Preventive Care Programs to Improve the Management of Perimenopausal and Postmenopausal Women: Guidance for Managed Care Organizations

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Continuing Education Activity
Gary M. Owens, MD, is the founder and President of Gary Owens Associates. Owens has more than 20 years of experience in medical and pharmacy management. He managed multiple operations in a large regional health plan and was directly responsible for the implementation of multiple strategic initiatives, which included the 2006 launch of FutureScripts, a wholly-owned PBM of Independence Blue Cross. He managed pharmacy operations for more than 2.0 million members and was a leader in the evaluation and management of biotech drugs at the health plan. While at Independence Blue Cross from 1986 to 2006, Owens was vice president for Medical Management and Policy from 2003 to 2006. From 1996 to 2003, Owens was vice president for Patient Care Management and was responsible for medical management services for 3.2 million members.

During his tenure at Independence Blue Cross, Owens had management responsibility for the Care Management and Coordination Department, the Pharmacy Services Department, and the Claims Payment Policy Department. He managed medical review services, including pre-certification of medical services, hospital care level reviews, high-tech radiology services pre-certification, discharge planning activities, and case management. Owens was responsible for the evaluation of new drugs and technologies as manager of the technology evaluation unit. In that capacity, he worked to develop the injectable medications management program, which included a program to assess and manage biotech and bio-oncology products.

Owens is a graduate of the University of Pennsylvania and received his MD from Thomas Jefferson University. He is a senior scholar for the Department of Health Policy at Thomas Jefferson University. He is involved in medical teaching and previously served as vice chairman of the Department of Family Medicine at the Medical Center of Delaware. He has lectured and published extensively on managed care, pharmacy, and biotechnology-related subjects, including recent articles in the *American Journal of Managed Care* and *Disease Management*.

Andrea Lukes, MD, MSHc, is the founder of the Carolina Women’s Research and Wellness Center, a private research company that offers many clinical research opportunities focused on women’s health and wellness and conducts multiple ongoing FDA clinical trials. Lukes is also the founder and chairman of the ObGyn Alliance, which is an online peer-to-peer group of obstetricians and gynecologists dedicated to primary care, clinical research, best practices, and new tests and devices. She was previously a faculty member of Duke University, where she co-founded the Women’s Hemostasis and Thrombosis Clinic and served as the Director of Gynecology for that clinic.

Lukes’ area of research interest is abnormal uterine bleeding and general women’s wellness. Past research has included support from the CDC, NIH, and many industry-sponsored trials. Her area of clinical research is within abnormal uterine bleeding, hemostasis and thrombosis, contraception, alternatives to hysterectomy, hysteroscopy, and menopause.

Elena M. Umland, PharmD, is the associate dean for Academic Affairs of the Jefferson School of Pharmacy at Thomas Jefferson University in Philadelphia. From 1996 to 2007, Umland was a full-time faculty member in the Department of Pharmacy Practice at the University of the Sciences in Philadelphia (USP). She served as director of the Doctor of Pharmacy Program from 2004 to 2007. During her time at USP, she developed practice and research interests in women’s health and maintained an active practice site with the Department of Family and Community Medicine at Thomas Jefferson University Hospital where she also held an appointment as adjunct clinical assistant professor of Family Medicine in the Jefferson Medical College. She served as the chair of the Women’s Health Practice and Research Network of the American College of Clinical Pharmacy (ACCP), as well as leadership positions within the Mid-Atlantic Chapter of ACCP. She has given numerous local and national talks on women’s health issues and has numerous publications focusing on these topics. During her tenure at USP, she was nominated for the Lindback Award for distinguished teaching and was awarded the Faculty Special Recognition Award in 2000. She was named the recipient of the Barbara H. Korberly endowed professorship in women’s leadership and health in 2005. Umland has been a member of the American Association of Colleges of Pharmacy since 1996 and has assumed active participation in this organization during the past several years, serving, most recently, on the Institutional Research Advisory Committee and chairing a sub-task force to evaluate a standardized preceptor survey.

Umland earned her BS and PharmD degrees from the Philadelphia College of Pharmacy and Science in 1993 and 1995, respectively. She completed a Primary Care Residency at the Veteran’s Administration Medical Center in Iowa City, Iowa, in 1996.
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Target Audience and Goal
The goal of this supplement is to educate managed care pharmacists and healthcare professionals about the gender differences in resource utilization and quality of care, specifically the treatment of vasomotor symptoms as an opportunity to reduce costs and improve the quality of preventive care.

Learning Objectives
At the completion of this activity, participants will be able to:
• Explain differences in resource utilization and health care expenditures incurred by women and men.
• Identify gaps in quality of preventive care for women, especially at the time of menopause.
• Describe the results of the Women's Health Initiative trial and its influence on consensus menopause treatment guidelines.
• Discuss pharmacologic options for the treatment of the vasomotor symptoms of menopause, including hormone replacement therapies, nonhormonal therapies, and herbal products.
• Present strategies that a managed care organization may use to reduce health care costs and improve the quality of care provided to perimenopausal and postmenopausal women.

Funding
This supplement was funded by Wyeth Pharmaceuticals.

The content in this 3-article supplement was initially presented as a live symposium held in conjunction with the Academy of Managed Care Pharmacy’s Educational Conference in Boston, Massachusetts, on October 25, 2007.

Speaker Disclosure of Commercial Affiliations
The speakers for this continuing education activity have been asked to disclose any significant financial interests, relationships, or affiliations they may have with commercial entities whose products, devices, or services may be covered in their article. Participants have the responsibility to assess the impact (if any) of the disclosed information on the educational value of the activity. All authors have been offered a modest honorarium from the accredited provider for their participation in this activity.

Product Disclosure
In this educational activity, Umland discusses the use of several products for the treatment of vasomotor symptoms of menopause that are not approved by the FDA for that indication: (1) paroxetine, fluoxetine, citalopram, venlafaxine, desvenlafaxine, clonidine, and gabapentin; (2) investigational drugs Org50081 and PD-0299685; and (3) nonprescription herbal remedies (e.g., soy isoflavones, red clover, black cohosh, vitamin E). Advanced Concepts Institute, University of the Sciences in Philadelphia, and Wyeth Pharmaceuticals do not recommend the use of any agent outside of the labeled indications.
ABSTRACT

BACKGROUND: Rising health care costs and quality of care concerns require a re-evaluation of various aspects of health care delivery. In order to properly manage costs, payers need to understand how different patient populations contribute to spending trends and where suboptimal quality of care is more prevalent, and, therefore, may drive cost trends.

OBJECTIVE: To demonstrate significant opportunities for improvement in the management of postmenopausal women by highlighting areas of imbalance between health care costs and quality of care.

SUMMARY: Women tend to use significantly more services and spend more health care dollars than men. The greatest disparity in health care spending between men and women has been noted in the population aged 45 to 64 years. In this age group, women’s health issues primarily revolve around chronic conditions and menopausal symptoms. With the onset of menopause, the risk of cardiovascular disease (CVD), breast cancer, and osteoporosis increases significantly. However, substantial evidence indicates that there are broad gaps in the quality of care received by postmenopausal women. In some populations, breast cancer screening rates are almost 20% below the national target. Stratification of health plan performance with the National Committee for Quality Assurance/Health Care Effectiveness Data and Information Set (NCQA/HEDIS) measures related to CVD demonstrates gender-based gaps, even when there are no disparities in access to care. The widest gender gap in CVD management is observed with low-density lipoprotein (LDL) cholesterol control rates. In the management of postmenopausal women with a history of fractures, standards of care are met only 19% to 50% of the time. After the age of 45, the majority of women either do not receive any information about menopause from their physicians or they are unsatisfied with the menopause counseling that they do receive. These quality gaps should be considered in light of the high prevalence of chronic illness and costs attributed to these conditions and menopausal symptoms in women.

CONCLUSION: When reviewing strategies for reducing health care costs, managed care organizations (MCOs) should focus on the management of postmenopausal women. With the use of proper screening, preventive care, and therapeutic management in postmenopausal women, an MCO could potentially achieve downstream reduction in overall costs for this population.

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spending in the study population attributable to women was $6.93 billion, whereas spending attributable to men was more than $1 billion less at $5.77 billion. In particular, analgesics, hormones, and psychotherapeutic agents use was found to be higher among women than among men. Earlier findings that women are significant contributors to total medical costs were recently confirmed by Woolhandler et al. in an analysis of the 2003 MEPS data. In the adult population aged 18 to 64 years, the median spending was $847 for males and $1,844 for females. The investigators noted that the greatest disparity in health care spending between men and women was in the population aged 45 to 64 years (Figure 1). In this age group, the median annual per capita expenditures for women were approximately 50% greater than for men ($2,871 vs. $1,849).

A Closer Look at Women’s Health Issues

Notable gaps in understanding the quality of care received by women attracted national attention more than 15 years ago when the Journal of the American Medical Association dedicated an entire issue to women’s health. The issue’s editorial, written by the current director of the Agency for Health Care Research and Quality (AHRQ), metaphorically referred to women’s health as “a patchwork quilt with gaps.” Since then, considerable progress has been made in prioritizing women’s health. This area has been incorporated into the national policy agenda, and it has become integrated into the mainstream scientific research.

Today, clinicians, payers, and health policy experts recognize that women’s health extends far beyond the issues of reproductive health and prenatal care. As women approach their mid- to late-forties, the relevance of reproductive health declines, and the importance of general medical conditions, which become more common with increasing age and/or onset of menopause, increases. On average, women enter menopause at age 51. At this time in their lives, the risk of chronic conditions increases substantially. At age 50, women have a 39% risk for developing CVD over the course of their remaining lifetime. The probability of being diagnosed with breast cancer, the most commonly diagnosed cancer in women, increases by almost 40% for those aged 40 to 69 years. CVD and cancer are presently the leading causes of mortality in women; these chronic conditions account for 63% of women’s deaths in the United States. The risk for developing osteoporosis also increases after menopause. In fact, postmenopausal women comprise the predominant majority of the osteoporotic population. The lifetime risk of fracture after age 50 is 39.7% for Caucasian women, which is 3 times greater than the rate for Caucasian men (13.1%). Finally, menopause itself is associated with symptoms that can significantly diminish a woman’s quality of life. The vasomotor symptoms (VMS) of menopause, such as hot flashes, affect more than 75% of women who are aged greater than 50 years.

Considering the disproportionate impact of chronic conditions and menopausal symptoms, it is important to understand the level of focus and quality of care dedicated to these unique health issues in older women.

Disparities and Gaps in the Quality of Care Received by Women

In the past several years, national health care quality and disparities have been closely followed by the AHRQ on an annual basis. Key findings demonstrate that significant care gaps still remain. Although 32 of the 42 core quality measures have improved in the past year, the average rate of improvement across all measures remains slow at 3% per year. Furthermore, disparities in quality of care are pervasive, especially for racial and ethnic minorities, people of lower socioeconomic status, and those residing in some geographic regions. Differences in quality of care also have been demonstrated between women and men. In 2004, the AHRQ reported that compared with men, women received better care for 18% of the measures, worse care for 22% of the measures, and the same level of care for 59% of the measures. When examining specific therapeutic areas, women tend to receive better preventive care for CVD and cancer than men. However, women are less likely to receive colorectal cancer screening. Men tend to receive better treatment for end-stage renal disease and heart disease than women. Racial and ethnic differences in quality of care also exist within the female population. In 2006, the AHRQ found that for services unique to women, African-Americans and Hispanics receive poorer quality of care than Caucasians for 75% of the performance measures.
Analysis of published literature, along with the data generated by the National Committee for Quality Assurance (NCQA) and the AHRQ, reveal that disparities and quality gaps are particularly associated with conditions that are linked with the onset of menopause. The evidence described below highlight the shortcomings in the management and/or prevention of breast cancer, CVD, osteoporosis, and menopausal symptoms in women.

**Breast Cancer.** According to the AHRQ, the national mammography rate in 2003 nearly reached the target of 70% set by the Healthy People 2010 initiative. However, this threshold was not attained in many subpopulations, including the elderly, the poor, and non-Caucasians. Similarly, health plan performance in breast cancer screening in 2006 was considerably higher among commercial and Medicare populations than among the Medicaid population (69% vs. 49%). Suboptimal quality of breast cancer care is also evident from the lack of improvement in the late-stage diagnosis rate and the mortality rate that remains above the goal attainment in many subpopulations, including the elderly, the poor, and non-Caucasians. Similarly, health plan performance in breast cancer screening in 2006 was considerably higher among commercial and Medicare populations than among the Medicaid population (69% vs. 49%). Suboptimal quality of breast cancer care is also evident from the lack of improvement in the late-stage diagnosis rate and the mortality rate that remains above the goal set for 2010.

**CVD.** CVD care for women is not receiving sufficient prominence in the U.S. health care system. The available data on a number of measures used to assess the quality of CVD care consistently show that there are substantial gender differences. In the acute care setting, women with myocardial infarction are less likely than men to receive diagnostic or therapeutic procedures, drug therapy, and cardiac rehabilitation. These findings are especially alarming considering that myocardial infarction is associated with a greater risk of mortality in women. In the outpatient setting, gender disparities are also highly prevalent; for instance in comparison with men, women receive less counseling on diet and exercise. Appropriate cholesterol screening and management is also significantly less common among women than men.

**Stratification of health plan performance with the National Committee for Quality Assurance/Healthcare Effectiveness Data and Information Set (NCQA/HEDIS) measures related to CVD support findings of gender-based gaps, even when there are no disparities in access to care.** In 2003, Bird et al. analyzed gender differences in performance with 6 HEDIS measures related to CVD for a sample of 2.3 million lives covered by 19 commercial and Medicare health plans. Overall, they found small to moderate differences between male and female cohorts. In addition, the extent of disparities in performance varied considerably between different health plans. In 2007, Chou et al. reported the results of a similar analysis that was based on a larger national sample representing 31 health plans. The investigators found that women were less likely to receive treatment and screening recommended after an acute cardiac event (Table). The greatest difference between women and men was observed in the percentage of people with a history of CVD who had low-density lipoprotein (LDL) cholesterol < 100 mg per dL (46.6% vs. 55.1%). Interestingly, women had better blood pressure control rates than men.

**Osteoporosis.** In the management of postmenopausal women with a history of fractures, physicians tend to adhere to clinical guidelines less than 50% of the time. Moreover, between 1998 and 2001, no improvement has been noted. A HEDIS measure of osteoporosis management in Medicare plans found that only 19% of women aged 67 and older who had a fracture received a bone mineral density test or prescription for a drug to prevent or treat osteoporosis in the 6-month period following the fracture in 2004. In addition, age and racial disparities are prevalent among women in this therapeutic area. Older women are less likely to receive osteoporosis treatment than younger women, even though aging increases the risk of fractures. Screening and treatment rates are also lower among postmenopausal African-American women than Caucasian women. New evidence regarding the quality of osteoporosis management is expected from the Physician Reporting Quality Initiative, a voluntary quality reporting program that has 4 osteoporosis-related measures.

**Menopause.** Despite the high prevalence of menopausal symptoms, counseling in this area has been found to be largely inadequate. After the age of 45, the majority of women either do not receive any information about menopause from their physicians, or they are unsatisfied with the menopause counseling that they do receive. Even before the release of the Women’s Health Initiative (WHI) study on the benefits and risks associated with hormonal therapy, only 38% of women aged 50 years or older reported being counseled by their physician about hormone replacement therapy. In 2000, the NCQA Management of Menopause (MoM) survey was used to evaluate the exposure, breadth, and personalization of menopause counseling provided to women aged 47 to 55 years. The results displayed significant deficits in most aspects of menopause counseling (Figure 2). The overall composite score was 56.8 out of a possible 100. The average woman surveyed received approximately half of the recommended information about treatment options (i.e., breadth) and unique characteristics that may affect her experience (i.e., personalization). In addition, when
counseling was provided, only 33% of the surveyed population felt that they received very high quality menopause information. Considering the confusion among providers and patients created by the findings of the WHI study, it is likely that the extent and quality of menopause counseling continued to diminish. Unfortunately, the MoM survey was discontinued in 2002, and the managed care community has no nationally recognized standardized means to assess the current state of menopause counseling.

**Economic Burden of Chronic Conditions in Postmenopausal Women**

As women generate significantly more health care costs than men during the time of menopause and their care might be suboptimal, it is also worthwhile to evaluate how CVD, breast cancer, osteoporosis, and menopausal symptoms affect resource utilization and costs. Costs associated with the management of chronic conditions in employed women aged 50 to 64 years were recently estimated by Sasser et al. The investigators noted that in comparison with the random sample, cohorts of women with CVD, breast cancer, or osteoporosis used more medical services and missed more days of work. Average annual direct costs were significantly higher for women treated for osteoporosis ($6,259), breast cancer ($13,925), and CVD ($12,055) than the cost reported for the random sample ($2,951). Significant increases in indirect costs were also observed with these conditions. Aggregate estimates showed that in 2002, U.S. employers spent approximately $6 billion in overall direct medical spending associated with these conditions. In another analysis, it was determined that the cost of treatment of VMS is approximately $681-$848 per patient per year. Given the high prevalence of these symptoms, the aggregate costs could also be significant. These estimates indicate that women with chronic conditions and menopausal symptoms require close management to ensure efficient and effective use of resources.

**Conclusion**

In search of strategies for reducing health care costs, U.S. health care payers should focus on the management of postmenopausal women. This population represents a great opportunity for balancing cost and quality of care. Between their late forties and early sixties, women tend to spend 50% more than men on health care. With the onset of menopause, the prevalence and impact of costly conditions increases substantially among women. However, management of CVD, breast cancer, osteoporosis, and menopause in women is often not meeting measurable standards of care. MCOs should focus on this population to ensure efficient and effective use of resources. Proper screening, preventive care, and therapeutic management in postmenopausal women could potentially lead to downstream reduction in overall costs. The following articles will provide a clinical update on the management of postmenopausal women. In addition, management of VMS will be presented as an opportunity for emphasizing overall standards of care in this segment.

**FIGURE 2** Management of Menopause Survey Scores Reported in 2000

![Bar chart showing survey scores reported in 2000](source: NCQA 2001 for reporting year 2000)

**DISCLOSURES**

Gary M. Owens discloses that Advanced Concepts Institute provided the support for this study, which was restricted to assistance in the research and writing of this article. Owens is a consultant to Amgen, Wyeth, Lilly, Novartis, Ortho Biotech, Collagenex, and Genentech. Owens was responsible for the entire study concept and design of this article. He performed all the data collection, data interpretation, writing, and revision of this article.

**REFERENCES**

Gender Differences in Health Care Expenditures, Resource Utilization, and Quality of Care


Evolving Issues in the Clinical and Managed Care Settings on the Management of Menopause Following the Women’s Health Initiative

Andrea Lukes, MD, MHSc

ABSTRACT

BACKGROUND: Publication of the Women’s Health Initiative (WHI) trial results in 2002 significantly reduced physician and patient confidence in and acceptance of hormone replacement therapy (HRT) as an appropriate treatment option for menopause-associated vasomotor symptoms (VMS). This was true despite the fact that the WHI trial was a primary prevention study conducted in postmenopausal women and was not designed to evaluate the efficacy of HRT in the treatment of VMS.

OBJECTIVE: To review data from the WHI, including recent analyses, demonstrating the risks and benefits of HRT in postmenopausal women, to describe changes in menopause treatment guidelines and HRT use since publication of early WHI results nearly 6 years ago, and to identify opportunities for improving the quality of care in perimenopausal women.

SUMMARY: Early results from the WHI demonstrated that the risks of long-term HRT in postmenopausal women outweighed the benefits, leading study investigators to conclude that HRT should not be initiated or continued for the primary prevention of coronary heart disease (CHD) in postmenopausal women. Treatment guidelines published by several professional and managed care organizations continue to advocate the use of HRT for treatment of moderate-to-severe VMS. Nevertheless, physician and patient confidence in HRT has declined, as evidenced by a decrease in new HRT prescriptions and an increase in the discontinuation rate of HRT immediately following publication of the preliminary WHI results. Recent analyses demonstrate that the risk for CHD in postmenopausal women is largely dependent upon the age of the woman and the number of years since menopause, with a lower risk for CHD in women aged 50 to 59 years and in women who experienced menopause within the previous 10 years. The highest risk for CHD was evident in women aged 70 to 79 years and in women who experienced menopause 20 or more years ago. Although these data do not support the use of HRT as a primary prevention strategy in postmenopausal women, they do suggest the need to further evaluate the benefits and risks of HRT in perimenopausal women based on patient-specific characteristics, including age and time since menopause.

CONCLUSION: Menopausal women present a unique opportunity for health care providers to improve the quality of care among women, not only as it relates to the treatment of VMS, but also as it relates to osteoporosis and cardiovascular disease, 2 common comorbidities in perimenopausal and postmenopausal women.

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Introduction

The use of hormone replacement therapy (HRT), the gold standard in the management of moderate-to-severe menopause-associated vasomotor symptoms (VMS) (i.e., hot flashes, night sweats),

VO has received increased media attention and has been debated among the health care community since the early results of the Women’s Health Initiative (WHI) were published in 2002.

Further, results from the Heart and Estrogen/Progestin Replacement Study Follow-Up (HERS II) and the Million Women Study were released, adding more evidence that HRT in postmenopausal women may do more harm than good, as evidenced by increased risks of breast cancer and venous thromboembolism, and the absence of a cardioprotective effect.

Since these data were published in 2002-2004, researchers have continued to analyze the data from the WHI to determine if the observed deleterious effects of HRT are limited to a specific subset of women. The purpose of this article is to (1) review data from the WHI, including recent analyses, demonstrating the risks and benefits of HRT in postmenopausal women; (2) to describe changes in menopause management guidelines and HRT use since the publication of the WHI results; (3) to summarize management guidelines for conditions related to menopause; and (4) to identify opportunities for improving the quality of care in perimenopausal women.

Women’s Health Initiative

Study Design

The WHI was a multiphase, multicenter, randomized, double-blind, placebo-controlled, primary prevention trial started in 1993 that was designed to evaluate the efficacy and safety of (1) a low-fat diet; (2) HRT (2 parallel studies of estrogen [0.625 mg conjugated equine estrogen] plus progestin [2.5 mg medroxyprogesterone acetate] in women with a uterus or estrogen alone in women who had a hysterectomy); and (3) calcium and vitamin D supplementation.

Each of these interventions was aimed at reducing specific morbidities (i.e., diet: breast and colorectal cancers and CHD; HRT: CHD, other cardiovascular disease [CVD], and hip and other fractures; calcium and vitamin D: hip and other fractures and colorectal cancer). Importantly, this trial was not designed to evaluate the benefits or risks of HRT when used for management of menopause-associated VMS. Postmenopausal women aged between 50 and 79 years who did not have a history of breast cancer were eligible for inclusion in the study. The first phase of the study was a controlled clinical trial in which subjects were randomized to the diet study or to the HRT study. After 1 year of study participation, subjects were eligible for inclusion in the calcium plus vitamin D
study. Women deemed ineligible for the controlled clinical trial, and those unwilling to enroll, were eligible to participate in the observational arm of the study. The planned average follow-up period was 9 years. The remainder of the discussion of the WHI will focus on the HRT study.

Objectives
The primary objective of the HRT study was prevention of CHD events, defined as acute nonfatal myocardial infarction (MI), (definite or probable) requiring hospitalization, silent MI, or CHD death. Secondary objectives were measures of other CVD, hip or other fractures, and endometrial (in women with a uterus), colorectal, or other cancers. Invasive breast cancer was identified as a primary adverse outcome. A global index, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes, was used to measure the relative risk to benefit ratio of HRT.

Results

**Evolving Issues in the Clinical and Managed Care Settings on the Management of Menopause Following the Women’s Health Initiative**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Absolute Risk (No. per 10,000 Person Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estrogen + Progestin Vs. Placebo</td>
<td>Estrogen + Progestin (N=8506)</td>
</tr>
<tr>
<td>coronary heart disease events</td>
<td>1.24 (1.00-1.54)</td>
<td>39</td>
</tr>
<tr>
<td>nonfatal myocardial infarction</td>
<td>1.28 (1.00-1.63)</td>
<td>31</td>
</tr>
<tr>
<td>coronary heart disease deaths</td>
<td>1.10 (0.70-1.75)</td>
<td>8</td>
</tr>
<tr>
<td>all strokes</td>
<td>1.31 (1.02-1.68)</td>
<td>31</td>
</tr>
<tr>
<td>ischemic stroke</td>
<td>1.44 (1.09-1.90)</td>
<td>26</td>
</tr>
<tr>
<td>deep vein thrombosis</td>
<td>1.95 (1.43-2.67)</td>
<td>26</td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td>2.13 (1.45-3.11)</td>
<td>18</td>
</tr>
<tr>
<td>invasive breast cancer</td>
<td>1.24 (1.01-1.54)</td>
<td>41</td>
</tr>
<tr>
<td>invasive colorectal cancer</td>
<td>0.56 (0.38-0.81)</td>
<td>9</td>
</tr>
<tr>
<td>endometrial cancer</td>
<td>0.81 (0.48-1.36)</td>
<td>6</td>
</tr>
<tr>
<td>total fracture</td>
<td>0.76 (0.69-0.83)</td>
<td>152</td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.67 (0.47-0.96)</td>
<td>11</td>
</tr>
<tr>
<td>total mortality</td>
<td>0.98 (0.82-1.18)</td>
<td>52</td>
</tr>
<tr>
<td>global index</td>
<td>1.15 (1.03-1.28)</td>
<td>170</td>
</tr>
</tbody>
</table>

a Final, centrally adjudicated data after a mean follow-up of 5.6 years, unless otherwise noted.
b Nominal (unadjusted) confidence intervals.

Includes silent myocardial infarction.

d Data not centrally adjudicated; mean follow-up = 5.2 years.

e Global index = the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

Data from References 4, 10-15, and 45.
Evolving Issues in the Clinical and Managed Care Settings on the Management of Menopause Following the Women’s Health Initiative

Table 2 Relative and Absolute Risks of Major Clinical Outcomes in the Estrogen Alone Substudy of the Women’s Health Initiative

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Absolute Risk (No. per 10,000 Person Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estrogen (N = 5310)</td>
<td>Placebo (N = 5429)</td>
</tr>
<tr>
<td>Coronary heart disease events</td>
<td>0.95 (0.79-1.16)</td>
<td>53</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.91 (0.73-1.14)</td>
<td>40</td>
</tr>
<tr>
<td>Coronary heart disease deaths</td>
<td>1.01 (0.71-1.43)</td>
<td>16</td>
</tr>
<tr>
<td>All strokes</td>
<td>1.37 (1.09-1.73)</td>
<td>45</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.55 (1.19-2.01)</td>
<td>38</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.47 (1.06-2.06)</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.37 (0.90-2.07)</td>
<td>14</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.80 (0.62-1.04)</td>
<td>28</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75-1.55)</td>
<td>17</td>
</tr>
<tr>
<td>Total fracture</td>
<td>0.71 (0.64-0.80)</td>
<td>144</td>
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<tr>
<td>Hip fracture</td>
<td>0.65 (0.45-0.94)</td>
<td>12</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.04 (0.88-1.22)</td>
<td>81</td>
</tr>
<tr>
<td>Global index</td>
<td>1.01 (0.91-1.12)</td>
<td>192</td>
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</tbody>
</table>

**Table 2** Relative and Absolute Risks of Major Clinical Outcomes in the Estrogen Alone Substudy of the Women’s Health Initiative

- **Estrogen Alone in Women Without a Uterus**

A total of 10,739 women were included in the estrogen alone (N = 5,310) versus placebo (N = 5,429) study. Baseline characteristics were similar between treatment groups. The mean age was 63.6 years at baseline, 75% of participants were Caucasian, and mean body mass index was 30.1 kg/m². Patients were considered to be at average risk for CHD and breast cancer.

As in the HRT arm in women with a uterus, the HRT arm in women without a uterus was also stopped early, after an average follow-up of 6.8 years. However, unlike the HRT arm in women with a uterus, which was discontinued at the recommendation of the independent data and safety monitoring board because of health risks, the HRT arm in women without a uterus was discontinued by the National Institutes of Health (NIH), the sponsors of the study. It was believed that no additional benefits or risks of estrogen therapy would be demonstrated if the study continued for the final planned year, and it was not considered acceptable to subject the study participants to the increased risk of stroke that had been identified during earlier interim analyses.

Estrogen therapy was associated with significant increases in the risks of stroke (primarily nonfatal ischemic stroke) and DVT (Table 2). Nonsignificant increases in the risks of PE and colorectal cancer were also observed as were significant reductions in total fractures and hip fractures and nonsignificant reductions in the risks for CHD and breast cancer. The reduced risk of breast cancer in women treated with estrogen was an unexpected finding and contrasts the findings in women with a uterus who were treated with estrogen plus progesterin. The HR for the global index, a measure of the relative risk-to-benefit ratio, was 1.01 (95% CI, 0.91-1.12), indicating neutrality. Interestingly, the HR for CHD was slightly higher in the estrogen arm than in the placebo arm.
early in the study but gradually declined with time. By the end of the follow-up period, the HR for CHD was lower in the estrogen group than in the placebo group; however, this difference did not reach statistical significance at any time during the study. Analysis of risk for CHD events by presence (HR, 1.12; 95% CI, 0.69-1.80) or absence (HR, 0.93; 95% CI, 0.75-1.15) of CHD at baseline revealed no significant difference in the risk of future CHD events (P = 0.33).19

Between-group differences in the cumulative HRs for stroke and hip fracture became apparent early in the study, whereas differences in the cumulative HR for breast cancer became apparent at 2 years; all continued to diverge throughout the follow-up period.9 No apparent between-group differences in cumulative HRs were observed for CHD, PE, colorectal cancer, death, or the global index. The statistical analysis did not show any benefit from HRT in terms of CHD; therefore, as in the estrogen plus progesterin arm in women with an intact uterus, the authors concluded that long-term estrogen therapy should not be initiated or continued for the primary prevention of CHD in postmenopausal women without a uterus.9

**Clinical Implications**

The results of the WHI led health care providers and patients to change the way they prescribed and used HRT, respectively. These changes occurred despite continued recommendation from professional societies, such as the American Association of Clinical Endocrinologists (AACE)1 and the North American Menopause Society (NAMS),2,3 managed care organizations,21 and FDA-approved product labeling of available therapies to use HRT at the lowest effective dose for the shortest duration possible for the management of moderate-to-severe menopause-associated VMS. These organizations recognized that the patient population included in the WHI was not representative of the typical menopause patient, as women in the WHI were older and postmenopausal. Thus, they did not change their recommendations for HRT for the management of VMS in menopausal women based on the results of the WHI study; however, they did caution against the use of HRT as a primary or secondary CHD prevention strategy.1,2,21

Major changes were evident in the preferences and prescribing patterns of health care providers following release of the results from the WHI. Results from several small surveys revealed a more conservative approach to HRT among family practitioners and internists than among gynecologists following the WHI.22,23 In fact, gynecologists, especially those who completed their residency prior to 1994, expressed a high degree of skepticism about the results of the WHI, held a stronger belief in the benefits of HRT, and were less concerned about the risks of HRT.22,24,25

A nationwide survey that combined results from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey evaluated changes over time in the number and rate of physicians’ office visits that included a prescription for HRT between 2001 and 2003.26 Office visits for HRT among women aged 40 years and older declined significantly between 2001 and 2003, from a high of 41.4% in 2001, to 32.7% in 2002, to 26.0% in 2003 (P = 0.002).26 These changes translate into a reduction in the number of office visits during which a prescription for HRT was written from 26.5 million visits in 2001 to 16.9 million visits in 2003 (P < 0.002). Similar findings were observed in an evaluation of the National Disease and Therapeutic Index database, which tracks the number of physicians’ office visits during which a prescription is written, and the National Prescription Audit database, which tracks the number of prescriptions filled at retail pharmacies. Between 1995 and 2001, there was a gradual increase in the number of prescriptions of HRT dispensed in the United States from 58.3 million in 1995 to 91.0 million in 2001.27 Between 2001 and 2003, however, the annual number of prescriptions for HRT fell to 56.9 million (2003 figures annualized based on January 2003–July 2003 data), a more dramatic decline than the increase observed during the preceding 6 years. Prescription data from 5 health maintenance organizations (HMOs) showed that the decline in the total number of prescriptions for HRT between September 1999–June 2002 and December 2002, was a consequence of both a significant increase in prescription discontinuations and a significant decrease in the number of new prescriptions written with changes becoming evident immediately following publication of the preliminary results of the WHI.28

The widespread release of the results of the WHI included patients as a target audience. Study results were disseminated via NIH press releases (www.nhlbi.nih.gov/whi/press_releases.htm), patient education materials developed for managed care members,21 mass media, and health care providers.29 Results from a telephone survey of 670 women in 1 HMO revealed that most patients (93%) had heard about the WHI findings, but less than one-quarter (23%) actually knew what the study results were.29 Despite the apparent lack of understanding of the benefits and risks of HRT, 56% of women surveyed attempted to discontinue their HRT within 6 to 8 months after study publication. Patients whose HRT was prescribed by their gynecologist were more likely to attempt to discontinue therapy (59.6%) than those whose HRT was prescribed by their primary care provider (49.3%).29 This finding conflicts with the more conservative view of HRT among family practitioners and internists than among gynecologists described above.22,23

**Study Limitations**

The WHI investigators acknowledge the evaluation of a single dose of a single formulation of estrogen (0.625 mg conjugated equine estrogen), with or without a single dose of progestin (2.5 mg medroxyprogesterone acetate), via a single route of administration (oral) as a limitation of the WHI.19 Thus, the study design does not allow the results to be extrapolated to other doses, formulations, or routes of administration of estrogen (with or without progestin). Other limitations identified by the authors include higher than expected drop-in and drop-out rates, early discontinuation of the 2 study arms, which preclude accurate assessment of long-term
effects, and the inability to distinguish the effects of estrogen from those of progestin in the combination therapy study in women with a uterus.

A major limitation of the study design was the patient population. The WHI enrolled older, postmenopausal women, with an average age of 63 years at baseline. This patient population is thought to be at increased risk for subclinical CHD relative to younger, perimenopausal women, a hypothesis supported by the presence of increasingly higher prevalence of CHD risk factors and pre-existing CVD with increasing age and years since menopause in WHI participants. Subgroup analyses of risk of CHD events by age revealed a nonsignificant trend toward a reduction in risk among women aged 50 to 59 years treated with estrogen alone (HR, 0.63; 95% CI, 0.36-1.08), with less of a benefit in women aged 60 to 69 years (HR, 0.94; 95% CI, 0.71-1.24); the highest risk was in women aged 70 to 79 years (HR, 1.11; 95% CI, 0.82-1.52) (P value for interaction = 0.07). Although this trend was not mirrored in women treated with estrogen plus progestin (HR, 1.27, 1.05, and 1.44, respectively), a similar trend was observed when women were grouped by years since menopause. In women treated with estrogen plus progestin who experienced menopause within the previous 10 years, the HR for CHD events was 0.89; in women who had experienced menopause 10 to 19 years ago, or 20 or more years ago, the risk was higher (HR, 1.22 and 1.71, respectively) (P value for interaction = 0.33). A secondary analysis of the WHI combined both arms of the HRT study and evaluated the risk of CHD in relation to age and years since menopause. Similar, nonsignificant trends were evident in the combined analysis. When analyzed by age at baseline, HRs were 0.93, 0.98, and 1.26, respectively, in women aged 50 to 59 years, 60 to 69 years, and 70 to 79 years (P value for trend = 0.16). When analyzed by years since menopause (<10, 10-19, ≥20), HRs were 0.76, 1.10, and 1.28, respectively (P value for trend = 0.02). Although only studying a surrogate marker and not a clinical outcome, results from the WHI Coronary-Artery Calcium analysis suggest a benefit of estrogen therapy in preventing heart disease in women aged 50 to 59 years at study enrollment. Coronary calcification correlates well with the extent of underlying atherosclerosis and the risk of future cardiovascular events. Treatment lasted a mean of 7.4 years and imaging occurred at a mean of 1.3 years after the end of the trial. Women randomly assigned to receive estrogen had significantly less coronary-artery calcification than women randomly assigned to placebo. Collectively, these data support the need to weigh the benefits and risks of HRT in menopausal women based on patient-specific characteristics, including age and time since menopause. They do not support a one-size-fits-all approach to HRT.

Management of Conditions Related to Menopause

The role of HRT in the management of menopause-associated VMS has been reviewed. Briefly, the AACE and NAMS recommend the use of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus) at the lowest effective dose for the shortest duration possible for the management of VMS. They do not advocate the use of HRT for the primary or secondary prevention of CHD. CVD and osteoporosis are common conditions in menopausal and postmenopausal women, and the menopausal transition creates a unique opportunity to initiate preventive or treatment strategies in these women.

Cardiovascular Disease

CVD is the leading cause of death among women in the United States. By age group, it is the second leading cause of death among women aged 45 to 64 years, second only to cancer, and is the leading cause of death among women aged 65 years and older. Preventive strategies include lifestyle modifications (e.g., diet, weight loss, exercise, smoking cessation), and appropriate management of underlying risk factors, such as obesity, especially abdominal obesity, hypertension, dyslipidemia, insulin resistance, and diabetes through nonpharmacologic and pharmacologic intervention, as necessary. The AACE suggests that HRT, specifically estrogen therapy, may offer some clinical benefit in women without CHD who are in the early stages of menopause (i.e., within 5 years of symptom onset), but should not be used in older postmenopausal women (i.e., those whose symptom onset occurred ≥5 years ago) or in women with pre-existing CHD.

Osteoporosis

Osteoporotic bone loss is a common occurrence that affects an estimated 55% of Americans aged over 50 years. Osteoporosis affects women at a disproportionately higher rate than men, with women accounting for 80% of cases. Osteoporosis increases the propensity for falls and fractures, the latter of which are estimated to occur 3 times as frequently in women as in men.

Both the AACE and the NAMS advocate a diet rich in calcium and vitamin D, regular weight-bearing exercise, smoking cessation, limited alcohol consumption, and in certain patients, a bisphosphonate (e.g., alendronate, risedronate, ibandronate) for the prevention of osteoporosis. Results from the WHI showed that calcium and vitamin D supplementation in healthy postmenopausal women resulted in a small but significant improvement in hip bone density; however, supplementation did not significantly reduce the incidence of hip fractures. Furthermore, supplementation increased the risk of kidney stones. Pharmacologic treatment options include HRT, bisphosphonates, selective estrogen receptor modulators (e.g., raloxifene), salmon calcitonin, and teriparatide (recombinant human parathyroid hormone). Readers are encouraged to consult the AACE and NAMS guidelines for a detailed explanation of benefits, risk, and dosing considerations for these agents.

Opportunities for Improving Quality of Care in Perimenopausal Women

The uncertainty about the benefits and risks of HRT that followed the initial release of the WHI results may be confounded by the...
Evolving Issues in the Clinical and Managed Care Settings on the Management of Menopause Following the Women’s Health Initiative

more recent finding that the risks of HRT may correlate with age of onset of menopausal symptoms or years since menopause. Although patient education initiatives followed publication of the initial WHI results, it is clear that continued education on VMS and its management is needed. In fact, in the telephone survey of 670 women described earlier, only 57% considered the quality of information they received about the WHI to be good and only 23% actually knew what the study results were. However, the need for improved education about HRT was apparent well before the WHI study results were published. In fact, the Commission on Women’s Health, a 5-year initiative aimed at increasing public awareness of women’s health issues and the quality of health care, found that only 34% of women aged 50 years and older were receiving HRT in 1998, an increase from 23% in 1993. This undertreatment was accompanied by a lack of appropriate counseling on HRT. In fact, of the 2,850 women surveyed, only 38% reported receiving counseling from their health care provider on HRT within the previous year. These results support the findings of a smaller Gallup survey of 833 women aged 45 to 60 years conducted in 1993, in which only 36% of respondents reported receiving the majority of their information about menopause from their physician and 69% reported being somewhat or very satisfied with the information they received. Of the women surveyed, 84% reported that their physician had discussed HRT with them, but only 42% reported using HRT to relieve menopausal symptoms. Results from the Management of Menopause survey in 2000 provided further evidence of the need to provide additional counseling on the treatment of menopause, as evidenced by a 73% exposure score, a 52% breadth score, and a 33% quality score.

Not only does menopause present an opportunity for primary care practitioners and gynecologists to educate women on the symptoms and management of typical menopause-associated symptoms, such as VMS, it also presents an opportunity to educate women on preventive care strategies for CVD, osteoporosis, and diet and weight management. The fact that breast cancer risk only developed 4 years of treatment in the estrogen plus progestin arm of the WHI and not at all in the estrogen alone arm should put some patients and health care providers at ease about using HRT for short periods to prevent VMS. The need for improved education on these topics was demonstrated in the Commission on Women’s Health Initiative described in the previous text. In 1998, a mere 36% of women surveyed reported being very familiar with osteoporosis compared with 30% of women surveyed in 1993. The number of women who reported receiving counseling on exercise, diet/weight, calcium intake, and smoking cessation from their physician within the previous year averaged 49%, 46%, 41%, and 29%, respectively, in 1998. In 2004, there was only a 19% compliance rate among Medicare plans with the HEDIS measure of osteoporosis management in women aged 67 years and older. This metric required a bone mineral density test or a prescription for an agent for osteoporosis in women who had had a fracture. Thus, quality of care improvements, including improved counseling and early implementation of preventive and treatment strategies, may lead to improvements in several HEDIS measures, including osteoporosis management in women who had a fracture, fall risk management, osteoporosis testing in older women, control of high blood pressure, cholesterol management for patients with cardiovascular conditions, medical assistance with smoking cessation, and physical activity in older adults.

Conclusions

Publication of the preliminary results of the WHI led to significant changes in the management of menopausal symptoms over the past several years. Recent analyses challenge the preliminary results, citing differences in risk of CHD based on age and years since menopause. Additional studies are warranted to determine the effect of HRT on CHD risk in those women beginning menopause in whom HRT is considered the standard of care for treatment of moderate-to-severe VMS. Women of menopausal age are at increased risk for CVD and osteoporosis, and data suggest that the quality of care for all 3 of these conditions is lacking. Thus, menopause presents a unique opportunity for health care providers to channel women seeking treatment for their menopausal symptoms into a preventive or treatment program for CVD and/or osteoporosis, as necessary. Such a proactive approach may lead to improvements in several HEDIS measures for CVD and osteoporosis.

DISCLOSURES

Andrea Lukes discloses that there was no financial relationship or financial interest relating to the topic of this activity. Lukes has received research/grant support from CDC/APTR, Xanodyne, AMS, Ethicon, and Cytyc, and is a consultant to Xanodyne, AMS, Cytyc, Daiichi, and Conceptus. Lukes was responsible for the entire study concept and design of this article. She performed all the data collection, data interpretation, writing, and revision of this article.

REFERENCES


**Treatment Strategies for Reducing the Burden of Menopause-Associated Vasomotor Symptoms**

Elena M. Umland, PharmD

**ABSTRACT**

BACKGROUND: Vasomotor symptoms (VMS), such as hot flashes and night sweats, are the most bothersome symptoms of menopause and affect an estimated 75% of women aged over 50 years.

OBJECTIVE: To discuss the burden, pathophysiology, and management of menopause-associated VMS and to evaluate pharmacologic options available for the treatment of VMS, including herbal remedies, hormone replacement therapy (HRT), and nonhormonal therapies.

SUMMARY: Lifestyle changes, including regulation of core body temperature, relaxation techniques, regular physical activity, weight loss, and smoking cessation may help reduce the risk of VMS and should be implemented by all women with menopause-associated VMS. The role of herbal remedies in the treatment of VMS remains unclear, as clinical trial efficacy data are inconsistent and inconclusive. Nevertheless, soy isoflavones, red clover isoflavones, black cohosh, and vitamin E are commonly used to treat VMS and may be considered in women with mild symptoms that are not controlled by lifestyle changes alone. These herbal remedies appear to be safe when used for short durations (≤ 6 months). HRT, consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus) is the most widely studied and most effective treatment option for relief of menopause-associated VMS and is considered the standard of care for women with moderate-to-severe VMS. HRT should be used at the lowest effective dose and for the shortest duration possible (preferably ≤ 5 years) in women in whom the potential benefits outweigh the potential risks. Nonhormonal therapies, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, and clonidine, may be appropriate alternatives in women who cannot or will not use HRT for VMS relief, such as those with a history of or at risk for breast cancer.

CONCLUSION: The physical and financial burden imposed by menopause-associated VMS is immense. Optimum management of VMS includes lifestyle changes in all women and HRT in women with moderate-to-severe symptoms. Less effective herbal remedies or nonhormonal therapies may be appropriate in certain women, such as those with mild symptoms or those who cannot or will not take HRT.

**Introduction**

Menopause, the cessation of menses that results from loss of ovarian hormone secretion, affects all women. Menopause can occur naturally or be induced through surgery, chemotherapy, or pelvic radiation. When menopause occurs naturally, it generally affects women aged 40 to 58 years (median onset of menopausal transition: 47.5 years), although premature menopause (i.e., menopause that occurs in women aged < 40 years) may occur. Menopause is a term that is often used to describe perimenopause or the menopausal transition when in fact it refers to a specific point in time. Menopause does not technically occur until 12 months after the last menstrual period. The time frame leading up to the last menstrual period, during which menstrual and hormonal changes occur, is termed perimenopause or the menopausal transition, and typically lasts for several years (average: 4 years) before the final menstrual period (Figure). Postmenopause is the term used to define the time period after the occurrence of the final menstrual period; it begins with the final menstrual period and ends with death. Symptoms of perimenopause include irregular menstrual periods, vasomotor symptoms (VMS) (i.e., hot flashes [rapid onset of intense heat sensation, sweating, and flushing lasting approximately 5-10 minutes], night sweats), sleep disturbances, vulvovaginal atrophy (e.g., dryness, itching, burning), sexual dysfunction, and mood disturbances. Of these, VMS are the most bothersome and are the main focus of menopausal treatment guidelines. The purpose of this review is to discuss the burden, pathophysiology, and management of menopause-associated VMS and to evaluate pharmacologic options available for the treatment of VMS.

**Vasomotor Symptoms**

**Physical and Financial Burden**

Although all women will eventually go through the menopausal transition, not all women will experience symptoms other than cessation of menstruation. As previously stated, VMS are the most bothersome symptoms of the menopausal transition. In fact, VMS are the leading reason why women seek medical attention for menopause. The top 4 reasons for seeking medical attention identified in a 2002 Gallup poll of menopausal women were hot flashes (70%), night sweats (68%), mood disturbances (50%), and sleep disturbances (49%). These data are supported by results of a more recent poll, which showed that 60% of peri- and postmenopausal women sought care for their menopausal symptoms.

It is estimated that 75% of women aged over 50 years experience hot flashes; however, the prevalence of VMS varies considerably with menopausal status and ethnicity. In fact, VMS is estimated to affect 14% to 51% of premenopausal women, 35% to 50% of perimenopausal women, and 30% to 80% of postmenopausal women. In a community-based survey of 16,065 women aged....
40 to 55 years conducted between 1995 and 1997, the prevalence of VMS, defined as hot flashes and/or night sweats, was found to be highest among African-American women (45.6%), followed by Hispanic-Americans (35.4%), Caucasians (31.2%), Chinese-Americans (20.5%), and Japanese-Americans (17.6%). These rates were mirrored by a more recent longitudinal study of 3,198 women followed from 1996 to 2002, in which the risk of VMS was highest among African-Americans (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.21-2.20; \( P<0.01 \) vs. Caucasians). Prevalence rates were lowest among Hispanic-Americans, followed by Chinese-Americans and Japanese-Americans. Other factors that were found to increase a woman's risk for VMS included age, higher body mass index, having less than a college education, smoking, baseline anxiety, and baseline depression. On average, most women experience VMS for 6 months to 2 years; however, approximately 10% of women report experiencing VMS for 10 or more years.

According to U.S. census data, there are more than 48 million American women aged over 50 years, and nearly 60 million women aged 45 years and over. Considering the fact that all these women will go through menopause, 75% of them will experience VMS, and 60% of them will seek medical attention for their symptoms. It isn't surprising that the financial burden of VMS is immense. Direct costs incurred by women with menopause-associated VMS include initial and follow-up physician office visits and telephone calls, which may include visits to specialists (e.g., psychologist, psychiatrist, neurologist), as well as primary care physicians or gynecologists, prescription, and over-the-counter (OTC) medications, dietary supplements, and laboratory tests. Indirect costs include loss of productivity at home or at work, hygiene-related supplies, increased energy usage for air conditioning and laundry, and management of treatment-related adverse events. One cost-effectiveness comparison estimated the yearly cost of VMS management to average $681 to $848 per patient per year.

Pathophysiology
There is currently no consensus on the pathophysiology of menopause-associated VMS; however, many hypotheses have been proposed. One proposed mechanism for hot flashes is a narrowing of the thermoregulatory threshold between sweating and shivering in the hypothalamus. This narrowing is thought to be caused by changes in the levels of circulating serotonin (decreasing concentration), norepinephrine (increasing concentration), or estrogen (decreasing concentration). The postmenopausal decline in ovarian estradiol production results in diminished negative-feedback effects on the anterior pituitary, leading to a compensatory increase in the secretion of luteinizing hormone from the pituitary, a process regulated by gonadotropin-releasing hormone in the hypothalamus. Pulsatile surges of gonadotropin-releasing hormone due to estrogen deficiency affect the hypothalamic neurons that control central thermoregulation centers.

It has also been hypothesized that the ratios of the specific types of estrogen (i.e., estradiol or estrone) may be better correlated with the occurrence of VMS than the overall circulating level of estrogen. Estrone, which is much lower in potency than estradiol, is the most abundant circulating estrogen in postmenopausal women. In premenopausal women, estradiol is the more abundant estrogen. Further, the occurrence of VMS has been found to correlate better with an acute decline in estrogen levels than with the actual measured levels of estrogen.

In addition to the impact of the change in the relative amounts of estradiol and estrone, another hypothesized contributor to VMS is the actual function of the available circulating estrogen. For example, the cytochrome p450 isoenzyme CYP1A1 is responsible for the hydroxylation of estrone and estradiol, forming hydroxyestrone (2HE). 2HE binds very weakly to the estrogen receptor. The relative amounts of the more potent estradiol is also affected by 17β-hydroxysteroid dehydrogenase (17HSD). The enzyme responsible for the bidirectional conversion of the less potent estrone and the more potent estradiol. Alterations in the estrogen receptors ERα and ERβ may also negatively affect the biologic activity of estrogen. It has been shown in one study that single nucleotide polymorphisms (SNPs) in the genes encoding estrogen-metabolizing enzymes (i.e., CYP1A1, CYP1B1, 17HSD) or ERs are associated with prevalence of VMS, and these polymorphisms correlate with ethnic differences in VMS prevalence noted previously. Additional studies are needed to confirm these results and further clarify the pathophysiology of VMS.

Treatment of Vasomotor Symptoms

Treatment guidelines, consensus statements, or position statements for the management of menopausal symptoms have been published by a number of professional societies in the United States and internationally. One recent published guideline was developed in cooperation with the Menopause and Osteoporosis Foundation (MOF), the North American Menopause Society (NAMS), and the North American Menopause Society Practice: A Clinician’s Guide. Section A: Overview of menopause and aging. Available at: www.menopause.org/educationalmaterials/studyguide/A.pdf.
States, including the North American Menopause Society (NAMS) in 2007, with a position statement dedicated specifically to the management of VMS in 2004, the American Association of Clinical Endocrinologists (AACE) in 2006, and the American College of Obstetricians and Gynecologists (ACOG) in 2004. This section will focus specifically on the treatment of menopause-associated VMS and will not address treatment of other menopause-associated symptoms, such as vulvovaginal atrophy, sleep disturbances, sexual dysfunction, or mood disturbances.

### Lifestyle Changes

Lifestyle changes should be implemented by all women with menopause-associated VMS. Interventions that help regulate core body temperature include wearing lightweight cotton clothing, dressing in layers, using fans or air conditioning, consuming cool or cold foods and drinks, and avoiding hot foods and drinks. Regular physical activity, weight loss, and smoking cessation may also reduce the risk of VMS; however, the efficacy of these endeavors has not been evaluated. Relaxation techniques may also provide relief of VMS; however, only paced respiration (i.e., slow, controlled, diaphragmatic breathing) has been proven effective in clinical trials.

### Pharmacologic Interventions

#### Herbal Remedies

According to NAMS, women with mild VMS that are not controlled by lifestyle changes may consider treatment with an herbal remedy, such as isoflavone supplements (i.e., soy, red clover), black cohosh, or vitamin E. However, it is important to note that this suggestion is not a consensus recommendation as efficacy data are inconclusive. This suggestion is based primarily on the fact that these herbal remedies have not been associated with serious side effects when used for short durations (i.e., ≤6 months). The AACE acknowledges that these herbal preparations are used for the management of VMS but does not advocate for or against their use. They do, however, caution about the lack of standardization and regulation of herbals, and the potential of herbals to interact with other medications and medical conditions. The ACOG does not recommend the use of these herbal remedies, citing lack of significant effects on VMS. The exact mechanism(s) by which herbal remedies reduce the frequency of VMS is unknown. Dosing recommendations for isoflavones, black cohosh, and vitamin E are listed in Table 1. Other herbal remedies, such as wild yam extract, natural progesterones, dong quai, primrose oil, ginseng, licorice, and Chinese herbal mixture are not recommended because of a lack of efficacy data.

#### Hormone Replacement Therapy

Hormone replacement therapy (HRT), consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus [to protect against endometrial hyperplasia or cancer]), is the most widely studied and most effective treatment option for relief of menopause-associated VMS and is considered the standard of care for women with moderate-to-severe VMS. The AACE, ACOG, and NAMS recommend the use of HRT at the lowest effective dose and for the shortest duration possible (preferably ≤5 years) in women for whom the potential benefits outweigh the potential risks (Table 2). The 5-year cut-off for HRT is suggested because most women will experience spontaneous cessation of menopausal symptoms within 5 years of onset. Use of HRT for longer durations may be appropriate in some women, such as those who judge the benefits of VMS relief to outweigh the potential risks after failing an attempt to discontinue HRT, those with continued VMS who are also at high risk for osteoporotic fractures, and those requiring osteoporosis prevention who cannot take alternate therapies. Several weeks may be required to determine the efficacy of HRT in treating VMS. There is currently no consensus on whether to discontinue HRT abruptly, to gradually taper the dose downward, or to lengthen the time between doses. Contraindications to the use of HRT are listed in Table 3.

Estrogen and progestin are both available in various oral, transdermal, vaginal, and injectable preparations, as well as in

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**TABLE 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
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<tbody>
<tr>
<td><strong>Herbal Remedies</strong></td>
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<tr>
<td>Isoflavone</td>
<td>40 mg-80 mg</td>
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<tr>
<td>Black cohosh</td>
<td>40 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>800 IU (divided)</td>
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<tr>
<td><strong>Estrogens</strong></td>
<td></td>
</tr>
<tr>
<td>Conjugated equine estrogens</td>
<td>0.3 mg-0.625 mg</td>
</tr>
<tr>
<td>Micronized 17β-estradiol</td>
<td>0.25 mg-1 mg</td>
</tr>
<tr>
<td>Transdermal estradiol</td>
<td>14 μg-100 μg</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>0.01 mg-0.02 mg</td>
</tr>
<tr>
<td>Vaginal estradiol ring</td>
<td>0.05 mg-0.1 mg</td>
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<tr>
<td><strong>Progestins</strong></td>
<td></td>
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<tr>
<td>Medroxyprogesterone acetate</td>
<td>2.5 mg (or 5 mg for 10-14 days/month)</td>
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<tr>
<td>Micronized progesterone</td>
<td>100 mg (or 200 mg for 10-14 days/month)</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>0.35 mg (or 5 mg for 10-14 days/month)</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>0.075 mg</td>
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<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>20 mg</td>
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<tr>
<td>Paroxetine</td>
<td>12.5 mg-25 mg</td>
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<tr>
<td>Venlafaxine</td>
<td>75 mg</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900 mg (divided)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1 mg orally daily or 1 transdermal patch per week (equivalent to 0.1 mg daily)</td>
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</tbody>
</table>

Data from References 2, 3, and 9.
combination products. In women with an intact uterus, progestin may be used continuously (daily) or cyclically (10-14 days per month). Cyclic progestin administration produces monthly menstruation. Although continuous progestin administration does not produce this, women may experience periodic breakthrough bleeding. Administration of estradiol via transdermal patches eliminates first-pass metabolism of estradiol to the less active estrone and maintains more constant blood levels as a result of sustained release. Transdermal administration results in an estrone to estradiol ratio of approximately 1 to 1, which closely resembles the premenopausal state. There is an absence of rigorous evidence from large-scale, prospective, randomized, double-blind clinical trials on differential effects by hormone formulation or route of delivery. Women needing VMS suppression and contraception may be effectively treated with low-dose oral contraceptives. Women who are unwilling to use estrogen but who are willing to use other hormone therapy may be treated with a progestin alone. The combination of estrogen plus an androgen should be reserved for women with symptoms of androgen deficiency or those whose VMS persist despite adequate estrogen therapy. Dosing recommendations for commonly used oral and transdermal estrogen and progestin preparations are listed in Table 1.

Nonhormonal Therapy

Nonhormonal therapies, such as antidepressants, anticonvulsants, and antihypertensives, have been used for relief of VMS; however, these drugs are not FDA-approved for this indication. Of these agents, AACE, ACOG, and NAMS consider the antidepressants to be the most effective nonhormonal therapy. Two advantages of antidepressants are almost immediate reduction in VMS scores and the added benefit of mood enhancement in women suffering from mood disorders. Nonhormonal treatment alternatives may be used in women who cannot or will not use HRT for relief of VMS, such as those with a history of or at risk for breast cancer. The mechanisms by which these nonhormonal therapies reduce the frequency of VMS are unknown. Recommended agents and doses are listed in Table 1.

Treatment Alternatives: Clinical Overview

The previous section outlined a number of pharmacologic interventions for the treatment of menopause-associated VMS that are recommended by the AACE, ACOG, and NAMS. This section will provide a brief overview of the clinical efficacy of these interventions. Readers are encouraged to consult the treatment guidelines and other cited resources for a more detailed explanation of benefits, risks, and dosing considerations, as a detailed review of available studies for all treatment options is beyond the scope of this review.

Herbal Remedies

ACOG and NAMS, which both published treatment recommendations in 2004, drew contrasting conclusions about the use of herbals for the management of VMS. ACOG, citing a lack of clinical efficacy, does not support their use. NAMS does support their use, despite acknowledging inconclusive efficacy data. The AACE recommendations, the most recent of the three, took a more neutral approach, neither recommending nor discouraging the use of herbals.

A recent meta-analysis of 6 trials of soy isoflavones, ranging in doses from 50 mg to 150 mg per day, resulted in mixed results, with numerical reductions in the mean number of daily hot flashes compared with placebo at 4-6 weeks (weighted mean difference, -1.15; 95% CI, -2.33 to 0.03), at 12-16 weeks (weighted mean difference, -0.97; 95% CI, -1.82 to -0.12), and at 6 months (weighted mean difference, -1.15; 95% CI, -2.33 to 0.03), at 12-16 weeks (weighted mean difference, -0.97; 95% CI, -1.82 to -0.12), and at 6 months (weighted mean difference, -1.15; 95% CI, -2.33 to 0.03). All 6 of these studies were judged by the authors of the meta-analysis to be of poor-to-fair quality based on a number of factors that reduce the quality of the study design; such factors include a study population of <50 participants, inadequate analysis, or <80% follow-up or follow-up not reported. A meta-analysis of 6 fair-to-good quality trials of 2 types of red clover isoflavones (promensil [40-160 mg per day] and rimostil [57 mg per day]) showed little difference...
between red clover isoflavones and placebo in reducing the mean number of daily hot flashes (weighted mean difference, -0.44; 95% CI, -1.47 to 0.58).21 Because soy isoflavones and red clover isoflavones are thought to act on estrogen receptors, they should not be used in women with a history of breast cancer.9

The AACE, ACOG, and NAMS recommendations on the use of black cohosh are based on the same 2 trials. One of these trials did demonstrate that black cohosh was superior to placebo at reducing VMS,22 while the other showed no significant difference between treatment groups.23 Because if its purported estrogenic effects, black cohosh should not be used in women with a history of breast cancer.9

Data from 1 clinical trial that evaluated the efficacy of vitamin E for the treatment of VMS found a significant difference compared with placebo; however, this difference equated to 1 less hot flash per day in the women receiving vitamin E.24 Collectively, these data do not provide conclusive support for the use of herbal or vitamin remedies for the relief of menopause-associated VMS.

Hormone Replacement Therapy
HRT is the standard of care for the treatment of moderate-to-severe VMS.2,3 This recommendation is based on a plethora of data demonstrating the effectiveness of estrogen or estrogen plus progestin in the reduction of VMS frequency and severity. In fact, a meta-analysis of 24 double-blind, randomized, placebo-controlled trials including a total of 3,329 subjects and ranging in duration from 3 months to 3 years demonstrated a significant 75.3% reduction in the frequency of hot flashes experienced per week (weighted mean difference, -17.92, 95% CI, -22.86 to -12.99) and a significant 87% reduction in the severity of symptoms (OR, 0.13; 95% CI, 0.07 to 0.23) relative to placebo.25 These relative reductions are significant considering that the placebo response rate in this meta-analysis was 57.7%. As previously stated, there are currently no data available to suggest that any 1 formulation of estrogen or estrogen plus progestin is clinically superior to another.9,18,20

Nonhormonal Therapy
Of the nonhormonal agents used for the treatment of VMS, antidepressants have been studied most extensively. In a recent meta-analysis of 6 trials of selective serotonin reuptake inhibitors (SSRIs; paroxetine, fluoxetine, citalopram) or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, antidepressants were found to be significantly more effective than placebo at reducing the mean number of daily hot flashes (weighted mean difference, -1.13; 95% CI, -1.70 to -0.57).21 The individual antidepressants had variable efficacy. Paroxetine was evaluated in 2 studies (1 fair and 1 good) and was found to reduce the mean number of daily hot flashes by 1.66 (95% CI, -2.43 to -0.89); fluoxetine was evaluated in 2 fair-quality studies and was found to reduce the mean number of hot flashes by 1.37 (95% CI, -3.03 to 0.29); citalopram was evaluated in 1 fair-quality study and was found to reduce the mean number of hot flashes by 0.20 (95% CI, -1.45 to 1.05); venlafaxine was evaluated in 2 studies (1 fair and 1 good) and was found to reduce the mean number of hot flashes by 0.49 (95% CI, -2.40 to 1.41).21 Meta-analyses of 4 trials of clonidine and 2 trials of gabapentin also demonstrated significant reductions in the mean number of daily hot flashes compared with placebo.21 Clonidine reduced the mean number of daily hot flashes by 0.95 (95% CI, -1.44 to -0.47) at 4 weeks (4 trials) and by 1.63 (95% CI, -2.76 to -0.50) at 8 weeks (2 trials). Gabapentin reduced the mean number of daily hot flashes by 2.05 (95% CI, -2.80 to -1.30). Although these nonhormonal agents have been proven significantly more effective at reducing the mean frequency of hot flashes by 1 to 2 per day, they are not as effective as HRT,25 according to reported efficacy rates from separate trials. Although these results are not from head-to-head comparisons, the vast difference in the efficacy rates for hormonal versus nonhormonal therapies is worth noting.

New Drugs in Development
There are several new therapies for the treatment of menopause-associated VMS that are in various stages of clinical development, including 2 antidepressants (low-dose paroxetine mesylate and desvenlafaxine succinate), a serotonin-2 antagonist (Org50081), and an alpha-2 delta receptor binding agent (PD-0299685) (www.clinicaltrials.gov). At this time, no data are available on the efficacy of low-dose paroxetine mesylate or Org50081. Preliminary data suggest that PD-0299685 reduces the mean number of hot flashes relative to placebo.26 Results from a recently completed and presented clinical trial demonstrate that desvenlafaxine (100 mg per day) reduced the frequency of moderate-to-severe hot flashes by 65% at 12 weeks compared with 51% in the placebo group with reductions seen as early as week 1.27 Additional data suggest that these differences may be sustained for 52 weeks.26 Desvenlafaxine also significantly reduced the severity of hot flashes compared with placebo. Adverse events were comparable to placebo, with nausea being the most frequently reported adverse event (25% vs. 7%).27 Additional clinical trial data on these investigational agents are eagerly awaited.

Conclusions
Current treatment of menopause-associated VMS is centered on a foundation of lifestyle changes in all women and HRT in women with moderate-to-severe VMS. Herbal remedies are commonly used for the treatment of VMS; however, the mechanisms by which they reduce the frequency of VMS remains unknown and clinical trial efficacy data are inconsistent and inconclusive. Isoflavones and black cohosh are thought to possess estrogenic properties, and like HRT, should not be used in women with a history of breast cancer. Additional studies are warranted to determine the efficacy and safety of herbal remedies in the treatment of menopause-associated VMS. SSRIs, SNRIs, gabapentin, and clonidine have been proven superior to placebo in reducing the mean number.
of hot flashes experienced per day; however, these nonhormonal therapies are less effective that HRT. The mechanisms by which nonhormonal therapies reduce the frequency of hot flashes remain unknown. These nonhormonal alternatives may be appropriate in women who cannot or will not take HRT, such as those with a history of breast cancer. HRT, consisting of estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus), remains the standard of care in women with moderate-to-severe VMS. Numerous hormonal and nonhormonal therapies in various stages of clinical development have shown promising results in the treatment of VMS. Efficacy and safety data from ongoing clinical trials are eagerly awaited. Comparative clinical trials and cost-effectiveness analyses will be needed to determine if any of these investigational therapies are capable of replacing HRT as the standard of care in women with moderate-to-severe VMS.

DISCLOSURES

Elena M. Umland discloses that there was no financial relationship or financial interest relating to the topic of this activity. Umland was responsible for the entire study concept and design of this article. She performed all the data collection, data interpretation, writing, and revision of this article.

REFERENCES

Preventive Care Programs to Improve the Management of Perimenopausal and Postmenopausal Women: Guidance for Managed Care Organizations

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1. Posttest form for this activity, “Preventive Care Programs to Improve the Management of Perimenopausal and Postmenopausal Women: Guidance for Managed Care Organizations,” on the AMCP.org (CE/CME Center) site. To receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.

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To complete this activity, go to www.amcp.org (CE/CME Center), where you will access the posttest and evaluation form.
1. What age group has the greatest disparity of health care expenditures between men and women?
   a. 0-18  c. 45-64
   b. 18-44  d. >64

2. Reproductive health accounts for what percentage of overall health plan costs?
   a. 10%  c. 25%
   b. 16%  d. 28%

3. Which of the following statements most accurately reflects quality gaps in osteoporosis prevention?
   a. Physician adherence to osteoporosis management guidelines has significantly improved over time.
   b. Treatment rates are similar between younger and older women.
   c. Bone mineral density testing rates are higher among postmenopausal African-American women as compared with Caucasian women.
   d. Less than 1 in 4 elderly women with fractures receive appropriate evaluation or treatment for osteoporosis.

4. Gender stratification of national rates for which of the following HEDIS performance measures related to cardiovascular disease showed the greatest discrepancy between men and women?
   a. Beta-blocker after myocardial infarction (MI)
   b. Low-density lipoprotein (LDL) screening after a cardiac event
   c. LDL control after a cardiac event
   d. Blood pressure control in hypertensives

5. What is the estimated percentage of women aged over 50 experiencing vasomotor symptoms (VMS) of menopause?
   a. 23%  c. 75%
   b. 50%  d. 100%

6. After the age of 45, the majority of women either do not receive any information about menopause from their physicians, or they are unsatisfied with menopause counseling that they do receive.
   a. True  b. False

7. Which of the following statements about the Women’s Health Initiative (WHI) is true?
   a. The estrogen plus progestin arm was stopped early because of an increased risk of invasive breast cancer and increased overall risk, defined by the global index.
   b. The estrogen alone arm was stopped early because of an increased risk of invasive breast cancer and increased overall risk, defined by the global index.
   c. Both study arms were stopped early, after an interim analysis of the estrogen plus progestin arm of the study revealed an increased risk of invasive breast cancer and increased overall risk.
   d. Both study arms were stopped early, after an interim analysis of the estrogen alone arm of the study revealed an increased risk of invasive breast cancer and increased overall risk.

8. The WHI found that estrogen plus progestin in women with an intact uterus was associated with significant increases in all of the following except:
   a. Invasive breast cancer
   b. Stroke
   c. Thromboembolism
   d. Total mortality

9. The WHI found that estrogen alone in women who had had a hysterectomy was associated with significant increases in which of the following:
   a. Invasive breast cancer
   b. Stroke
   c. Coronary heart disease (CHD) events
   d. Total mortality

10. Subgroup analyses of the WHI revealed which of the following regarding CHD risk?
    a. Significant between-group differences were noted in the risk of subsequent CHD events in women with a history of CHD events (history of myocardial infarction or revascularization procedure) at baseline.
    b. Nonsignificant between-group differences were noted in the risk of CHD events in women treated with estrogen alone when analyzed by age.
    c. No between-group differences were noted in the risk of CHD events in women treated with estrogen alone when analyzed by age.
    d. No between-group differences were noted in the risk of CHD events in women treated with estrogen alone or estrogen plus progestin when analyzed by age.

11. Which of the following statements about the use of hormone replacement therapy is false?
    a. Low-dose, short-course hormone replacement therapy is the standard of care for the treatment of moderate-to-severe menopause-associated VMS.
    b. Hormone replacement therapy is considered safe and effective for the primary prevention of CHD in postmenopausal women.
    c. Hormone replacement therapy is considered an appropriate option for the treatment of osteoporosis.
    d. None of the above.

12. Since publication of the initial WHI study results in 2002-2004, comprehensive educational initiatives have been instituted to educate menopausal women on the risks and benefits of hormone replacement therapy so that they may make informed decisions regarding their treatment options.
    a. True  b. False

13. Which of the following symptoms has been identified as the leading reason menopausal women seek medical attention?
    a. Hot flashes  c. Mood disturbances
    b. Night sweats  d. Sleep disturbances

14. Theories on the pathophysiology of menopause-associated VMS include all of the following except:
    a. Decreased concentration of estrogen
    b. Change in the ratio of estradiol to estrone
    c. Decreased concentration of progesterone
    d. Decreased concentration of serotonin

15. All of the following factors have been found to affect a woman’s risk of experiencing VMS except:
    a. Ethnicity  c. Body mass index
    b. Age  d. Number of pregnancies

16. What is the average duration of time that women experience VMS?
    a. 6 months to 2 years
    b. 2 to 4 years
    c. 4 to 6 years
    d. more than 6 years

17. According to the American Association of Clinical Endocrinologists (AACE), the American College of Obstetricians and Gynecologists (ACOG), and the North American Menopause Society (NAMS), which of the following is considered the standard of care for the treatment of moderate-to-severe menopause-associated VMS?
    a. Behavioral modification
    b. Herbal remedies (i.e., isoflavones, black cohosh)
    c. Hormone replacement therapy
    d. Antidepressants

18. All of the following patient populations may be appropriate for long-term hormone replacement therapy (i.e., >5 years), except:
    a. Women who judge the benefits of VMS relief to outweigh the potential risks after failing an attempt to discontinue HRT.
    b. Women who are at high risk for osteoporotic fractures.
    c. Women requiring osteoporosis prevention who cannot take alternate therapies.
    d. Women requiring cardioprotection who are younger at age of onset of menopause and who do not have a history of CHD.

19. Which of the following nonhormonal therapies is considered by AACE and NAMS to be the most effective in the treatment of menopause-associated VMS?
    a. Antidepressants
    b. Gabapentin
    c. Clonidine
    d. All are considered equally effective

20. Which of the following treatment alternatives is considered safest to use in women with a history of breast cancer?
    a. Isoflavones  c. Estrogen only
    b. Black cohosh  d. Antidepressants