 4.5 g/d powdered aqueous extract of *A. sinensis* standardized to 0.5 mg/kg of ferulic acid. After 24 weeks, the investigators found no statistically significant difference between placebo and treatment groups

in KI scores, hot flash frequency, or measures of vaginal dryness. There were also no indications of estrogen-like stimulation of the uterine lining associated with dong quai use. One 24-week study[26] that randomized 56 women to either placebo or four 500 mg capsules of evening primrose oil 2 times daily found a significant reduction in the number of nocturnal sweating episodes, but no significant reduction in hot flash frequency was found.

In summary, black cohosh extracts may ease menopausal symptoms. Ongoing NIH-supported research on this botanical should provide more definitive information on safety and efficacy. Phytoestrogen products exert minimal or no effects. Kava improves mood but safety concerns limit use. And dong quai, ginseng extract, and evening primrose seed oil appear to be ineffective in ameliorating menopausal symptoms at the doses used in these studies.

When looking at the larger literature on botanicals used to treat menopausal symptoms, we find equivocal findings, with some studies reporting efficacy for specific botanical products and others not. Lack of treatment effect may reflect inadequate doses used in trials. Few botanical products have undergone dose escalation studies, which should be conducted prior to conducting expensive clinical studies. Variation in findings across studies of the same botanical may be a function of less than optimal designs, variation in products used, length of treatment, use of small or noncomparable samples as well as other factors. However, it is often difficult to assess why such variation is seen, given that many studies do not provide adequate descriptions of the products used, the population from which subjects were selected, or the processes used in the conduct of the study. In addition to implementing rigorous clinical trial designs, it is essential that authors of research articles provide an adequate description of the product used in the study given the complex nature of botanicals and variation in constituents between species, plant part used, and method of preparation.

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Other Complementary and Alternative Medicine Modalities: Acupuncture, Magnets, Reflexology, and Homeopathy

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A multitude of complementary and alternative medicine modalities are commonly recommended to treat a variety of menopausal symptoms. The purpose of this review is to evaluate the scientific evidence for efficacy of therapies based on acupuncture, magnets, reflexology, and homeopathy to alleviate menopause-related symptoms.

Relevant studies were identified using electronic search engines (PubMed, PsychINFO, MEDLINE), direct searches of specific journals, and reviews of reference lists of related publications. This produced 11 intervention studies, including 7 on acupuncture,[1–7] 1 on magnets,[8] 1 on reflexology,[9] and 2 on homeopathy.[10,11]

The design and study populations varied across the seven acupuncture studies. (See Table 1.) Three small, uncontrolled studies showed significant improvement in self-reported hot flash frequency[3] and mean vasomotor and physical/somatic symptoms.[2,7] In one study, the average number of hot flashes decreased from 7.9 per day prior to treatment to 2.5 at 10 weeks after treatment initiation.[3] In another study,[2] the mean vasomotor symptom score dropped from 4.2 to 1.9 at the end of treatment, in the absence of any change in sex hormones measured, and the mean score for the physical domain (i.e., digestion, stamina, energy, muscle and joint pain) improved significantly during this period. In this same study,[2] there was no improvement in the mean score for the psychosocial domain (i.e., depression, anxiety, memory, patience with others, life satisfaction) after 5 weeks of acupuncture while another[7] reported significant improvement in anxiety and depression after 12 weeks of treatment. However, the findings from these uncontrolled studies should be interpreted cautiously since they are quite small and some of the outcomes (e.g., hot flash frequency) are known to be subject to placebo effects.

The findings from controlled studies of acupuncture are less consistent and report improvements in symptoms, such as hot flash number and severity and sleep disturbances, in control groups.[1,4,6] Overall, in this group of studies, acupuncture did not consistently improve hot flashes, sleep disturbances, or mood when compared to nonspecific acupuncture, estrogen therapy, or superficial needling.[1,4–6] For example, when 56 women were randomized to either estrogen therapy or acupuncture plus auriculotherapy (acupuncture of the ear), greater improvement in menopausal symptom severity (measured using the Kupperman Index) was seen in the acupuncture group ($p < .01$).[4] The acupuncture group's Kupperman index scores improved from a mean of 30.33 before treatment to 2.43 after treatment, whereas the estrogen group improved from a mean of 29.54 before treatment to 13.35 after treatment.[4] Similarly, when 17 women were randomized to either acupuncture at menopause-specific meridians (active acupuncture) or acupuncture at general health meridians (placebo acupuncture), the active acupuncture group reported a statistically significant decrease in self-reported hot flash severity and improvement in sleep disturbance over the course of the study.[1] However, the placebo acupuncture group reported no significant improvement in these parameters. Two other controlled studies found no differences

in climacteric symptoms, including hot flash frequency and severity and sleep disturbances, between women receiving electro-acupuncture and those receiving superficial needling.[5,6]

Table 1: Design of Acupuncture Studies

Ref.	N	Sample	Control	Treatment	Outcome Measures
1	17	Menopausal women	Acupuncture at meridians for general health using same schedule	Acupuncture at meridians specific for menopausal symptoms; once a week for 3 weeks, then once every other week for 6 more treatments (9 total sessions); 20–30 minutes per session	Daily symptom diary (hot flash frequency and severity, mood, sleep disturbances)
2	9	Menopausal women	None	Acupuncture; twice per week for 5 weeks (10 total sessions); 40 minutes per session	MenoQol (vasomotor, psychological, physical, and sexual symptom bother), FSH, LH, estradiol, progesterone, prolactin
3	7	Medically castrated men with prostate cancer	None	Electro acupuncture at 2 Hz; twice a week for 2 weeks; once a week for 10 weeks (14 total sessions); 30 minutes per session	Daily hot flash frequency diaries
4	56	Menopausal women	Estriol 1–4 mg os for 3 weeks, then off 1 week, then repeat; Vitamin B6 20 mg if needed; Diazepam if needed (dose not specified)	Acupuncture plus auriculotherapy; daily or every other day with needle manipulation every 5 minutes (total number of sessions not specified); 20 minutes per session	Kupperman 11 symptom index (all pts), serum FSH, LH, estrogen (8 pts)
5	30	Menopausal women	Superficial needling same schedule	Electro acupuncture at 2 Hz; twice a week for 2 weeks; once a week for 10 weeks (14 total sessions); 30 minutes per session	MOOD scale, Symptom Check List–90 for general psychological well-being, Greene Climacteric Index
6	24	Menopausal women	Superficial needling same schedule	Electro acupuncture at 2 Hz for 8 weeks, twice a week for 2 weeks; once a week for 6 weeks (10 total sessions); 30 minutes per session	Psych well-being index, sleep dysfunction test, Modified Kupperman Index, urinary neuropeptides, calcitonin gene-related peptide, substance P, neurokinin A, neuropeptides Y-like immunoreactivity
7	15	Women with breast cancer on tamoxifen	None	Acupuncture; 12 weekly sessions; No other specific information provided	Greene Menopause Index

While changes in mood were comparable across groups in the Cohen study,[1] another study[5] found that individuals receiving electro-acupuncture had a statistically significant improvement in the MOOD Scale when compared to individuals receiving superficial needling, but no change was seen in general psychological well-being as measured by the Symptom Check

List–90. However, it should be noted that in the former study, subjects received acupuncture while in the latter they received electro-acupuncture for a longer period of time.

Our search produced one placebo-controlled study on the use of magnets to treat hot flashes.[8] This study used a cross over design and was conducted in a sample of 11 female breast cancer survivors. During the first treatment cycle, women were randomized to either magnets or placebo devices placed over six acupressure points. In the second cycle of treatment, women were assigned to the opposite condition that they were randomized to in the first cycle. Hot flashes were measured objectively (frequency as determined by sternal skin conductance monitors) and subjectively (self-reported measures of frequency, severity, bother interference with activities, and quality of life). Magnets were not more effective than placebo in decreasing hot flash severity, interference with activities, or overall quality of life. Contrary to expectations, the placebo was significantly more effective than magnets in decreasing objective hot flash frequency and subjective bothersomeness.[8]

We found one randomized controlled trial of foot reflexology for menopausal symptoms.[9] This study compared nine sessions of foot reflexology (n=35) to nine sessions of foot massage with no reflexology (n=31). They found no differences between treatment and placebo groups with respect to hot flash frequency or severity, night sweats, sleep disturbances, anxiety, depression, and menopausal quality of life scores. Both groups reported improvement in anxiety, depression, hot flashes, and night sweats over time.

Two uncontrolled, open-label studies suggested that individualized homeopathic remedies for hot flashes may be effective.[10,11] Clover and Ratsey[10] provided individualized homeopathic treatment, including herbs, to 31 women, 20 of whom were breast cancer survivors. Treatment was associated with a 48–75 percent decrease in self-reported measures of hot flash frequency and 53–73 percent decrease in self-reported hot flash severity. Similarly, Thompson and Reilly[11] provided individualized consultation and treatment to 45 breast cancer survivors. This study reported improvement in self-reported measures of hot flash frequency, mood disturbance, sleeplessness, and effect of daily living scores. However, it should be noted that there was no control group in either study. In addition, neither study specified the type or dose of the homeopathic treatments that were provided to participants.

Limitations of many studies of menopause, including the ones referenced above, include small numbers of subjects, short duration of treatment, and the presence of significant placebo effects. Of particular concern is the inaccuracy of self-reported hot flash frequency, which has been well-documented.[13–16] In 10 of the 11 studies referenced here, hot flash frequency was measured subjectively, using self-reported diaries and questionnaires without objective sternal skin conductance monitoring.[1–7,9–11] Although self-reports provide valuable information about whether subjects *perceived* the intervention to be effective, these measures do not provide any evidence of physiological effect of treatment. We know from ambulatory studies comparing self-reported measures of hot flashes to those captured by sternal skin conductance monitors that women report fewer hot flashes over time, making it appear as though hot flashes are decreasing when in fact such reporting changes may be due to intervention expectancy effects, memory recall biases, and/or personal characteristics, such as mood.[12,13] In prior research, both prospective daily diaries and recalled average summaries of hot flash frequency have been shown to

significantly underestimate objective hot flash frequency as measured using ambulatory sternal skin conductance monitoring.[14,15]

In summary, this review suggests there is some evidence from uncontrolled studies that acupuncture and homeopathy may have some effect on hot flashes and other menopausal symptoms. However, the small sample sizes and weak designs limit our ability to draw firm conclusions. Overall, the empirical base for the range of treatments addressed here is limited, due to small sample sizes, short treatment times, compromised designs, and weak measures of critical outcomes, such as hot flash frequency. Understanding whether, for whom, and how these interventions work, or not work, requires improving methods and building the evidence base needed to make decisions concerning the continued use of these complementary and alternative medicine modalities for management of menopausal symptoms.

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Centrally Active, Nonhormonal Hot Flash Therapies

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Given the problems associated with hormonal therapy, and the prominent problem of hot flashes in menopausal women, there is a need for nonhormonal agents to alleviate hot flashes. Several compounds, which appear to act on the central nervous system, have been investigated. Potential mechanisms for their effects on hot flashes have been described.[1]

Bellergal, a combination preparation sedative, which consists of low-dose phenobarbitol, ergotamine tartrate, and levorotatory alkaloids of belladonna, is an old agent which was popular approximately two decades ago. Nonetheless, there is limited suggestion of efficacy for this agent.[2,3]

Clonidine, an older antihypertensive drug, is another centrally active agent which has been studied. Randomized trials have demonstrated that it clearly works for reducing hot flashes,[4–6] but the magnitude of efficacy is somewhat limited. Toxicity from this agent limits its utility in the clinic.

Methyldopa is another centrally active agent which has been studied but to a more limited degree.[7] It appears to have minimal efficacy and too much toxicity to make it clinically useful.

In the nineties, anecdotal information from a number of sources suggested that newer antidepressants could alleviate hot flashes in women utilizing these drugs for other reasons. This led to the conduct of pilot trials evaluating venlafaxine (a serotonin and norepinephrine re-uptake inhibitor (SNRI)) and paroxetine (a selective serotonin re-uptake inhibitor (SSRI)). Published results from the pilot studies of venlafaxine and paroxetine were promising,[8,9] suggesting the drugs were efficacious and well-tolerated.

Subsequently, a placebo-controlled, double-blind dose finding randomized trial was conducted to evaluate venlafaxine in women with hot flashes.[10] This trial evaluated doses of 37.5 versus 75 versus 150 mg per day. Hot flashes were reduced by 27 percent after 4 weeks of therapy in the placebo group compared to 40 percent in the 37.5 mg/day venlafaxine group and 60 percent in the higher two venlafaxine dose groups ($p<=0.008$). Although this drug was well-tolerated in most patients, there was evidence of some toxicity, with venlafaxine-receiving patients having nausea/vomiting, a decrease in their appetite, mild mouth dryness, and constipation (the latter being only at the highest dose). Nausea and vomiting appeared to be the most significant toxicity leading to drug discontinuation, affecting approximately 10 percent of patients. However, in patients who reported nausea but continued to take the venlafaxine, the nausea largely abated over a week or two. A subsequent manuscript, reporting on patients from the prior trial who continued to take venlafaxine for an extended period of time, provided information to suggest that this drug did continue to control hot flashes for at least several months.[11]

A double-blind, placebo-controlled, dose-finding clinical trial of controlled-release paroxetine was also conducted.[12] This evaluated 2 doses of paroxetine, 12.5 and 25 mg per day in menopausal women. Statistically, the paroxetine significantly reduced hot flashes, compared to the placebo group, with similar efficacy seen with both paroxetine doses. Hot flashes were

reduced, at 6 weeks, by 38 percent in the placebo group and by 62–65 percent in the paroxetine arms. Paroxetine was well-tolerated in this trial with the placebo group reporting more toxicities than the paroxetine groups. There was, however, a trend for the highest dose paroxetine treatment to have more nausea (p=0.06), insomnia (p=0.141), lethargy (p=0.12), and constipation (p=0.12). A second double-blind, placebo-controlled trial with a cross-over design of immediate release paroxetine, 10 or 20 mg per day, enrolled primarily breast cancer survivors. In this study, published in abstract form, 48 percent and 58 percent reductions in hot flashes were reported in the low and high doses, respectively; statistically, both were significantly better than what was seen with the placebo.[13]

A placebo-controlled clinical trial of another newer antidepressant, fluoxetine, has also been reported. This trial was placebo-controlled, double-blinded, and had a crossover component. Patients were treated with 4 weeks of fluoxetine (20 mg per day) versus a placebo, followed by 4 weeks of the alternative therapy.[14] In this trial, there was a statistically significant reduction of hot flashes seen with fluoxetine, compared to placebo. The reduction of hot flashes, however, was less impressive than had been reported in the other trials evaluating venlafaxine and paroxetine. Fluoxetine was well-tolerated in this clinical trial, with mouth dryness being the only toxicity with a trend for being more prominent in the fluoxetine arm (23 percent versus 45 percent, p=0.07).

Finally, preliminary results reported only in abstract form of a small, and probably underpowered, randomized clinical trial were unable to confirm the prestudy hypothesis, that sertraline (an SSRI) would be more effective than placebo in reducing hot flashes.[15]

Pilot trials of two other newer antidepressants, mirtazapine and citalopram, have also suggested that they are efficacious and well-tolerated.[16,17]

Gabapentin was anecdotally noted to decrease hot flashes, as reported in a case series published in 2000.[18] Subsequently, two prospective pilot trials looked at this agent for treating hot flashes, both reporting promising appearing results.[19,20] The potential mechanism of action of gabapentin for alleviating hot flashes has not been clarified, but it has been proposed that it might be related to gabapentin's ability to modulate calcium currents.[18] Two placebo controlled, double-blind, randomized clinical trials have demonstrated that gabapentin does reduce hot flashes in patients.[21,22] Hot flash score reduction in one of these studies was 46 percent (versus a 19 percent reduction with a placebo) and in the other study was 54 percent (versus a 31 percent reduction with a placebo). Gabapentin appears to be relatively well-tolerated by most patients. Side effects include light-headedness and dizziness; also, mild peripheral edema associated with decreased serum albumin levels was reported in some patients.[21]

In conclusion, centrally active nonhormonal agents clearly do decrease hot flashes in women. The most efficacious and clinically appropriate agents for use are newer antidepressants and gabapentin. Continued evaluation of the efficacy and toxicity of these agents is ongoing.

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Hot Flashes: Behavioral Treatments, Mechanisms, and Relationship With Sleep

Robert R. Freedman, Ph.D.

Hot flashes are the most common symptom of the climacteric and occur in about 75 percent of perimenopausal and postmenopausal women in the United States.[1] The frequency of hot flashes varies from 5 per year to 50 per day. They generally persist for 1–5 years but can last as long as 44 years.[2] There is no accepted metric for measuring the severity of hot flashes.

Hot flashes are an exaggerated heat dissipation response and comprise widespread cutaneous vasodilation and profuse upper body sweating.[3] They are described as sensations of heat, sweating, flushing, chills, clamminess, and anxiety.[2]

Hot flashes appear to be triggered by small elevations in core body temperature (T_c)[3] acting within a reduced thermoneutral zone[4] in symptomatic postmenopausal women. This reduction is probably due to estrogen withdrawal[5] and elevated central sympathetic activation,[3] among other factors. There is a circadian rhythm of hot flashes,[6] with their occurrence being more frequent when T_c is highest. They can be provoked by procedures that increase T_c, such as peripheral heating, and inhibited by cooling.[4] Estrogen ameliorates hot flashes by raising the T_c threshold for sweating, so that greater elevations in T_c are needed to provoke them.[5]

Since elevated sympathetic activation has been implicated in the genesis of hot flashes, relaxation-based procedures have been used to treat them. In the first investigation,[7] postmenopausal women with frequent hot flashes were randomly assigned to receive six weekly sessions of progressive muscle relaxation and slow, deep breathing (paced respiration) or alpha brain wave biofeedback determined by EEG (alpha EEG biofeedback). The latter was used as a control procedure because it is plausible as a treatment but has no demonstrable physiological effects. The relaxation procedure significantly reduced objective symptoms recorded in the laboratory and diary-recorded hot flash frequency by about 50 percent compared to the control procedure. A second study was performed in which one group of subjects received slow, deep breathing alone, another group received muscle relaxation exercises alone, and a third group received alpha EEG biofeedback.[8] Treatment outcome was assessed by ambulatory monitoring of sternal skin conductance responses. Only the paced respiration group showed a significant decline in hot flash frequency (about 50 percent). There were no significant changes shown by the other two groups. We then sought to determine if reduced sympathetic activation was the mechanism by which paced respiration ameliorates hot flashes.[9] We, therefore, measured plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), epinephrine, norepinephrine, and platelet (2-receptors during paced respiration or alpha EEG biofeedback in 24 symptomatic women. Treatment outcome was again assessed by ambulatory monitoring of sternal skin conductance. The paced respiration group showed a significant decline in hot flash frequency (again about 50 percent) compared to no change in the control group. However, there were no significant changes in any biochemical measure for either group. Thus, the mechanism through which paced respiration reduces hot flash frequency remains to be determined. The last controlled study[10] randomly assigned symptomatic postmenopausal women to receive relaxation response training (paced respiration plus mental

focusing), a reading control group, or no treatment. The relaxation response group showed a significant decline in hot flash intensity but not frequency. There were no significant changes in the other groups.

Thus, we conclude that paced respiration training produces a significant decline in hot flash frequency and, perhaps, intensity. There are no known harmful effects.

Physical exercise has also been used as a potential treatment for hot flashes. There have been three randomized clinical trials and three other studies. The largest randomized clinical trial (n=173)[11] compared a moderate-intensity exercise intervention with a stretching control group over 1 year. Exercise significantly increased the severity of hot flashes with no change in their occurrence. A Japanese study[12] compared 20 women in a 12-week education and exercise program with 15 no-treatment controls. There were no significant effects on hot flashes. A Swedish study[13] compared 15 women in a 3x/week exercise program with 15 women receiving oral estradiol. There was no change in hot flash frequency in the exercise group but a 90 percent decline in the estradiol group.

A large (n=1,323), population-based, retrospective study in Linkoping, Sweden,[14] found no significant effect of moderate exercise (1–2 hours per week) on hot flash occurrence. A case-control study (n=171)[15] at an HMO in California also found no effects of exercise on hot flashes. A retrospective, population-based study in Lund, Sweden, (n=6,917)[16] found that vigorous exercise (less than 3 hours per week) was associated with significant reductions in hot flash frequency and intensity in a small number of women (4 percent), but this was confounded by other factors.

Taken together, the above studies do not demonstrate significant, positive effects of physical exercise on menopausal hot flashes.

Many epidemiologic studies[17–21] have found increased reports of sleep disturbance during the menopausal transition. It is generally believed that hot flashes produce arousals and awakenings from sleep, leading to fatigue and, possibly, impaired performance. However, this notion is challenged by two recent laboratory investigations.[22,23] In the most recent study, symptomatic and asymptomatic postmenopausal women and premenopausal women of similar ages were recorded under controlled laboratory conditions. They were screened to eliminate those with any drug use; sleep, physical, or mental disorder; or a body mass index of greater than 30. There were no group differences whatsoever on any sleep stage measure, sleep or fatigue questionnaire, or performance test. When hot flashes occurred (mean per night ± SD = 5.2 ± 2.9), they tended to follow, rather than precede, arousals and awakenings. These data provide no evidence that hot flashes produce sleep disturbance in symptomatic postmenopausal women.

These findings are strongly supported by those of a large, recent epidemiologic investigation.[23] The Wisconsin Sleep Cohort Study measured sleep quality by complete laboratory polysomnography and by self-reports in a probability sample of 589 premenopausal, perimenopausal, and postmenopausal women. Sleep quality was not worse in perimenopausal or postmenopausal women nor in symptomatic versus asymptomatic women on any measure.

Taken together, these two studies suggest that sleep complaints in midlife women should not routinely be attributed to hot flashes or to menopause. Rather, the underlying disorder (e.g., sleep apnea) should be ascertained and treatment should be given based on these findings.

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Nonhormonal Treatment of Menopause-Related Symptoms: Evidence From Randomized Controlled Trials

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Use of nonhormonal therapies to manage symptoms related to menopause has gained interest among women and clinicians in order to avoid adverse effects associated with hormone therapy. A systematic review was undertaken to describe the evidence about benefits and adverse effects of therapies for symptoms related to menopause, factors that influence therapies, and future research needs—three of the five Key Questions specified by the Planning Committee for the National Institutes of Health State-of-the-Science Conference on Management of Menopause-Related Symptoms. This report summarizes alternative and complementary strategies, including antidepressants (selective seratonin reuptake inhibitors, moclobemide, veralipride); other drugs (clonidine, methyldopa, gabapentin, Bellergal); phytoestrogens (dietary and extract forms of soy isoflavones, other forms of phytoestrogen, combinations); complementary and alternative medicine (acupuncture, Chinese herbs, red clover, black cohosh, combinations, other types of supplements, manual therapies, energy therapies); and behavioral interventions (exercise and other types of interventions).

Relevant studies were identified from multiple searches of MEDLINE, PsycINFO, DARE, the Cochrane database, MANTIS, and AMED (1953 to November 2004); and from recent systematic reviews, reference lists, editorials, Web sites, and experts. The review included randomized controlled trials of midlife women transitioning through the stages of menopause and experiencing symptoms related to menopause. Specific inclusion and exclusion criteria were developed to determine study eligibility. All eligible studies were reviewed and relevant data were extracted, entered into evidence tables, and summarized by descriptive methods. Two reviewers independently rated the quality of studies using predefined criteria. A total of 96 trials were included.

Key Question 3. What is the evidence for the benefits and harms of commonly used interventions for relief of menopause-related symptoms?

- Several agents demonstrate benefits in managing vasomotor symptoms in some, but not all trials, or in only a few available trials, including paroxetine,[1] veralipride,[2] gabapentin,[3] soy isoflavones,[4–7] and other phytoestrogens.[8–10]

- Trials of soy isoflavones and other complementary and alternative medicine therapies report benefits in improving nonvasomotor symptoms; although, results vary widely, methods are lacking, and studies are typically small and not generalizable.

- Placebo effects in trials are large.

- Most trials provide insufficient data to evaluate adverse effects.

Key Question 4. What are the important considerations in managing menopause-related symptoms in women with clinical characteristics or circumstances that may complicate decisionmaking?

- Evidence is not available to determine if the effectiveness of therapy or adverse effects differ for women with bilateral oophorectomy, premature ovarian failure, concurrent use of SERMs or other potentially interacting agents, lifestyle and behavioral factors, recent discontinuation of menopausal hormone therapy, or very low or very high body mass index.

- For women with breast cancer, results of 15 randomized controlled trials indicate that clonidine,[11,12] venlafaxine,[13] and megestrol acetate[14] are associated with significantly improved measures of hot flashes and vitamin E, black cohosh, isoflavones, magnets, and fluoxetine are not. Results for nonvasomotor outcomes are mixed.

Key Question 5. What are the future research directions for treatment of menopause-related symptoms and conditions?

- Determination of optimally effective doses, combination regimens, durations of use, and timing of therapy.

- Evaluation of approaches to identify optimal candidates for specific therapies.

- Better reporting of adverse effects in trials and use of standardized categories of adverse effects so data can be combined across trials.

- Improved analysis of results, including analysis by hysterectomy and oophorectomy status, stage of menopause, age, concurrent conditions and medications, and other factors.

- Enrollment of women with specific characteristics who have not previously been evaluated.

- Use of standard definitions, measures, and outcomes so results can be compared across trials.

- More comprehensive trials to determine the role of regular exercise, sleep management, optimal nutrition, healthy relationships, social support, and relaxation; effects of mind-body techniques, such as biofeedback and breathing; effects of a whole system approach with Chinese medicine.

- Additional, well-designed and controlled trials of phytoestrogens, botanicals, and bio-identical hormones, especially estriol, estradiol, and progesterone, and antidepressants.

Although evidence is not definitive, several agents demonstrate benefits in managing vasomotor symptoms in a limited number of trials enrolling women with and without breast

cancer. Available trials are limited in many ways, including use of highly selected small samples of women; short durations; inadequate reporting of loss to followup, methods of analysis, and adverse events; use of dissimilar measures and outcomes that are often not standardized or validated; unclear inclusion and exclusion criteria; and industry sponsorship. Future research addressing these deficiencies would provide important information about benefits and adverse effects of nonhormonal therapies.

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Special Considerations: Bilateral Oophorectomy and Premature Menopause

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Premature menopause occurs secondary to bilateral oophorectomies or premature ovarian failure. The usual and common indications for a bilateral oophorectomy include ovarian, endometrial or fallopian tube cancers; stage IV endometriosis; bilateral tubo-ovarian abscess (ruptured or chronic); familial breast-ovarian cancer syndrome; and severe premenstrual syndrome. Premature ovarian failure is the development of amenorrhea with concomitant sex hormone deficiency and elevated serum gonadotropin levels before the age of 40. It can be spontaneous or induced by chemotherapy, radiation therapy, and oophorectomy.

Approximately 600,000 hysterectomies are performed each year in the United States and between 50 to 60 percent of those procedures involve oophorectomy.[1,2] Because of the simplicity of the procedure, routine prophylactic oophorectomies to remove both ovaries is oftentimes performed concomitantly with hysterectomies in women over the age of 40. The theoretical benefits of prophylactic oophorectomies include the prevention of ovarian cancer and fewer reoperations for ovarian pathology which occur in 4–5 percent of women who have had a previous hysterectomy.[3–5] Despite ovarian ultrasound, the CA 125 antigen test, and other tumor marker and genetic tests in development, nothing has proven to be sensitive or specific enough to detect the early presence of cancer. This is important because 70 percent of the patients with ovarian cancer present after it has spread beyond the ovary.

Ovarian cancer is the fourth most common cause of cancer death and the most common cause of gynecologic cancer death in women with an estimated 23,300 new diagnoses and 13,900 deaths related to ovarian cancer each year.[6] U.S. women have a lifetime risk for ovarian cancer of 1 in 70 and approximately 4–14 percent of these women had preceding hysterectomies in which the ovaries were preserved.[7] Oophorectomies do not eliminate the risk of ovarian cancer (women can develop peritoneal carcinoma, which acts like ovarian cancer), however, reported cases are rare.[8] It has been suggested that, in the United States, approximately 1,000 cases of ovarian cancer can be prevented if a prophylactic oophorectomy is practiced in all women older than 40 years of age who undergo hysterectomies.[9] This assumes an annual incidence of 24,000 new ovarian cancer cases and does not take into account the incidence of peritoneal carcinoma. The dilemma for the patient and the clinician is whether the estimated number of cancer cases prevented (1,000) is worth the number of oophorectomies performed (approximately 300,000).

Prophylactic oophorectomies are a consideration in women with a hereditary disposition for ovarian cancer because of the limitation of current screening modalities for early detection of this high-mortality cancer. These women may have up to a 50 percent lifetime risk of ovarian cancer and a prophylactic oophorectomy is indicated after childbearing or the age of 35–40, at the latest. Most women with a positive family history of ovarian cancer do not have one of the recognized hereditary cancer syndromes. Women with one or two affected relatives do have an increased lifetime risk of ovarian cancer from a baseline of 1.6 to 5–7 percent. This risk is not high enough to warrant prophylactic oophorectomy recommendation for a large number of

women. The familial cancer syndromes include breast-ovarian cancer syndrome; the Lynch II syndrome, involving cancers of the colon, breast, endometrium, and ovary with hereditary nonpolyposis colorectal carcinoma syndrome; and site-specific ovarian cancer syndrome.

The primary disadvantage of a oophorectomy is the loss of natural ovarian hormone secretion resulting in a need for hormone therapy to relieve the clinical manifestations of surgical castration (e.g., hot flashes and vaginal dryness) and to prevent long-term risks of estrogen deficiency (e.g., osteoporosis and fracture). Other possible disadvantages include decreases in self image and libido (attributed to loss of ovarian testosterone production). In premenopausal women, the mean reduction in serum testosterone and estradiol concentration is 50 and 80 percent, respectively.[10] Premature menopause from all causes is associated with earlier onset of osteoporosis and coronary heart disease, but there are no clear data as to the effects of the long-term administration of hormone therapy.[11] Recent findings suggest women with bilateral oophorectomies have elevated subclinical atherosclerosis compared with women of similar age who had natural menopause.[12]

The ovary is a complex metabolic organ. The follicles produce both androgens and estrogens, and stromal tissue synthesizes androgens only. During menopause, when follicles decrease, both androgen and estrogen levels decrease as well. However, the ovary remains a source of endogenous androgens that are converted to estrogen. The role of those endogenous androgens and the consequences of their premature removal through oophorectomy may be significant, but research has not yet shed much light on this issue.

Once the ovaries are removed or fail to produce endogenous sex steroids, exogenous estrogens are almost always needed for symptom relief. The risks and benefits of these agents in women with premature menopause have not been studied. Hormone therapy is used in these women as true replacement therapy, just as thyroid hormone is replacement for thyroid deficiency. The only guidance available on the balance of benefits and risks are from the two randomized trials of hormone therapy in the Women's Health Initiative. The estrogen plus progestin trial showed the risks (e.g., increased breast cancer, heart attacks, strokes, and blood clots in the lungs and legs) outweigh the benefits (e.g., fewer hip fractures and colon cancers).[13] Use of conjugated equine estrogens alone increases the risk of stroke, decreases the risk of hip fracture, and does not affect coronary heart disease incidence with no overall benefit in postmenopausal women with prior hysterectomies.[14]

However, data from the Women's Health Initiative should not be extrapolated to women with premature menopause in whom hormone therapy is generally initiated at a younger age. Women who have had a prophylactic oophorectomy have more severe symptomatology with surgical menopause and will be faced with the decision to discontinue estrogen therapy sometime in their life. As a result, some of these women will experience intense symptoms, such as hot flushes, night sweats, and insomnia. They must be given informed consent about the need for long-term use of estrogen therapy and the greater difficulty in discontinuing hormone therapy.

Conclusions

Hysterectomies are extremely common surgical procedures among women, accounting for 600,000 surgeries in the United States each year. Approximately half of all hysterectomies

involve oophorectomies. While there are reasonable arguments in favor of prophylactic oophorectomies concurrent with hysterectomies, there are a number of equally reasonable counterarguments in favor of retention of otherwise healthy ovaries. A careful assessment of symptoms before and after a hysterectomy is crucial to making the choice about whether to remove or retain the ovaries and will help in the understanding of additional problems that may occur following hysterectomies with or without an oophorectomy.

The consequences of long-term hormone exposure for women with premature menopause are unknown. It remains to be determined at what age hormone therapy should be stopped in women with premature menopause. However, results from the Women's Health Initiative suggest that continuing hormone therapy beyond the natural age of menopause may not be beneficial and, in some women, might cause harm.

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Breast Cancer, Menopause, and Long-Term Survivorship: Critical Issues for the Twenty-First Century

Patricia A. Ganz, M.D.

Breast cancer accounts for almost one-third of all incident cases of cancer in women, with over 215,000 cases expected in 2004.[1] In Western industrialized countries, there are two peaks in incidence—one in the fifth decade and the second in the eighth decade. These two peaks reflect lifetime exposure to endogenous sex steroid hormones, with the first peak influenced primarily by ovarian hormones and reproductive history (e.g., menarche, age at first pregnancy or nulliparity, lactation) and the second influenced extra-ovarian sources of estrogens (e.g., androgens that are converted to estrogens via aromatization) as well as postmenopausal hormone therapy (HT). Observations from the epidemiological literature strongly support the influence of endogenous hormonal exposure on breast density and bone density, suggesting that these are surrogate markers for tissue responsiveness in individual women[2] and reflect the range of benefits (e.g., good bone health) and risks (e.g., increased breast tissue proliferative activity) of this exposure. The vast majority of women who develop breast cancer (approximately 75 percent) have no familial or hereditary/genetic risk for breast cancer, but their tissue response to endogenous hormones is likely controlled by a variety of genes involved in estrogen metabolism or tissue response. Even the small number of women at high risk of developing breast cancer secondary to inheritance of a deleterious mutation in BRCA 1 or 2 may have their risk influenced by the same environmental exposures as noncarriers.[3]

Given the critical role of reproductive hormones in the initiation and promotion of breast cancer, it is not surprising that targeted endocrine therapies are the cornerstone of breast cancer treatment (in the preventive, adjuvant, or metastatic disease setting). Breast cancer tissue is tested at diagnosis for the presence or absence of estrogen and progesterone receptors, and women whose tumors contain these receptors (about 75 percent of cases) receive adjuvant endocrine therapy with tamoxifen or an aromatase inhibitor for 5 years or longer.[4,5] Evidence from randomized clinical trials provide excellent clinical guidance on the selection of endocrine therapy, with the choice of agent usually determined by the hormonal milieu of the woman at the time of treatment (premenopausal, perimenopausal, or postmenopausal). For example, aromatase inhibitors are only indicated in postmenopausal women, whereas tamoxifen may be used in all women with breast cancer. There is also renewed interested in ovariectomy and ovarian suppression therapy in the adjuvant treatment of premenopausal women with breast cancer.[6]

Chemotherapy is widely used as adjuvant therapy for all women with tumors that are larger than a centimeter in size across all age groups,[7] irrespective of the tumor hormone receptor status. In premenopausal or perimenopausal women, chemotherapy accelerates the menopausal transition and may lead to premature menopause.[8,9] Thus, menopausal symptoms often co-occur with initial adjuvant treatment of breast cancer either through the withdrawal of pre-diagnosis HT, the development of amenorrhea after initiation of chemotherapy, or as a side effect of breast cancer directed endocrine therapy.[10]

The widespread use of adjuvant therapy for breast cancer has led to dramatic improvements in survival. However, the price of this successful therapy is a range of short- and long-term health consequences, including premature menopause, infertility, vasomotor symptoms, vaginal dryness, dyspareunia, weight gain and osteoporosis.[9–14] With the increasing numbers of breast cancer survivors,[15] it is important to understand the late health effects of adjuvant therapy, some of which will be menopause-associated. In addition, the substantial proscription against the use of HT in these survivors has forced the use of nonhormonal alternative therapies for management of symptoms and health consequences. Although it is estimated that there are over 2 million breast cancer survivors in the United States today, we do not have population estimates for the number of these survivors with menopause-associated problems.

During the past decade, there have been many studies designed to test non-HT management strategies for management of menopausal symptoms in breast cancer survivors; these will be reviewed by other speakers.[16–21] Prior to the results of the Women's Health Initiative hormone trials, HT was widely advocated for healthy postmenopausal women, and some observational studies suggested that HT was safe in breast cancer survivors.[22] Recently, a randomized, controlled trial of HT after breast cancer (the HABITS trial) was closed early due to an increase in adverse events in the women treated with HT.[23] The Women's Health Initiative and HABITS results make it clear that there is limited benefit from HT and there may be serious risks for breast cancer recurrence with such therapy. Although safety data in breast cancer survivors are not available, low-dose vaginal estrogen preparations are being considered for management of vaginal dryness. Prevention and management of osteoporosis is another area of major concern for breast cancer survivors.

Although not specifically the focus of this presentation, women at risk for breast cancer due to deleterious mutations in a hereditary susceptibility gene (e.g., BRCA1/2) form another relevant special target population worthy of discussion. These women often undergo prophylactic ovariectomy for prevention of ovarian cancer and breast cancer risk reduction. In addition, some may choose chemopreventive therapy with tamoxifen.[24] These interventions will put them at risk for premature menopause and/or menopausal symptoms, just as with breast cancer survivors.

In conclusion, we can expect growing numbers of breast cancer survivors in the decades to come. Menopause-associated symptoms in this target population are likely to be complicated by an even longer duration of cancer-directed endocrine therapy than currently used. In addition, more women are likely to be taking endocrine-directed treatments for prevention of breast cancer in the future. Important research questions include: (1) how can we reconcile the benefits and harms of breast cancer therapies with overall quality of life and health of women across a broad age span; and (2) can we find better methods of managing menopausal symptoms in breast cancer survivors and women at high risk for the disease who are receiving anti-cancer therapy?

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Ethnic/Racial Diversity

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Midlife and menopause transition are frequently discussed within the context of an emerging biopsychosocial perspective.[1] Cultural factors and attitudes towards menopause and aging may influence a woman's experience of menopause and an understanding of these beliefs can help health professionals provide culturally appropriate care.[2–4]

Vasomotor, depressive-type, and somatic symptoms and a perceived decline in cognitive functioning affect more than 50 percent of women during the menopausal transition.[5,6] Previously, many women took hormone therapy (HT) for these symptoms; however, results from the Women's Health Initiative citing significant risks associated with HT use[7,8] have led to treatment discontinuation or tapering to lower doses.[9] Investigators are now seeking to determine whether lifestyle factors, such as overweight, smoking, alcohol consumption, and low dietary fat intake,[10] can be modified to prevent menopausal symptoms and whether these factors differ based on race/ethnicity.[11]

Frequencies of vasomotor symptoms differ by race and ethnicity.[12] Results from the Study of Women's Health Across the Nation (SWAN) suggest that Japanese and Chinese women report fewer vasomotor symptoms due to low fat intake and a decrease in estrogen variability. Among the women in SWAN, an increase in vasomotor symptoms was attributed to higher body mass index, history of premenstrual symptoms, and passive smoke exposure, whereas current smoking or intake of phytoestrogen, dietary fiber, total calories, or antioxidants were not found to have an effect.[11]

Limited data suggest higher rates of clinical depression and depressive symptoms may occur among racial/ethnic groups that can be correlated with low socioeconomic status, financial strain, physical inactivity, low social support, stress, and poor physical health.[13] An analysis of depressive symptoms among women in SWAN found unadjusted prevalence varied by race/ethnicity, with African-American and Hispanic women having the highest odds and Chinese and Japanese women having the lowest odds for a Center for Epidemiologic Studies Depression (CES–D) Scale score of 16 or higher when compared with Caucasian women. After adjusting for socioeconomic status, however, the odds ratios remained lower only for Chinese women.[13]

Similarly, a study of persistent mood symptoms among women in SWAN found that compared with white women, African-American, Chinese, and Japanese women had lower odds for individual mood symptoms, such as "feeling blue," "feeling irritable," "feeling nervous," and "experiencing mood changes."[14] Other SWAN studies have found significant ethnic differences in health-related quality of life, some of which may be explained by differences in health, lifestyle, and social circumstances,[15] such as education, marital status, perceived stress, and social support.[16] A cognitive decline, however, was not observed among the women in SWAN.[17]

In a study of African-American and Caucasian women aged 35–47 years, an increased likelihood of depressive symptoms during transition to menopause was significantly associated with increasing estradiol levels. This likelihood decreased in those with a rapidly increasing

follicle stimulating hormone (FSH) profile and age compared with premenopausal women. After adjusting for employment, menopausal status, history of depression, PMS, poor sleep, hot flashes, and FSH level, African-American women were nearly twice as likely as white women to report depressive symptoms, both on CES–D and among a subgroup with a diagnosis of major depressive disorder.[18]

Ethnic differences in the pituitary-ovarian relationship, such as a difference in feedback regulation of the pituitary or in pituitary sensitivity to gonadal-negative feedback, were detected in several SWAN studies. Serum sex steroid, FSH, and sex hormone binding globulin levels were found to vary by ethnicity, but were highly confounded by ethnic disparities in body size.[19] Ethnic differences in estradiol over time were found to differ from ethnic differences in FSH, and the effect of body mass index on estradiol and FSH concentrations varied based on menopausal status.[20] Dehydroepiandrosterone sulfate (DHEAS) concentrations were highest among Chinese and Japanese women and lowest among African-American and Hispanic women, with changes in circulating testosterone and estradiol correlated to changes in DHEAS.[21] Women who weighed less had shorter cycles and high total-cycle luteinizing hormone, FSH, and progesterone. Chinese- and Japanese-American women had overall lower adjusted total-cycle estradiol excretion.[22] Asian women have also been found to have menstrual cycles lasting 35 days or longer and follicular phases longer than 23 days when compared with Caucasian women.[23]

Whether race/ethnicity affects how a woman views treatment of menopausal symptoms, including complementary and alternative medicines (CAM), has not been widely studied, especially since the Women's Health Initiative. Earlier studies suggest that race/ethnicity plays a role in response to hormone replacement therapy (HRT);[24] with fewer symptoms of depression and lower aggression and cynicism scores reported among Caucasian, but not African-American, users of HRT.[25] A self-administered Menopausal Health Survey found that although the African-American and Caucasian women studied had similar geographic locations, incomes, educational backgrounds, and health-seeking practices, significant differences in knowledge about and perceptions of estrogen replacement therapy existed between the two groups.[26] Among poor, African-American women residing in the inner city, younger age, undergoing a hysterectomy and physician discussion of HRT were significantly associated with current HRT use,[27] while those enrolled in the Black Women's Health Study had highest hormone use due to bilateral oophorectomies, lower body mass, greater years of education, vigorous exercise, and past oral contraceptive use; a pattern similar to Caucasian women.[28] Data from the National Health and Nutrition Examination Survey III found that 40 percent of non-Hispanic white women, 20 percent of non-Hispanic black women, and 24 percent of Mexican-American women reported HRT use. Those with the lowest use did not complete high school or had a low family income.[29]

The 1998 Complementary and Alternative Menopausal Practices Survey found that Caucasian women are more likely to use both conventional and CAM to a greater extent than either African-American or Hispanic women.[5] Caucasian women have also been found to take medication more consistently than African-American or Hispanic women.[30]

Summary

Racial and ethnic differences exist with respect to how a woman approaches the menopause transition, including reporting of menopausal symptoms. Understanding of these differences can be used to promote lifestyles that may decrease symptoms and increase quality of life. Future research on menopausal symptoms among women of different racial/ethnic groups should focus on further exploration of the role of dietary factors and body mass index; use of CAM in symptom management, with a better understanding of the risks/benefits of such therapies; and additional evaluation of pituitary sensitivity.

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Lifestyle Factors: Are They Related to Vasomotor Symptoms and Do They Modify the Effectiveness or Side Effects of Hormone Therapy?

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Overview

This presentation will address two major questions: (1) Are lifestyle factors related to the occurrence of vasomotor symptoms (VMS) in the perimenopause and postmenopause; and (2) Do lifestyle factors modify the effectiveness or side effects of menopausal hormone therapy (HT)? The term, "lifestyle factors" can encompass many domains of behavior, including diet, smoking, physical activity, and alcohol use. The breadth of this topic precludes considering all domains, thus this discussion will feature the lifestyle factors of physical activity and alcohol use. In addition, although it is not a lifestyle factor *per se*, this presentation will review the relation of body mass index (BMI) to VMS and as a potential effect modifier of the effectiveness or side effects of HT.

Proposed Mechanisms for a Relation Between Alcohol and VMS or Effect Modification of HT by Alcohol

The interest in a relation between alcohol consumption and VMS and alcohol use as an effect modifier of HT arises from two related research themes. First, alcohol use is implicated as a risk factor for reproductive cancers that are believed to be estrogen-related. For example, a pooled analysis of cohort studies found that breast cancer risk increased linearly with grams of alcohol consumed.[1] One thesis offered as an explanation for the alcohol and breast cancer link is that alcohol consumption raises endogenous estrogen levels, a hypothesis borne out by some,[2–5] but not all,[6–10] reports. Second, experimental studies of acute alcohol administration to postmenopausal women who have been pretreated with HT afford strong evidence that alcohol rapidly raises the estrogen levels achieved as a result of HT.[11–14] While this experimental paradigm in HT users should not be directly translated to the means by which alcohol may affect endogenous hormone levels, it offers some insight into why the effects of alcohol on endogenous hormones may be difficult to capture. In the experimental setting, the acute effects of alcohol are of short duration. Thus, "spikes" in estrogen levels as a result of alcohol use may be transitory and difficult to ascertain in the observational setting.

Alcohol and VMS

Results of cross-sectional studies of alcohol use and VMS in midlife premenopausal, perimenopausal, and postmenopausal women are mixed. A study of 334 African-American and Caucasian postmenopausal women suggested that, after adjustment for relevant covariates, those who had ever consumed alcohol recalled more hot flashes during their menopause transition than nondrinkers (OR (95 percent confidence interval (CI))=1.3, p=0.13).[15] In a community-based

sample of 436 African-American and Caucasian premenopausal women aged 34–47, Freeman and colleagues found a statistically significant relation between alcohol use (number of drinks per week) and reporting any hot flashes (OR (95 percent CI) =1.1, p=0.002). In contrast, in a cross-sectional analysis from the Study of Women's Health Across the Nation, among 3,302 premenopausal and early perimenopausal women of African-American, Caucasian, Chinese, Hispanic, and Japanese descent, Gold, et al. discerned no effect of average daily alcohol consumption in the past year (overall sample mean was approximately 6 grams daily and mean among the drinkers was approximately 12 grams daily) and VMS reporting.[16]

Proposed Mechanisms for a Relation Between Physical Activity (PA) and VMS or Effect Modification of HT by PA

The hypotheses that PA may protect against VMS is based on reciprocal effects on the hypothalamic beta-endorphin system: Lowered beta-endorphin may be one mechanism underlying VMS pathogenesis[17] and vigorous PA elevates beta-endorphin.[18,19] An alternative theory is that PA, due to the associated increase in body temperature, could provoke VMS in perimenopausal and postmenopausal women who have a narrowed thermoneutral zone.[20]

PA and VMS

Observational studies of PA and VMS that have adjusted for relevant covariates largely report null results.[21–24] In a case-control study of 169 women recruited from a large health maintenance organization, participation in vigorous recreational activity in the year prior to the final menstrual period was unassociated with lower odds of having frequent VMS in the year after menstrual cessation.[21] A cross-sectional substudy of 214 perimenopausal participants in a community-based study of heart disease risk factors noted no relation between VMS and PA.[22] Similarly, in a volunteer sample of 386 premenopausal, perimenopausal and postmenopausal women participants in a bone health study, Wilbur and colleagues found no association between self-reported PA or measured PA (by ergometer) and VMS.[23] However, null results may be attributable to the infrequency of VMS in the latter two studies. PA and VMS were also unassociated in a community-based sample of 239 postmenopausal women in which the overall prevalence of VMS was 50 percent and approximately 20 percent of non-HT using women were classified as active (at a level of moderate or greater).[24] In unadjusted analyses of a Swedish population-based cohort study, the odds of VMS among postmenopausal women who reported strenuous PA were 0.26 compared to those who were sedentary; adjusted analyses were not reported.[25]

Two PA intervention studies found no change in VMS with the intervention, but neither was designed to examine VMS as a primary outcome.[26,27] A 2-year randomized control trial in postmenopausal osteopenic women of a 4-times-per-week mixed aerobic and strength training program intended to reduce bone loss found no relation between active treatment and the incidence of VMS (N=85 randomized and 50 analyzed) compared to a control condition (N=51 randomized 33 analyzed).[26] A 6-month randomized control trial of diet and moderate intensity exercise in overweight postmenopausal women (BMI of greater than 25) did not find an effect of the exercise intervention on VMS occurrence, but baseline VMS prevalence was modest at 20 percent.[27]

Proposed Mechanisms for a Relation Between BMI and VMS or Effect Modification of HT by BMI

Weight is positively related to endogenous estrogen levels, likely due to adipocyte-based aromitization of estrone and conversion of androstenedione to estrone.[2,6] Thus, it has long been postulated that higher weight would be protective against menopause symptoms. With respect to effect modification of exogenous HT's effects by BMI, one might propose a lesser effect of HT due to a higher volume of distribution in heavier women (if levels of hormone achieved relate to positive or negative outcomes). Recent data, reviewed below, contradict both of these hypotheses.

BMI and VMS

BMI, before and after adjustment for numerous other lifestyle and demographic characteristics, was positively associated with the occurrence of VMS in premenopausal and early perimenopausal women.[16] It is plausible that the heat insulation afforded by greater adiposity leads to more hot flushes as the thermoneutral zone narrows.[20,28]

Effect Modification of HT by BMI

A small amount of intriguing data suggests that with transdermal estradiol administration, heavier women experience greater serum estradiol levels and clear the estradiol more slowly than their lighter counterparts.[29,30] The Estrogen in the Prevention of Atherosclerosis (EPAT) study, which randomized postmenopausal women to 1 mg of oral mirconized estradiol daily versus placebo, conducted an analysis of estradiol levels achieved on-treatment as a function of BMI greater than (N=36) or less than 30 (N=56).[30] The mean change in estradiol on treatment among the heavier women was 42 percent greater than that of those with BMI less than 30. A small (N=8) clinical research center study of the half-life of transdermal estradiol in nonsmoking postmenopausal women taking no medications and with a BMI of less than 28 found a strong, positive relation between the half-life of estradiol and BMI ($r=0.79$, $p=0.02$).[29]

EPAT also conducted a post hoc analysis, asking if BMI modified the effectiveness of oral estradiol on the study's primary endpoint, intima-media thickness of the common carotid artery; no evidence for effect modification by BMI was evident.[29] The Women's Hope study, a large (N=2,673) randomized trial of 7 regimens of various doses of oral conjugated equine estrogens with and without medroxyprogesterone acetate, also conducted a post hoc analysis of effectiveness in heavier (BMI equal to or greater than 25) and lighter (BMI less than 25) participants.[31] This study was restricted to postmenopausal women who were within 20 percent of ideal body weight. Considering the aggregate of all active treatments, the mean daily number of VMS declined similarly in each BMI group (by about 11). Changes in other effectiveness endpoints (bleeding patterns, vaginal maturation index, bone density) were also similar in the two groups. In the Women's Health Initiative Estrogen Plus Progestin clinical trial, the increased risk of venous thromboembolism risk that occurred in the active treatment arm was magnified by body weight.[32] In the overall sample, the hazard ratio for venous thromboembolism among active, compared to placebo-treated, women was 2.06 (95% CI=1.57–2.70). Compared with normal weight women in the placebo arm, the hazard ratio for overweight women (BMI between 25 and 30) was 3.5

(95% CI=2.08–6.94) and the hazard ratio for obese women (BMI greater than 30) was 5.61 (95% CI=3.12–10.11).

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The Impact of Risk Status, Pre-Existing Morbidity, and Polypharmacy on Treatment Decisions Concerning Menopausal Symptoms

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The past decade has witnessed a burgeoning of information on the effects of menopausal hormone therapy (HT) and other menopausal treatments on a variety of clinical endpoints. Findings from the randomized, controlled Heart and Estrogen/progestin Replacement Study[1] and Women's Health Initiative(WHI)[2] overcame many of the methodological shortcomings of previous observational studies, providing point estimates of the impact of HT on the risks of numerous clinical endpoints. Despite the availability of this robust evidence, decisions about menopausal treatment remain difficult, largely due to the number of clinical endpoints affected by HT and challenges in applying this complex body of evidence to guide clinical decisions of individuals who present with a variety of risk factors, comorbidities, and concurrent medications.

Balancing Net Risks and Benefits of Treatment

Deciding whether HT or other menopausal treatments are appropriate for an individual patient requires a careful assessment of the risks and benefits of each treatment, along with the individual's risk factors, comorbidities, and current medications. Each treatment has a unique benefit-risk profile. Because of the number of endpoints affected by HT and other menopausal treatments, weighing the risks and benefits of treatment on an individual basis can be complex. There are several different theoretical frameworks available for assessing multiple treatment effects on multiple outcomes.[3] The WHI developed a "global index" to determine whether the net impact of treatment was positive or negative, taking into consideration the principal clinical outcomes affected by HT. This global index sums all of the clinical events whether they induced or prevented HT (except for menopausal symptom relief), giving equal weight to each event. Events included in this global index were coronary heart disease, coronary heart disease death, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death from other causes. The net balance for combination HT was negative in the WHI (i.e., its overall health risks exceeded its benefits). However, this might not be the case for women with different clinical characteristics than those in the WHI study—changing the baseline risk of the cohort could alter the benefit-risk ratio (in either direction) because the risk of HT inducing or preventing any specific clinical event depends on the woman's baseline (pretreatment) risk for developing that outcome.

Relative Versus Absolute Risks

Population-based trial evidence, typically expressed as a relative risk, can be translated to individual decisions by transforming relative risks into absolute risks. Relative risks describe the ratio of the risk of disease in one group compared to that in another and does not take into consideration a person's baseline risk. Absolute risks vary according to baseline levels of risk and

could be very small, even for large relative risks, when the disease is uncommon.[4] For example, a physician may inform patients that a treatment such as HT might increase the relative risk of breast cancer by 40 percent. However, the absolute risk of this treatment will depend on an individual's baseline risk. A woman who has a 25 percent baseline chance of breast cancer will experience a 10 percentage point increase in risk, from 25 percent to 35 percent (25% x 1.4 = 35%), whereas a woman who has a 5 percent baseline chance of breast cancer will experience only a 2 percentage point increase in risk (from 5 percent to 7 percent). Framing the effects of treatment in relative, rather than absolute, terms can affect a patient's perception of a therapy's effectiveness,[5] making the benefits of a treatment appear more favorable,[6] or, conversely, emphasizing its risks.[7] Patients need to understand the impact of treatment choice on their personal risks, translating relative risks into absolute risks.

Comparability of the Study Participants to the General Population

How closely do the characteristics of women in the WHI or other clinical trials of HT match those of women in the general population? Women in the WHI were, on average, over a decade older than most women entering the menopause transition and healthier than an average American woman. However, women from a large age span were included (50–79) as were women with differing risk levels for many, but not all, outcomes. Women enrolled in the observational Nurses Health Study were also healthier than average women.[8] While such differences would affect the generalizability of the global benefit-risk index to women who are dissimilar to those in the WHI, they would not limit the applicability of specific findings (relative risks) unless subgroup analyses found relative risk estimates to differ across age and risk strata.

Homogeneity of Risk Estimates Across Age and Risk Strata

Subgroup analyses from the WHI, Heart and Estrogen/progestin Replacement Study, Nurses Health Study, and Breast Cancer Detection Demonstration Project found the relative risk of HT on cardiovascular disease (CVD),[9,10] breast cancer,[11] and ovarian cancer[12] to be relatively uniform across strata defined by age, race/ethnicity, antecedent risk status, or prior disease. Some data suggest that body mass index may possibly be an effect modulator for breast cancer,[11] though differences between subgroups defined according to body mass index did not achieve statistical significance. Data are limited for pulmonary embolism, hip fracture,[13] and colorectal cancer,[14] but no data demonstrate heterogeneity of risk across strata.

Other Considerations in Balancing Benefits and Risks

By attaching equal weights to each clinical event, the global index is completely insensitive to differences in mortality, morbidity, and patient preferences concerning clinical outcomes. Changing the weight attached to any outcome can potentially affect the net benefit-risk index.

Because the global index does not take into consideration the impact of HT on menopausal symptoms or menopausal quality of life, this index is less relevant for women experiencing menopausal symptoms, for whom the principal benefit of HT would be symptom relief. Other

conceptual frameworks have been developed that emphasize the values and preferences that a woman places on these outcomes. Examples include the Eddy balance sheet[15] and O'Connor balance scale.[16] However, these more qualitative approaches do not enable calculation of the absolute impact of treatment on 'hard' events, such as CVD.

Findings From a Decision Analytic Model

A recent decision analytic model balanced the short-term benefits of HT on menopausal quality of life against its risks among healthy, newly menopausal women.[17] This decision model translates the relative risks of HT (using estimates from the WHI) into absolute risks for a variety of cohorts and implicitly weighs clinical events according to their morbidity and mortality. HT was associated with losses in survival but gains in quality adjusted life expectancy for women with menopausal symptoms. Women expected to benefit from short-term HT can be identified by the severity of their menopausal symptoms and CVD risk. Note that this model did not pertain to women with a history of breast cancer, CVD, or pulmonary embolism.

Critical Gaps in Knowledge

The benefit-risk of treatment for an individual depends not only on the patient's baseline disease risks but on the concurrent use of any drugs that might interact with the treatment and on the impact of that treatment on quality of life. Because of the strict eligibility criteria of most randomized trials, safeguards to protect patients, and the tendency of healthier people to participate in prevention trials, there are limited data available on many population subgroups, especially those with many comorbid conditions. Unlike strata defined by age or risk status, strata defined by the usage of drugs that could interact with HT would not be expected to be homogenous. This gap in knowledge affects our ability to confidently estimate the effect of treatment on such populations because it may not be valid to infer homogeneity of risk across these strata.

There are limited data on the benefits of menopausal treatment on menopausal quality of life, according to stage of menopause. The absolute benefit of treatment on menopausal symptoms might well vary according to menopausal stage and the specific symptoms experienced, but no data are currently available to help guide treatment according to stage.

In addition to needing more data about the specific effects of menopausal treatments on different outcomes among clinically and ethnically diverse populations, more attention is needed to translate this evidence in clinical practice and to develop tools to support informed decisionmaking. Because an individual's symptoms and risks for breast cancer, CVD, osteoporosis, colorectal cancer, and other outcomes change dramatically with age (even while holding other risk factors constant), the net benefit-risk ratio of HT (or other menopausal treatment) is dynamic over time for any individual—the benefit-risk ratio of a treatment changes with age even if other risk factors remain unchanged. Dynamic decision aids that incorporate these important temporal changes are needed to help patients and their clinicians make more rational treatment decisions and to help patients reassess the appropriateness of treatment as they age.

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Issues Related to Discontinuation of Menopausal Hormone Therapy

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Current guidelines recommend that postmenopausal hormone therapy be used primarily for treatment of vasomotor and urogenital symptoms associated with the menopause transition and that women use the lowest effective dose for the shortest time necessary.[1,2] Since vasomotor symptoms generally improve or resolve within a few months to a few years of onset,[1,3,4] these guidelines suggest that hormone therapy (HT) should be discontinued in most women within a few years of starting therapy. Following these guidelines is problematic in clinical practice. HT is very effective for relief of vasomotor symptoms,[4] so determining when symptoms have resolved is difficult without stopping treatment. This has led some experts to recommend that women using HT for treatment of symptoms attempt to stop periodically, perhaps every 6–12 months, to determine if symptoms have improved to the point that treatment is not needed.[5] Most women tolerate mild vasomotor or other symptoms that occur after stopping HT. However, when severe vasomotor symptoms occur after stopping HT, it is not clear whether these symptoms have persisted since starting therapy (but been adequately treated) or occur due to declining hormone levels mimicking menopause.

Many women who begin taking HT for treatment of symptoms have no difficulty quitting. About half of the women who start HT, even those who begin therapy for treatment of symptoms, quit within a year, often with no help from their health care provider.[6,7] However, about 10–15 percent of women continue to have hot flushes for many years after menopause and may need prolonged symptomatic treatment.[8,9]

While many women stop HT without apparent problems, some who would like to quit are unable to do so, mainly due to the development of vasomotor symptoms.[10] In the 6–8 months following publication of the results of the Women's Health Initiative trial of estrogen plus progestin, 56 percent of women who were enrolled in a large health maintenance organization and had been taking postmenopausal hormone therapy for over a year reported that they had tried to discontinue therapy.[11] Among those who tried to stop, 1 in 4 resumed HT within about 6 months of stopping.[10] After stopping HT, 70 percent reported either no or mild withdrawal symptoms, but 30 percent reported troublesome vasomotor symptoms that began about a week after stopping. In a clinical trial in which postmenopausal women who had been taking estrogen plus progestin for an average of 3 years were randomized to continue HT or to take a placebo for 12 weeks, 60 percent of those assigned to a placebo recorded development of hot flushes, with the peak number and severity of flushes occurring at about 8 weeks after stopping.[12] Troublesome symptoms appear to be more common among women who start HT for treatment of symptoms, but are also reported by women who start HT for reasons other than treatment of symptoms.[10]

In women who develop severe vasomotor symptoms after stopping HT, there is currently no way to determine whether these symptoms will persist for a prolonged period or resolve within an acceptable period of time off therapy. If stopping HT actually mimics the hormonal changes that occur at menopause, symptoms should resolve in most women over time.[1,3,4]

Given this, the clinician must decide whether to restart HT or try to help a woman tolerate symptoms until they improve or resolve. This decision may be affected by the woman's age, risk for the adverse effects of HT, severity of her symptoms, and willingness to tolerate the symptoms.

Unfortunately, there is little information to guide physicians in helping women who have difficulty stopping HT. Many clinicians suggest that women who have difficulty stopping HT abruptly try to taper off therapy, either by slowly decreasing the dose or the number of days per week that HT is used.[5] The optimal approach and duration of tapering are not known. In one survey of women who tried to stop HT, those who reported tapering were a little more successful in quitting than those who stopped abruptly (30 percent versus 24 percent), but the details of how HT was tapered were not ascertained.[10] Some clinicians add another medication at the time women stop HT, but the effectiveness of this approach has not been evaluated.

In summary, many women who would like to stop using HT have difficulty stopping. We know very little about this problem and have not identified effective methods for helping women stop.

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Managing Symptoms: Where Have We Come From and Where Do We Go?

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The two major symptoms that distinguish premenopausal from postmenopausal women are vasomotor flushes and vaginal atrophy. Studies in the sixties and seventies in hospital and clinical settings demonstrated that estrogens were powerful medications to relieve women of these symptoms. They were effective by different routes and different doses. In the eighties, there was a major thrust to find other positive benefits of estrogens, including prevention of osteoporosis and prevention of heart disease as well as other chronic medical conditions, such as Alzheimer's disease. Thus, estrogens were prescribed during that time for more than just symptom relief. However, we then learned of the complications of estrogens which included the potential for breast cancer. In addition, randomized controlled trials were at variance from observational trials in that the benefits on heart disease evaporated. Health care providers and, especially, our patients were reluctant to utilize estrogens and sought alternatives. These included soy products as well as complementary medicines. Unfortunately, these agents are not as effective as estrogens for the relief of severe symptoms. The pendulum is now swinging back towards utilization of estrogens as long as the patient understands the benefits and risks of therapy. We are learning to use a much lower dose and different routes of administration, which may be safer, for shorter periods of time. Ideally, we would like to have a therapy that has only benefits and no risks.