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Management of Menopause-Related Symptoms

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Management of Menopause-Related Symptoms

Summary

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Introduction

Menopause is defined as the permanent cessation of menses resulting from reduced ovarian hormone secretion that occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is recognized after 12 months of amenorrhea that is not associated with a pathologic cause. The average age of menopause in the United States is 51 years, and can vary normally between 40 and 58 years.[1] The menopausal transition can span over several years, and often begins with variations in menstrual cycle length in response to rising levels of follicle stimulating hormone (FSH). The mean age of onset of the menopausal transition is 47.5 years and commonly lasts approximately 4 to 5 years.[1]

Stages and nomenclature of the menopausal transition were defined by experts in 2001 at the Stages of Reproductive Aging Workshop (STRAW).[2] The group recognized seven stages of the reproductive aging continuum, and acknowledged that most women do not progress precisely through each stage. These stages are also described by the following terms:

- Premenopause: the time up to the beginning of the perimenopause, but is also used to define the time up to the last menstrual period.
- Perimenopause: the time around menopause during which menstrual cycle and endocrine changes are occurring but 12 months of amenorrhea has not yet occurred.
- Postmenopause: begins at the time of the last menstrual period, although not recognized until after 12 months of amenorrhea.

A hot flash or flush refers to the spontaneous sensation of warmth, often associated with perspiration, resulting from a vasomotor response to declining estrogen levels. Nightsweats are hot flashes or flushes occurring at night, often while sleeping. Other symptoms, such as vaginal dryness, sleep disturbance, mood symptoms, cognitive disturbances, somatic complaints, urinary complaints, uterine bleeding problems, sexual dysfunction, and reduced quality of life are also attributed to the menopausal transition.

Although many measures have been developed to assess menopausal symptoms, few demonstrate standardization, validity, or reliability. Some measures are based on self-reports of the presence, severity, and frequency of individual symptoms, such as hot flashes. Others utilize cumulative or global scores based on lists or scales of symptoms attributed to menopause, such as mood, cognition, quality of life, sexual function, and somatic symptoms. Many studies base their measures on study-specific checklists, questionnaires, or scales. Ninety-two measures of menopausal symptoms were reported by studies included in this evidence review.

Purpose

This systematic evidence review focuses on five Key Questions relating to symptoms of menopause and their management, as specified by the Planning Committee for the National Institutes of Health State-of-the-Science

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Evidence-Based Practice

Conference on Management of Menopause-Related Symptoms. The target population includes adult women in the United States undergoing the menopausal transition.

1. What is the evidence that the symptoms more frequently reported by middle-aged women are attributable to ovarian aging and senescence? These include vasomotor symptoms, vaginal dryness, sleep disturbance, mood symptoms, cognitive disturbances, somatic complaints, urinary complaints, uterine bleeding problems, sexual dysfunction, and reduced quality of life.
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? Factors include race and ethnicity, age at onset of the menopause transition, body mass index (BMI), surgical versus natural menopause, depression, and smoking.
3. What is the evidence for the benefits and harms of commonly used interventions for relief of menopause-related symptoms? Interventions include estrogens, progestins, androgens, tibolone, antidepressants, other drugs, phytoestrogens, complementary and alternative medicine, and behavioral interventions.
4. What are the important considerations in managing menopause-related symptoms in women with clinical characteristics or circumstances that may complicate decision-making? These include bilateral oophorectomy, premature ovarian failure, breast cancer, concurrent use of selective estrogen receptor modulators (SERMs) and other interacting therapeutic agents, lifestyle and behavioral factors, recent discontinuation of menopausal hormone therapy, and very low or very high BMI.
5. What are the future research directions for treatment of menopause-related symptoms and conditions?

Methods

A Technical Expert Panel was assembled to provide input from experts and clinicians in the field to ensure that the scope of the project addressed important clinical questions and issues. The panel included obstetrician/gynecologists, internists, naturopathic physicians, behavioral experts, and researchers. The panel was convened for periodic conference calls during the course of the project. Expert reviewers, including several panel members, provided comments on the draft evidence report.

Literature Search and Strategy

Relevant studies were identified from multiple searches of MEDLINE®, PsycINFO, DARE, the Cochrane database of systematic reviews and controlled trials, MANTIS, and AMED (1953 to November 2004); and from recent systematic reviews, reference lists, reviews, editorials, websites, and experts. Retrieved abstracts were entered into an electronic database (EndNote®).

Inclusion and Exclusion Criteria

Full text cohort studies with data on women experiencing menopause and at least one of the symptoms listed in Key Question 1 were initially reviewed and subsequently included if the study enrolled 100 or more subjects, subjects represented the target population, and data on symptoms associated with menopause were provided. Exclusions included studies of women not undergoing the menopausal transition and experiencing menopause related symptoms, studies of aging and its effects, and biologically based studies that did not report epidemiological data relating to symptoms (e.g., studies of hormone levels). Non-English language papers and studies of animals or cadavers were also excluded. Cross-sectional studies meeting similar inclusion/exclusion criteria were examined for contributory data and included if they reported relevant data about symptoms by menopausal stage, such as prevalence rates.

Full text randomized controlled trials and meta-analyses of randomized controlled trials providing data on treatment of menopausal symptoms, using one or more of the interventions listed in Key Question 3, were included. Trials enrolling women with breast cancer were considered separately from those enrolling women without breast cancer. Exclusions included studies of women not undergoing menopause and experiencing menopause related symptoms during the course of the study, studies of animals, and non-English language papers.

Data Extraction and Synthesis

All eligible studies were reviewed and a "best evidence" approach was applied, in which studies with the highest quality and most rigorous design are emphasized.[3] Data were extracted from each study, entered directly into evidence tables, and summarized descriptively. Benefits and adverse effects of therapies were considered equally important and both types of outcomes were abstracted. Trials of alternative and complementary therapies were grouped according to the National Center for Complementary and Alternative Medicine categories[4] most closely related to included topics. Results of

recently published meta-analyses on estrogens[5-7] and isoflavones[8] are included in this report. No new meta-analyses were conducted because of heterogeneity of trials of other therapies.

Two reviewers independently rated the quality of randomized controlled trials and cohort studies using criteria specific to different study designs developed by the United States Preventive Services Task Force.[9] Similar criteria for cross-sectional studies are not available. The overall rating is a combination of internal and external validity scores. When reviewers disagreed, a final rating was reached through consensus. Studies reporting several different outcomes may have different quality ratings for each outcome depending on how completely it controlled for key confounders in multivariable models.

Size of Literature

A total of 10,059 unique citations were reviewed, including 6,342 about symptoms and factors influencing them (Key Questions 1 and 2); 4,078 about therapies (Key Question 3); and 806 about specific characteristics that may influence the effects of therapies (Key Question 4).

Results

To address Key Questions 1 and 2, the review focused on prospective studies of cohorts of midlife women transitioning through the stages of menopause. Forty-eight studies conducted among 14 cohorts met inclusion criteria. Seven cohorts were based in the United States (Massachusetts Women's Health Study, Seattle Midlife Women's Health Study, Ohio Midlife Women's Study, National Health Examination Follow-up Study [NHANES], Study of Women's Health Across the Nation [SWAN], University of Minnesota/Tremin Trust Longitudinal Study, and Pennsylvania Ovarian Aging Study). Seven cohorts were based outside the United States (Gothenburg, Sweden, Australian Longitudinal Study on Women's Health, Medical Research Council [MRC], U.K., Melbourne Women's Midlife Health Project, Australia, Manitoba Project on Women and Their Health in the Middle Years, Canada, Copenhagen, Denmark, and Eindhoven, Netherlands). An additional 22 cross-sectional studies from other populations meeting similar inclusion criteria were obtained to provide additional prevalence data.

Major limitations of studies include dissimilar methods for evaluating and reporting symptoms and for assessing menopausal change. Some cohort studies based results on cross-sectional data reported at serial time points rather than individual tracking of women over time. Some studies failed to adjust or stratify for potentially important variables such as age, race, BMI, life events, or history of depression when attempting to attribute symptoms to change in menopausal stage. Although most included studies were population-based, in many cases, enrolled women were additionally selected from the initial recruited cohort and may have been less representative of the general population. Also, many studies were based on cohorts recruited from community populations and are more representative of volunteers than entire communities.

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 and cross-sectional studies supports the association between vasomotor symptoms and 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.
- *Vaginal dryness:* Vaginal dryness is associated with menopause and prevalence rates increase as women transition through the menopausal stages. 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, and this may be due to vasomotor symptoms. Up to 40 percent to 60 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 report no associations between menopausal stage and mood symptoms, development of a mental disorder, or general mental health. Studies of prevalence rates report wide ranges that are similar across menopausal stages.
- *Cognitive disturbances:* No cohort studies are available. Cross-sectional studies indicate no difference in forgetfulness, memory, or concentration.
- *Somatic complaints:* Most studies report no association of somatic symptoms with menopause, although somatic symptoms were increased among perimenopausal women

compared with premenopausal women in one cohort and two cross-sectional studies.

- *Urinary complaints:* Urinary leakage increased among perimenopausal women compared with premenopausal women in one study, and another reported no associations. Studies of prevalence rates report wide ranges that are similar across menopausal stages.
- *Uterine bleeding* problems: No studies meeting inclusion criteria addressed uterine bleeding problems, most likely because currently accepted definitions of menopause rely historically on changes in uterine bleeding.
- *Sexual dysfunction:* Women from one study cohort reported declines in some or all of the measured sexual parameters as they transitioned through menopausal stages. 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 provide adequate details to characterize the onset, 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 SWAN cohort.
- *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. Adjustment for confounders is necessary because women undergoing hysterectomy differ from women with natural menopause in ways that may also influence their menopause related symptoms.
- *Depression:* One cross-sectional study reported that prior anxiety or depression did not predict menopausal symptoms. Cohort studies show that a history of depression predicts depression in the menopausal transition. No studies evaluated depression in associaton with other menopausal symptoms.
- *Smoking:* Available studies are inconclusive.

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

- A total of 192 randomized controlled trials of therapies for managing menopause-related symptoms were evaluated, including trials of estrogens, progestins, androgens (testosterone and DHEA [dehydroepiandrosterone]), tibolone, antidepressants (selective serotonin 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).
- Estrogen, in either opposed or unopposed regimens, is the most consistently effective therapy for vasomotor symptoms, and demonstrates benefit in most trials evaluating urogenital symptoms. 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.
- 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.
- 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. Sexual symptoms were improved with testosterone/estrogen compared to estrogen alone or placebo in two other trials.
- For women using testosterone combined with estrogen, acne and hirsutism occur significantly more often than for women using estrogen alone.
- Based on only a few fair or good-quality trials, tibolone demonstrated benefit for vasomotor symptoms, sleep, and somatic complaints compared to placebo, and was similar to estrogen for some, but not all, symptoms.
- Uterine bleeding, body pain, weight gain, and headache were more common in tibolone vs. placebo groups.

- Several agents demonstrate benefits in managing vasomotor symptoms in some, but not all trials, or in only a few available trials, including paroxetine, veralipride, gabapentin, soy isoflavones, and other phytoestrogens.
- 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 reflecting underlying fluctuations of symptoms.
- Although benefits and adverse effects of therapies were equally important in this review, most trials did not report adverse effects or reported them incompletely.

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

- Evidence is not available to determine if the effectiveness of therapy for menopause related symptoms 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 BMI.
- For women with breast cancer, results of 15 randomized controlled trials indicate that clonidine, venlafaxine, and megestrol acetate 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?

In order to fill evidence gaps, future research could focus on:

- Determination of optimally effective doses, combination regimens, durations of use, and timing of therapy.
- Evaluation of approaches to identify optimal candidates for specific therapies (e.g., identification of thrombophilias).
- Head-to-head and placebo comparisons of estrogen alone and combined with other types of therapies including non drug interventions.
- Trials demonstrating how to discontinue estrogen when symptoms subside, including the effectiveness of tapering doses and/or replacing with other therapies including non drug 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.
- 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. Further study of antidepressants for vasomotor symptoms would be justified based on evidence of currently available trials.
- Enrollment of women with specific characteristics who have not previously been evaluated such as nonwhite women, women with premature ovarian failure, those using SERMs and other agents influencing symptoms concurrently, women with very high or low BMI, and those with lifestyle and behavioral factors influencing symptoms. Trials should report data specific to these groups in order to interpret their influence on therapy.
- Use of standard definitions, measures, outcomes, and statistical methods for longitudinal data so results can be compared across trials and population cohorts.
- Prevalence data in U.S. women.
- Details about onset, timing, and duration of symptoms in relation to menopausal stage.
- Studies of symptoms after surgical menopause with and without hormonal therapy.

Conclusions

Based on review of currently available cohort and cross-sectional population studies, 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 cohort studies provide data on cognition, but cross-sectional studies suggest no association. There are no studies about uterine bleeding problems, onset, duration, and severity of specific symptoms, or conclusive data on the influence of race/ethnicity, age of onset of menopause, BMI, oophorectomy status, presence of

depression, or smoking status. 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.

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 follow up, maintenance of comparable groups, contamination, 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, as outlined in Key Question 5, would guide patient and clinician decision making when managing menopause related symptoms.

The evidence review is limited in several ways. For Key Questions 1 and 2, literature searches focused on population studies of women undergoing the menopausal transition reporting symptoms, and did not include epidemiologic or biologically-based etiologic studies. In addition, studies that may not have been identified by searches include those in which menopause was not a primary focus of the study, but a predictor variable included in a multivariable model evaluating the outcome or symptom of interest. Studies potentially not identified would be those that identified no association between menopausal stage and the outcome of interest. Studies with a positive association would probably have reported it in the abstract and be identified by the searches. Also, the review was limited to English-language randomized controlled trials of therapies. Exploratory studies of agents may provide contributory data that were not included in this report.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Oregon Evidence-Based Practice Center, under Contract No. 290-02-0024. It is expected to be available in March 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 120, *Management of Menopause-Related Symptoms.* In addition, Internet users will be able to access the report and summary online through AHRQ's Web site at www.ahrq.gov.

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References

1. North American Menopause Society. Available at: www.menopause.org. Accessed 13 Dec, 2004.
2. Soules MR, Sherman S, Parrott E, al. e. Executive summary: stages of reproductive aging workshop (STRAW) Park City, Utah, July 2001. Menopause. 2001;8:402-407.
3. Slavin RE. Best practice synthesis: An alternative to meta-analytic and traditional reviews. Education Research. 1986;15:5-11.
4. National Center for Complementary and Alternative Medicine. http://nccam.nih.gov/health/whatiscam/. Accessed 10 Jan. 2005
5. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA. 2004;291(13): 1610-1620.
6. MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004.
7. Nelson HD, Nygren P, Freeman M, Benjamin K. Drug Class Review on Estrogens. Final report. http://www.ohsu.edu/drugeffectiveness/reports/documents/Estrogens%20Final%20Report%20u2pdf.2004. Accessed 10 Jan. 2005
8. Krebs EE, Ensrud KE, MacDonald R, Wilt TJ. Phytoestrogens for treatment of menopausal symptoms: A systematic review. Obstet Gynecol. 2004;104(4):824-836.
9. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med. 2001;20(3S): 21-35.

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