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Number 120

Management of Menopause-Related Symptoms

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Office of Medical Applications of Research, National Institutes of Health, requested and provided funding for this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Acknowledgments

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Structured Abstract

Context: Although many symptoms have been attributed to the menopausal transition, it is unclear which symptoms are actually associated and how to effectively manage them.

Objective: To describe the evidence about symptoms associated with menopause, factors that influence them, benefits and adverse effects of therapies, factors that influence therapies, and future research needs.

Data Sources: Relevant studies were identified from multiple searches of MEDLINE®, PsycINFO, DARE, the Cochrane database, MANTIS, and AMED (1953 to November 2004); and from recent systematic reviews, reference lists, reviews, editorials, websites, and experts.

Study Selection: Specific inclusion and exclusion criteria were developed to determine study eligibility. The target population includes adult women in the U.S. undergoing the menopausal transition.

Data Extraction: All eligible studies were reviewed and relevant data were extracted, entered into evidence tables, and summarized by descriptive methods. Two reviewers independently rated the quality of studies using predefined criteria.

Data Synthesis: Forty-eight studies conducted among 14 cohorts and 22 studies from other populations provide data about symptoms. Vasomotor symptoms and vaginal dryness are most consistently associated with menopause; sleep disturbance, somatic complaints, urinary complaints, sexual dysfunction, mood, and quality of life are inconsistently associated. No studies provide data on cognition and uterine bleeding problems, duration and severity of specific symptoms, or conclusive data on the influence of race/ethnicity, age of onset of menopause, body mass index, oophorectomy status, depression, or smoking. Results of 192 randomized controlled trials of therapies indicate that for vasomotor symptoms, estrogen is effective; tibolone demonstrates benefit, but most studies are poor-quality; paroxetine, veralipride, gabapentin, soy isoflavones, and other phytoestrogens report benefit in some trials. Results for other symptoms are mixed, adverse effects are inadequately reported, and placebo effects are large. No trials describe the influence of bilateral oophorectomy, premature ovarian failure, use of potentially interacting agents, lifestyle and behavioral factors, recent discontinuation of hormones, or body mass index. For women with breast cancer, clonidine, venlafaxine, and megestrol acetate improve vasomotor symptoms, and results for other symptoms are mixed.

Conclusions: Vasomotor symptoms and vaginal dryness are most consistently associated with the menopausal transition. Results of treatment trials are consistent and conclusive only for estrogen. For other agents, the evidence base is limited by lack of studies demonstrating effectiveness, poor quality of existing studies, and incomplete information on adverse effects.

Keywords: Menopause, menopause transition, menopause symptoms, treatment of menopause symptoms

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Note: Appendixes and Evidence Tables are provided electronically at http://www.ahrq.gov/clinic/tp/menopstp.htm

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Evidence Report/Technology Assessment

Number 120

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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Evidence Report

Chapter 1. Introduction

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 Conference on Management of Menopause-Related Symptoms:

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?

The target population includes adult women in the U.S. undergoing menopause. The evidence review emphasizes the patient's perspective in assessment of symptoms, the choice of interventions, outcome measures, and potential adverse effects, and focuses on those that are applicable to clinical practice. It also considers the generalizability of efficacy studies performed in controlled settings. Although the evidence review attempts to assess research findings from the perspectives of clinicians and patients, it is not intended to propose practice recommendations.

Menopausal Transition

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 U.S. 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), sponsored by the American Society for Reproductive Medicine, the National Institute on Aging, the National Institute of Child Health and Human Development, and the North American Menopause Society.[2] The group recognized seven stages of the reproductive aging continuum, and acknowledged that most women do not progress precisely through each stage (Figure 1). 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.

Menopausal Symptoms

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. Although the term “flash” indicates a prodromal phase and “flush” the vasomotor dilation phase, they are combined in this report because they are reported inconsistently in studies. 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.

Measures of Menopausal Symptoms

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 (Table 1). The most common measures are described below.

The Kupperman Index, or Kupperman Blatt Index, assesses overall menopause symptoms, and is frequently used to determine severity of hot flashes. The Kupperman Index grades the self-reported severity of 11 symptoms (hot flashes, paresthesias, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and formication) on a scale from 0 to 3. Item scores are weighted to create a composite score. This measure has been validated and is responsive to change, however, it lacks statistical justification for weights.[3] The Greene Climacteric Scale assesses the severity of 21 self-reported symptoms on a 4-point scale.[4] Psychological, somatic, and vasomotor symptoms are assessed, along with one question on sexual dysfunction. The Women's Health Questionnaire was developed for use primarily as a quality of life instrument, although it is also used to measure overall symptoms. It includes 36 items with 4-point self-report response categories. It has demonstrated reliability, has undergone psychometric evaluation, and allows for cross-cultural comparisons.[3]

The Beck Depression Inventory and Hamilton Depression Rating Scale are widely-used and validated measures of depression that are highly correlated.[5,6] The Hamilton Depression Rating Scale is the usual standard against which other depression rating scales are validated. The Psychological General Well-Being Index is less commonly used, and has demonstrated validity in assessing general psychological well-being.[7]

The Brief Index of Sexual Functioning for Women is a 22-item validated self-report instrument measuring current levels of female sexual functioning and satisfaction, assessing both quantitative and qualitative aspects.[8] The McCoy Sex Scale assesses sexual experience and responsiveness in the 30 days prior to testing utilizing 14 items on a 7-point scale.[9]

The Menopause Specific Quality of Life Questionnaire is a validated instrument that assesses physical, vasomotor, psychosexual, and sexual domains of life quality using a 7-point scale. A difference in one point on a domain score represents a 15 percent change.[10] The Nottingham Health Profile includes 38 yes/no questions in six subsections (physical mobility, pain, sleep, energy, social isolation, and emotional reactions).[11] The Short-Form 36 Health Survey measures eight health concepts and has been extensively tested and validated.[12]

Chapter 2. Methods

Analytic Framework and Key Questions

The Key Questions for this evidence review were determined by the Planning Committee for the National Institutes of Health State-of-the-Science Conference on Management of Menopause-Related Symptoms. Key Questions examine a chain of evidence about symptoms commonly associated with menopause, factors that may influence the frequency, severity, or persistence of these symptoms, the effectiveness, benefits, and adverse effects of interventions for managing menopausal symptoms, and how the effects of interventions may differ for women with specific characteristics. The analytic framework (Figure 2) outlines the organization of key questions by identifying the target population, treatment interventions, health outcomes, and their relationships.

Technical Expert Panel (TEP) and Expert Reviewers

A Technical Expert Panel (Appendix 1) 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 (Appendix 2).

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) (Appendix 3). Additional articles were obtained from recent systematic reviews, reference lists, reviews, editorials, websites, and by consulting experts. Retrieved abstracts were entered into an electronic database (EndNote®).

Inclusion and Exclusion Criteria

Key Questions 1 and 2

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) (Appendix 4). 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.

Key Questions 3 and 4

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 (Appendix 4). For this report, abstracts of unpublished trials are included in evidence tables, but not in summary tables and text.

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.[13] 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[14] most closely related to included topics. For this report, acupuncture and Chinese herbal treatments were categorized in the alternative healthcare systems category, and lifestyle modifications, such as exercise, counseling and education, were placed within the mind-body category. Additional categories include biologically based therapies (e.g., red clover), manual medicine (e.g., osteopathic manipulations), and energy therapies (e.g., reflexology).

Results of recently published meta-analyses on estrogens[15-17] and isoflavones[18] 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 U.S. Preventive Services Task Force (Figure 3).[19] 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 well it measured the symptom and how completely it controlled for key confounders in multi-variable 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 interventions (Key Question 3); and 806 about specific characteristics that may influence the effects of interventions (Key Question 4) (Appendix 5).

Chapter 3. Results

To address Key Questions 1 and 2, 6,342 abstracts were reviewed to identify relevant studies evaluating menopause related symptoms and their associations with the menopausal transition. The review focused on prospective studies of cohorts of midlife women transitioning through the stages of menopause. Forty-nine studies conducted among 14 cohorts met inclusion criteria. Seven cohorts were based in the U.S. (Massachusetts Women's Health Study, [20-25] Seattle Midlife Women's Health Study,[26-28] Ohio Midlife Women's Study,[29] National Health Examination Follow-up Study [NHANES],[30] Study of Women's Health Across the Nation [SWAN],[31-39] University of Minnesota/Tremin Trust Longitudinal Study [includes a small subset from other countries],[40] and Pennsylvania Ovarian Aging Study[41,42]). Seven cohorts were based outside the U.S. (Gothenburg, Sweden,[43-45] Australian Longitudinal Study on Women's Health,[46,47] Medical Research Council [MRC], U.K.,[48-51] Melbourne Women's Midlife Health Project, Australia, [52-62] Manitoba Project on Women and Their Health in the Middle Years, Canada,[63] Copenhagen, Denmark,[64-66] and Eindhoven, Netherlands.[67,68]). Cohorts are described in Table 2, results are listed by symptoms in Table 3, and full details are provided in Appendix 6-1.

Major limitations of cohort studies include dissimilar methods for evaluating and reporting symptoms and for assessing menopausal change. Some 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.[44,52,53,55,57-59] Also, many studies were based on cohorts recruited from community populations and are more representative of volunteers than entire communities.

A total of 51 cross-sectional studies meeting similar inclusion criteria were obtained to provide additional prevalence data including 29 studies from the 14 study cohorts[21-25,27,30,33-40,42,45,48-50,56,60-66,69] and 22 studies from other populations.[70-91] Results of cross-sectional studies are summarized in Table 4.

Key Question 1. Symptoms Associated with Menopause

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

Vasomotor Symptoms

Four studies from four population-based cohorts evaluated the association between vasomotor symptoms and menopausal stage, including three rated good-quality[46,51,53]and one

fair.[26] Women transitioning from premenopause to either perimenopause or postmenopause had increased vasomotor symptoms in the three good-quality studies.[46,51,53]

The prevalence of hot flashes was reported in 33 cross-sectional studies.[25,27,33,35-37,40,48,60,62,64,66-67,69-76,78-85,87-90] Prevalence rates ranged from 14 percent to 51 percent for premenopausal women, were approximately 50 percent for perimenopausal women, and between 30 percent to 80 percent for postmenopausal women, depending on the age and population studied. In one study, approximately 29 percent of women age 60 years reported hot flashes, suggesting only a modest decline in frequency with increasing time from menopause.[66]

Vaginal Dryness

Vaginal dryness was associated with menopause, and became more common with the transition from premenopause to postmenopause, in the one good-quality cohort study examining this relationship.[53] Thirteen cross-sectional studies[37,40,48,69,71,72,74-76,80,83-85] reported prevalence rates ranging from 4 percent to 22 percent for premenopausal women, 7 percent to 39 percent for perimenopausal women, and 17 percent to 30 percent for early postmenopausal women. Two cross-sectional studies showed either no association,[84] or a weak association,[83] between vaginal dryness and menopausal stage.

Sleep Disturbance

Three cohort studies evaluated the impact of menopausal status on sleep; two were rated good-quality[46,53] and one fair.[26] In the good-quality studies, women had more difficulty sleeping as they progressed through the menopausal stages,[46,53] and sleeping difficulty was associated with the presence of hot flashes.[53] The fair-quality study reported no association.[26]

Eighteen cross-sectional studies evaluated the prevalence of sleep disturbance at different menopausal stages.[25,35-38,48,60,69,78-82,84,85,87,90,92] Of these, eight reported prevalence rates ranging from 16 percent to 42 percent for premenopausal women, 39 percent to 47 percent for perimenopausal women, and 35 percent to 60 percent for postmenopausal women (including women with either surgical or natural menopause and hormone therapy users).[37,60,78,80-82,85,90] Some studies,[79,82,87] but not others,[38,90] reported an association between hot flashes and sleep disturbance. When hot flashes/night sweats and insomnia were considered together in one study, 27 percent of premenopausal women, 46 percent of perimenopausal women, and 38 percent of postmenopausal women reported disturbances.[25]

Four cross-sectional studies reported increased adjusted odds ratios for difficulty sleeping for menopausal women compared to premenopausal women[37,48,69,92] In one study, an age-adjusted significant correlation between sleep problems and menopausal status was reported, but increases among perimenopausal and postmenopausal women were small, and social class was a stronger predictor.[69] A factor analysis of sleep-related problems found sleep was not associated with menopausal status.[84] In another study, sleep disordered breathing increased across the menopausal stages after multivariate adjustment and stratification by BMI and age.[92]

Mood Symptoms

Fourteen studies from 11 cohorts evaluated the impact of menopausal stage on mood.[20,24,26,28-30,41,44,47,51,54,55,63,68] Of these, seven were rated good-quality,[29,41,47,51,54,55,68] four

fair,[20,26,28,63] and three poor. [24,30,44] Symptoms included anxiety,[29] depression,[20,24,28-30,41,63,68] dysphoric or negative mood,[26,54] and positive mood.[55] Development of a mental disorder,[44] psychological symptom reporting,[51] and general mental health[47] were also assessed.

Twelve of the 14 studies, including five good-quality, four fair, and three poor, found no influence of menopausal stage on mood symptoms, development of a mental disorder, or general mental health.[20,24,26,28-30,44,47,51,54,55,63] Two good-quality studies demonstrated a change in mood symptoms with the menopausal transition.[41,68] A well-designed, nested case-control study of age-matched menopausal and premenopausal women from the Pittsburgh cohort found no differences between the groups in depression, anger, anxiety, or stress symptoms.[93]

Twenty-four cross-sectional studies reported relevant data.[22-24,33,35,36,48,50,60,63,64,66,67,69,70,72,76,80-85,90] The prevalence of depressed mood ranged from 8 percent to 37 percent for premenopausal women, 11 percent to 46 percent for perimenopausal women, 8 percent to 47 percent for women with natural menopause, and 8 percent to 38 percent for women with surgical menopause.[23,66,67,80,85]

Cognitive Disturbances

No cohort studies longitudinally assessed cognitive symptoms. Eight cross-sectional studies showed no differences in the prevalence rates of memory or concentration problems by menopausal stage.[37,48,67,69,80,81,84,85]

Somatic Complaints

Somatic complaints were evaluated in four studies conducted among three cohorts rated good-quality[46,47,53] or fair-quality.[26] Perimenopausal women had increased somatic symptoms compared to premenopausal women in one cohort.[46,47] Symptoms included back pain, severe tiredness, stiff or painful joints, bodily pain, and worse general health. Other studies reported reduced breast tenderness,[53] or no association with somatic or neuromuscular symptoms.[26]

Fourteen of 18 cross-sectional studies evaluating changes in somatic symptoms showed no significant increases as women transitioned from premenopause to postmenopause in adjusted analytic models.[36,37,48,64,66,67,69,71,72,81-85,87] Three studies showed slight increases in somatic symptoms during perimenopause that decreased during postmenopause,[78,89] or remained stable.[67] Another study showed significantly fewer somatic symptoms for women at menopause compared with those at premenopause.[90]

Urinary Complaints

Three good-quality cohort studies evaluated the impact of menopausal stage on urinary symptoms.[46,53,56] In one study, women who were perimenopausal at baseline were more likely to report leakage of urine two years later than women who remained premenopausal.[46] Two studies from the Melbourne cohort found no association of menopausal status with urinary symptoms.[53,56]

Fourteen cross-sectional studies[37,45,48,49,56,60,67,71,75,77,84-87] provided relevant data. Prevalence rates of urinary incontinence or leakage ranged from 10 percent to 36 percent for premenopausal women, 17 percent to 39 percent for perimenopausal women, 14 percent to 36 percent for

women undergoing natural menopause, and 18 percent to 36 percent for women undergoing surgical menopause.[37,46,56,67,86]

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

Sexual dysfunction was evaluated in two fair-quality studies from the Melbourne cohort.[57,58] Sexual function was variably measured and included decreased responsivity, decreased libido, and/or decreased frequency of sexual activity. In that cohort, women demonstrated decreases in some or all of the sexual parameters as they transitioned from early to late perimenopause or postmenopause.[57,58]

Thirteen cross-sectional studies, including one from the Melbourne cohort, also evaluated sexual function.[22,40,42,48,61,65,66,69,83,84,86,89] Five studies showed the prevalence of sexual disinterest, dysfunction, or discomfort to increase from premenopause to perimenopause to postmenopause,[48,61,67,69,86] and four showed no change.[40,65,84,89]

Reduced Quality of Life

Four cohort studies addressed the impact of menopausal stage on quality of life, three rated good-quality[47,52,59] and one poor.[30] Two studies from the Melbourne cohort had conflicting results.[52,59] One study showed declines in well-being across progressive menopausal stages (lowest for the one to two years postmenopause) that improved when women were more than two years postmenopause.[52] A second study showed increased well-being from early to late perimenopause and postmenopause.[59] In another good-quality study, women who remained perimenopausal over a two year follow-up period reported significant decreases in quality of life compared to women who remained premenopausal, although significant decreases were not reported by women in other stages.[47] A poor-quality cohort study found that well-being was not associated with change in menopausal status.[30]

Three cross sectional studies also evaluated quality of life.[22,34,74] Satisfaction with life,[22] and impaired functioning[34] did not vary with menopausal stage in multivariate regression modeling of data from the Massachusetts Women's Health Study. In another study, various aspects of general well-being were lower among postmenopausal women compared to premenopausal women.[74]

Summary

- 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: The few studies evaluating cognitive disturbances in menopause have inadequate measures.

- 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 two study cohorts 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. Factors Influencing Symptoms

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

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

Race and Ethnicity

Two cohort studies[38,41] addressed the influence of race and ethnicity on menopausal symptoms, while many adjusted for it in multivariable models. Depression was reported more often among African American women compared to Caucasian women,[41] and sleep difficulties were reported more often among Caucasian and Hispanic women and less often among African American, Chinese, and Japanese women.[38]

Seven cross-sectional studies conducted in the large SWAN cohort also evaluated symptoms by race or ethnicity.[33-37,39,70] In SWAN, vasomotor symptoms were reported more often among African American women and less often among Hispanic, Chinese, and Japanese women compared with Caucasian women.[33,37] Japanese, Chinese, African American, and Hispanic women reported fewer mood symptoms compared to Caucasian women,[33,35,36] although "impaired social function" was reported among Hispanic women in two studies[34,70] and among African American women in one study.[34] Hispanic women also reported more bodily pain than Caucasian women.[34] A cross-sectional study conducted outside the SWAN cohort found that Mexican American women had similar prevalence rates of vasomotor symptoms and vaginal dryness as Caucasian women.[72]

Age at Onset of the Menopause Transition

Long term studies evaluating menstrual cycles over many years among large cohorts of women showed the median onset of menstrual irregularity to begin between the ages of 45 and 47.5 years with a mean duration of the menopausal transition lasting 5 years.[94-96] Factors associated with earlier menopause include smoking,[97-99] shorter cycle length during menstruating years,[100] and shorter stature and leaner body weight.[101] Factors associated with later age at menopause include higher gravidity or parity[98,99] and higher BMI.[99]

A cross-sectional study reported increased rates of hot flashes among women with menopause prior to age 53 after adjustment for other factors.[88] Another found that earlier age of inception of perimenopause was related to a longer perimenopause stage.[21]

Body Mass Index (BMI)

Two good-quality cohort studies evaluated BMI and its effect on symptoms among menopausal or perimenopausal women and found that BMI was a significant predictor of urinary incontinence,[56] but not positive mood.[55] A cross-sectional study reported a slight increase in vasomotor symptoms (15 percent) among women with a BMI of 27 or greater, although,

vasomotor symptoms were less common at the extremes of BMI.[37] Lower BMI was independently associated with increased hot flashes in another cross-sectional study.[88] Three cross-sectional studies[22,42,74] found no significant differences for increased BMI. Other studies evaluating menopausal symptoms adjusted for BMI in multivariate models but did not report the contribution of BMI to symptoms.[46,47,53,92]

Surgical Versus Natural Menopause

Two good-quality[29,56] and one fair-quality cohort studies[63] reported data for women with surgical menopause. The Ohio Midlife Women's Study found that hysterectomy was not a predictor of anxiety or depression.[29] In contrast, a community-based study of women in Manitoba, Canada reported that women with hysterectomies had increased odds of depression.[63] In the Melbourne Women's Midlife cohort, surgical menopause was not a significant predictor of urinary incontinence.[56] Other symptoms were not addressed in these studies.

Sixteen cross-sectional studies reported symptoms among women with surgical and natural menopause.[30,38,45,48,56,63-66,70,72,73,80,86,89,90] Four studies showed no significant differences in vasomotor symptoms,[48,70,80,90] and three studies showed slightly higher rates of vasomotor symptoms among women with surgical menopause (seven percent to eight percent higher).[64,66,73] Vasomotor symptoms were similar among Japanese and Canadian women with surgical and natural menopause in another study.[70] Three studies evaluated vaginal dryness; two showed similar rates,[48,72] and one reported a nine percent higher prevalence among women with surgical compared to natural menopause.[80] One cross-sectional study found no differences in rates of sexual dysfunction by type of menopause,[48] and another showed higher rates of urinary incontinence (36 percent vs. 22 percent) among women with surgical menopause.[86]

The prevalence of anxiety and depression was evaluated in four cross-sectional studies,[66,70,80,89] and two showed higher prevalence rates among women with surgical menopause.[66,80] In a cross-sectional study from the Massachusetts Women's Health Study evaluating depression, women who had undergone surgical menopause in the previous three months were twice as likely as the rest of the cohort to have elevated depression scores.[24]

Depression

The interaction of baseline depression with menopausal stage and/or transition and the presence or absence of symptoms was not evaluated in any cohort study. A cross-sectional study reported that prior anxiety or depression did not predict menopausal symptoms.[48] One other cross-sectional study evaluating menopausal symptoms adjusted for depression in a multivariate model but did not report the contribution of depression to symptoms.[92]

Smoking

Three good-quality studies from the Melbourne Women's Midlife cohort examined the association of smoking status with mood symptoms and urinary incontinence.[54-56] In this cohort, current smoking was associated with negative mood,[54] but not positive mood,[55] and was not evaluated as an interaction term with menopausal transition or stage. Smoking was not a significant predictor of urinary incontinence.[56] Two good-quality studies adjusted for smoking in multivariate models, but did not report any data for this variable.[46,47]

Five cross-sectional studies provide data on smoking and menopausal symptoms.[35,37,48,62,88] Two studies showed no association between smoking and menopausal symptoms,[37,62] one reported that smoking was associated with psychological distress but did not evaluate smoking as an interaction term,[35] and another showed that smoking at anytime in the past predicted greater vasomotor symptoms during menopause.[48] Another study reported no association between hot flashes and smoking, but identified higher rates of vasomotor symptoms among thin smokers than among thin non-smokers.[88] Other studies evaluating menopausal symptoms adjusted for smoking status in multivariate models but did not report the contribution of smoking status to symptoms[39,74,92]

Summary

- 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: Only one cross sectional study was included and reported that prior anxiety or depression did not predict menopausal symptoms.

- Smoking: Available studies are inconclusive.

Key Question 3. Benefits and Adverse Effects of Therapies

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

Estrogen

Three recent good-quality systematic reviews and meta-analyses of randomized controlled trials of estrogen, alone (unopposed) or combined with progestin or progesterone (opposed), describe benefits and harms of various forms, doses, and regimens for treating menopausal symptoms. These include a Cochrane review of trials of oral estrogen for hot flashes,[16,102,103] a meta-analysis of trials of oral conjugated equine estrogen (CEE) and oral and transdermal estradiol for hot flashes,[15,104] and a review of commonly used types of estrogen for several menopausal symptoms.[15] Trials were conducted predominantly in the U.S. or western Europe and recruited participants from primary care or gynecology practices. Most trials focused on healthy menopausal women in their early 50s with baseline symptoms that varied by study. All trials were double blind, of 12 weeks duration or more, and rated good or fair quality.

Vasomotor symptoms. The Cochrane meta-analysis indicated a significant reduction in frequency of weekly hot flashes for oral estrogen compared to placebo with a pooled weighted mean difference of -17.9 hot flashes per week (95% confidence interval [CI], -22.9 to -13.0; nine trials), equivalent to a 75.3 percent reduction in frequency (95% CI, 64.3 percent to 82.3 percent).[16] Severity of symptoms was also significantly reduced compared to placebo (odds ratio [OR] 0.13; 95% CI, 0.07 to 0.23; 13 trials). Differences between types of estrogens were not determined, although trials of estradiol and CEE predominated. The review also found that the reduction in weekly hot flash frequency was similar for opposed and unopposed estrogen regimens compared to placebo (opposed: -19.9 per week; 95% CI, -26.7 to -12.6; three trials; unopposed: -14.7; 95% CI, -20.1 to -8.7; six trials). Symptom severity seemed to be better treated by opposed (OR 0.10; 95% CI, 0.06 to 0.19; 10 trials) than by unopposed estrogen (OR 0.35; 95% CI, 0.22 to 0.56; four trials), although heterogeneity of trials could also explain this difference.

Hot flash frequency, severity, or both improved in nine of 10 trials of oral estradiol and in all 11 trials of transdermal estradiol compared to placebo in a review of these agents.[15] The pooled weighted mean differences in hot flashes were -16.8 per week (95% CI, -23.4 to -10.2; five trials) for oral estradiol, and -22.4 per week (95% CI, -35.9 to -10.4; six trials) for transdermal estradiol. Results were similar when opposed and unopposed regimens were considered separately.[15] All eight trials of oral CEE reported statistically significant improvements in hot flash frequency, severity, or both compared with placebo. One trial of CEE that provided data comparable to the estradiol meta-analyses reported a mean reduction of -19.1 hot flashes per week (95 percent CI, -33.0 to -5.1). Four trials comparing estrogen agents head-to-head (CEE compared with oral or transdermal estradiol) indicated improved number and severity of hot flashes for all treatment groups with no significant differences between them (pooled weighted mean difference in hot flashes -0.3; 95 percent CI, -3.4 to 2.7; three trials).

In a review of 32 trials of estrogen for treatment of vasomotor symptoms, all but five were less than one year in duration and only three trials enrolled more than 500 participants, limiting

evaluation of adverse effects.[15] Trials reported multiple specific adverse effects including atypical bleeding and endometrial hypertrophy, nausea and vomiting, breast tenderness, headache, weight change, dizziness, venous thromboembolic events, cardiovascular events, rash and pruritus, cholecystitis, liver effects, and other adverse events. These outcomes were reported unevenly across studies and could not be combined in summary statistics. Trials included in the Cochrane review indicated similar adverse effects with breast tenderness and uterine bleeding most commonly reported.[16]

Urogenital symptoms/sexual dysfunction. In a systematic review of good and fair-quality trials of a variety of estrogen agents, urogenital symptoms improved in eight of nine trials, and sexual function (including pain during intercourse and responses to questionnaires) in eight of 11 trials.[15] Vaginal forms of estrogen were evaluated in five trials. In a placebo controlled trial, vaginal dryness and pain during intercourse improved with use of the estradiol intravaginal ring compared to placebo.[105] A trial of the estradiol intravaginal ring and oral estradiol reported improved vaginal dryness, involuntary loss of urine, and pain during intercourse for both groups.[106] Head-to-head trials comparing the intravaginal estradiol ring with CEE vaginal cream among women with signs and symptoms of urogenital atrophy indicated that the two agents were comparable for relief of vaginal dryness and pain during intercourse, resolution of atrophic signs, improvement in vaginal mucosal maturation indices, and reduction in vaginal pH.[107,108] Similar findings were reported in a trial of the estradiol vaginal tablet and CEE cream.[109]

Four placebo controlled trials of transdermal estradiol indicated improvements in some, but not all, urinary and sexual symptoms. Two trials reported improvements in responses to the McCoy Sex Scale Questionnaire compared to placebo,[9,110] although, another trial indicated no differences for symptoms of vaginal discomfort, loss of libido, and incontinence.[111] Another trial of transdermal estradiol indicated improvement in vaginal dryness, but not pain during intercourse, frequent urination, dysuria, stress incontinence, and nocturia, compared to placebo.[112]

A trial of oral CEE reported significantly improved vaginal dryness and urinary frequency, but no significant improvement on six other items related to sexual function on a General Health Questionnaire compared to placebo.[113] A trial comparing oral CEE and transdermal estradiol indicated that the majority of women reported either no change or improvements in vaginal dryness and itching, pain during intercourse, and urinary pain and burning in all treatment groups with no major differences between groups.[114] All treatment groups demonstrated improved vaginal cytology, measured by the maturation index, with the biggest improvement in the higher dose estradiol group (0.1 mg/day).

Sleep disturbance. Improved measures of sleep were specifically reported in three trials included in the systematic review.[15] Transdermal estradiol provided significant improvements in sleep quality, sleep onset, and decreased nocturnal restlessness and awakening compared to placebo.[115] In a subanalysis of the Women's Health Initiative (WHI) that considered women ages 50 to 54 years old who reported moderate to severe vasomotor symptoms at baseline, there was a positive effect on sleep disturbance with CEE compared to placebo.[116] In contrast, a trial of CEE in women with hot flashes and nighttime awakening at baseline indicated improvement in menopausal symptoms and measures of psychological well-being, but not in parameters of sleep quality such as total sleep time, sleep onset time, number of awakenings, and REM sleep duration compared to placebo.[117]

Mood symptoms. Thirteen trials of estrogen reporting mood and depression outcomes met eligibility criteria (Table 5, Appendix 6-2), including three trials rated good-quality,[118-120] four fair,[121-124] and six poor.[125-130] Trials compared placebo with CEE,[119,121,124,126,128] oral estradiol,[120,122,125] transdermal estradiol,[118,126] piperazin oestrone sulphate,[129,130] and estropiate.[127] Head-to-head comparisons included estradiol and estradiol valerate,[123] CEE and clonidine,[128] CEE and raloxifene,[119] and estradiol and raloxifene.[120]

Two of the four good and fair-quality placebo controlled trials reporting between group differences found improved depressive symptoms among women using transdermal estradiol[118] and oral estradiol with norethindrone acetate.[122] No differences were found in trials comparing placebo with CEE/medroxyprogesterone acetate (MPA)[121] or placebo with CEE.[119] There were no differences in symptoms when comparing estradiol with estradiol valerate[123] and estradiol with raloxifene.[120] Another trial indicated improved anxiety with raloxifene vs. CEE, but no differences in depressed mood.[119]

Reduced quality of life. In a systematic review,[15] four trials of transdermal estradiol,[112,131-133] two trials of oral estradiol,[122,134] and one trial of esterified estrogens[135] indicated improved health related quality of life and well-being compared to placebo, as measured by various instruments. In a subanalysis of the WHI that considered women ages 50 to 54 years old who reported moderate to severe vasomotor symptoms at baseline, there was no effect on health-related quality of life measures on the RAND 36-item Health Survey, despite significant improvements in vasomotor symptoms.[116] A head-to-head comparison of CEE vs. transdermal estradiol utilizing the Menopause Specific Quality of Life Questionnaire indicated improvement in all areas with no significant differences between groups.[136]

Progestin/progesterone

A total of 244 abstracts were identified and five randomized controlled trials met inclusion criteria (Table 6),[137-141] including one rated good-quality,[137] one fair,[138] and three poor.[139-141] Studies included transdermal progesterone,[137,138] intramuscular progesterone,[139] medroxyprogesterone acetate (MPA) tablet,[141] and MPA injection.[140]

Two trials of transdermal progesterone report conflicting results. A good-quality trial reported no differences between progesterone (32 mg/day) and placebo groups for vasomotor or somatic symptoms, mood, or sexual feelings as measured on previously validated instruments.[137] A fair-quality trial of a lower dose (20 mg/day) reported significant reductions in vasomotor symptoms, but not depression scores, with progesterone compared to placebo (83 percent vs. 19 percent; $p<0.001$).[138] A poor-quality trial of intramuscular progesterone described small differences between groups, however, the clinical significance of these are unclear.[139] Two poor-quality trials of MPA did not provide adequate statistical comparisons.[140,141]

None of the trials reported adverse effects.

Androgens

Testosterone. A total of 1,095 abstracts were identified from a search for trials of androgens that included testosterone and dehydroepiandrosterone (DHEA). Of these, 10 trials of testosterone met inclusion criteria including one rated good-quality,[142] four fair,[144-146,148] and five

poor[143,147-149,151] (Table 7, Appendix 6-3). Major limitations of studies include few subjects, undefined inclusion and exclusion criteria, use of unclear outcome measures, and using open label rather than double blind methodology. Two additional studies were reported in abstract form and are included only in the evidence table (Appendix 6-3).[152,153]

Trials used methyltestosterone,[142,143,145-149] testosterone undecanoate,[150,151] and transdermal testosterone.[144] All trials combined testosterone with estrogen and compared it head-to-head with estrogen, and two studies compared it with placebo.[144,149] Outcomes included sexual dysfunction,[142,144-146,150,151] hot flashes,[143-149] mood,[144,145,147,149,150] sleep disturbances,[143,145,147-149] vaginal dryness,[143,146-149] and quality of life.[144,145,150]

Only one good-quality and two fair-quality trials reported statistical comparisons between testosterone/estrogen and estrogen or placebo groups.[142,143,144] One trial indicated no differences between testosterone/estrogen and estrogen alone for hot flash severity, vaginal dryness, or sleep problems.[143] Sexual interest and responsiveness were improved with testosterone/estrogen compared to estrogen alone based on scores on the Sexual Interest Questionnaire in another trial.[142] Sexual symptoms were also improved in a trial comparing testosterone/estrogen with placebo.[144]

Adverse effects were reported in all 10 trials. Acne[142,143,146,148] and hirsutism[146,148] occurred significantly more often among women using methyltestosterone/estrogen than with estrogen alone. Adverse effects were not always separated by treatment group, making it difficult to determine which drug was responsible for the reported effect.[144,149-151]

Dehydroepiandrosterone (DHEA). One fair-quality[154] and one poor-quality[155] randomized controlled trial met inclusion criteria (Table 7, Appendix 6-4). Studies were small, lacked clear exclusion criteria,[155] and had high losses to follow up.[154]

Trials used dehydroepiandrosterone (DHEA)[154] and dehydroepiandrosterone sulfate (DHEAS)[155] alone[154,155] or combined with transdermal estradiol.[155] No significant differences between DHEA and placebo were determined on any measures of symptoms including hot flashes, vaginal dryness, insomnia, depression, urinary difficulties, libido, concentration, dizziness, forgetfulness, irritability, aches, anxiety, headaches, and fatigue in the one trial reporting between group differences.[154]

Adverse effects were reported for DHEA only and included paresthesia of an upper extremity.[154]

Tibolone

A total of 162 abstracts were reviewed and 20 randomized controlled trials met inclusion criteria (Table 8, Appendix 6-5) including three rated good-quality,[156-158] four fair,[159-162] and 13 poor.[163-175] Four additional studies were reported in abstract form and are included only in the evidence table (Appendix 6-5).[176-179]

Trials compared tibolone with estrogen alone,[169] estrogen combined with progestin or progesterone,[158-160,162,163,166,170,171,173-175]or placebo.[156,157,161,164,165,167,168,172] Outcomes included hot flashes, sexual dysfunction, mood, uterine bleeding, somatic complaints, vaginal dryness, sleep disturbance, cognitive effects, urinary complaints, and quality of life.

Three good or fair-quality trials reported between group differences for tibolone and placebo.[156,157,161] Results indicated improved hot flashes,[157] sleep,[157] and somatic complaints[156]

with tibolone, but no differences between groups in Greene Climacteric Score,[156] quality of life,[157,161] or mood, energy, pain, social isolation, or urinary symptoms.[157]

Four good or fair-quality trials reported between group differences for tibolone and estrogen alone or estrogen combined with progestin or progesterone.[158-160,162] Two trials indicated improved hot flashes with estrogen compared to tibolone.[159,160] Sexual interest, drive, and/or performance were improved with tibolone compared to CEE/MPA in another trial.[160] No differences between groups were determined for several other menopause related symptoms.[158-160,162]

Uterine bleeding was increased with tibolone in four trials,[157,167,168,180] decreased in two,[159,167] and was not significantly changed in four others.[158,162,163,174] Uterine bleeding was dose related in two studies.[168,180] Adverse effects that occurred significantly more often among women using tibolone than placebo were reported in 16 of 20 trials and included body pain,[156,160,163,164,166,170,174,175] weight gain,[156,158,160,164,166,169,175] and headache.[156,160,163,166,167,170] Four studies did not report adverse effects.[162,171-173]

Antidepressant drugs

A total of 184 abstracts were reviewed and eight randomized controlled trials met inclusion criteria including one trial rated good-quality,[181] three fair,[182,183,188] and four poor[184-187] (Table 9, Appendix 6-6). Trials used paroxetine,[181] venlafaxine,[183] moclobemide,[188] and veralipride.[182,184-187] Most studies were limited by small sample sizes, short durations of follow-up, lack of follow-up data, inadequate descriptions of inclusion criteria, and, in one trial, lack of blinding.[187]

Selective serotonin reuptake inhibitors (SSRIs). A good-quality trial of paroxetine reported statistically significant reductions in mean hot flash frequency and hot flash composite score at two doses compared with placebo.[181] No differences were detected in sleep, depression, anxiety, sexual interest, disability, or side effects.[181] A fair-quality trial of venlafaxine reported improvement on a single item measuring how significantly hot flashes interfered with daily activities compared to placebo, but no differences in hot flash frequency or severity as measured on daily diaries.[183] The venlafaxine group also had improved mood and vitality compared with placebo.[183] Other trials of SSRIs enrolled women with breast cancer and are described below.

Moclobemide. A fair-quality trial evaluating two doses of moclobemide showed reduced hot flash composite scores with moclobemide at both doses, although comparisons with placebo were not reported.[188] This trial was further limited by including only 30 participants and lasting only five weeks.

Veralipride. Veralipride, an antidopaminergic drug, was evaluated in five trials; one rated fair-quality[182] and four poor-quality.[184-187] Two poor-quality trials comparing veralipride to placebo reported reduced rates of hot flashes with veralipride.[184,185] Of the two studies comparing veralipride to estrogen, a poor-quality trial found that veralipride had less benefit,[187] and a fair-quality trial found it to be equivalent.[182]

In four of the five studies, the side effects of mastodynia and/or galactorrhea occurred more frequently in the veralipride group.

Other Drugs

A total of 51 abstracts were identified and 15 randomized controlled trials met inclusion criteria (Appendix 6-7). Trials used clonidine,[128,189-197] gabapentin,[198] methyldopa,[199-201] and Bellergal Retard.[202] Major limitations of trials include few subjects, lack of clear inclusion and exclusion criteria, high attrition or loss to follow up, no washout period in crossover trials, lack of data for pre-crossover comparisons, and short treatment duration.

Clonidine. Clonidine was compared to placebo in eight trials,[189-195,197] and compared to other active drugs in trials with lisuride, sodium valproate, transdermal estradiol,[195] and CEE and medrogestone[128,196] (Table 10). Two trials were rated fair-quality,[189,192] and eight were poor.[128,190,191,193-197] Outcomes included hot flashes, insomnia, and mood symptoms.

Of the trials for which pre-crossover statistics were provided or could be calculated, there were no statistically significant differences between clonidine and placebo in the improvement of hot flash symptoms.[189,191,192] In the non-crossover placebo controlled trials, one trial reported that clonidine was more effective than placebo in reducing hot flash frequency and intensity,[195] and the other found no differences between groups in number of hot flashes, although women on clonidine were significantly more likely to report a decrease in subjective frequency, severity, and duration of hot flashes.[197] Of the 3 remaining crossover studies reporting only summary statistics,[190,193,194] one trial demonstrated that clonidine was more effective than placebo in reducing the number of hot flashes and improving subjective hot flash measures.[193] Two head-to-head trials found that estrogen, not clonidine, effectively decreased the number of hot flashes and improved measures of depression and anxiety.[128,196] Two trials found no differences between clonidine and placebo in measures of psychological symptoms,[191,192] and one found no difference in frequency of insomnia.[192]

Adverse effects were reported in six of 10 trials; dry mouth occurred more frequently in women taking clonidine than placebo,[189,191,193] and blood pressure was not affected by clonidine.[189,190,192-194,197]

Methyldopa. Three crossover trials, two rated fair-quality[200,201] and one poor,[199] compared methyldopa with placebo (Table 11). All trials provided pre-crossover statistics regarding improvement in hot flash frequency and none found significant differences between groups. A fair-quality study reporting post-crossover data separately found that methyldopa was more effective than placebo in reducing the number of hot flashes and improving Visual Analog Scores after crossover.[201]

All trials noted substantially more adverse effects with methyldopa than placebo. Fatigue or drowsiness, dizziness, and dry mouth occurred more often among women using methyldopa than placebo. One patient on methyldopa developed a lupus-like rash.[200] No significant changes in blood pressure were noted,[199,201] however, one study reported orthostatic hypotension in one patient.[200]

Gabapentin. In a good-quality study comparing gabapentin to placebo, hot flash frequency and a composite menopause symptom score were significantly improved with gabapentin (Table 11).[198] No significant differences in mood, quality of life, Patient Global Impression of Change scores, and sleep quality were detected.[198]

Gabapentin use reduced levels of albumin, total protein, total bilirubin, blood urea nitrogen, and platelets compared to placebo. Somnolence, dizziness, rash, and peripheral edema were reported for gabapentin but not placebo. Fifty percent of the gabapentin group and 28 percent of the placebo group reported at least one adverse event.

Bellergal. One poor-quality trial compared Bellergal Retard, a combination of 0.6 mg ergotamine, 40 mg phenobarbital, and 0.2 mg levorotatory alkaloids, with placebo (Table 11).[20] There were no statistically significant differences between Bellergal and placebo in measures of vasomotor symptoms, insomnia, nervousness, hyperirritability, headache, paresthesia, loss of libido, and dizziness.

Adverse effects were similar between groups and included dry mouth, dizziness, and sleepiness.

Phytoestrogens

A total of 195 abstracts were identified and 21 randomized controlled trials met inclusion criteria (Table 12, Appendix 6-8). Trials used dietary soy isoflavones,[203-213] soy isoflavone extracts,[214-218] other forms of phytoestrogens,[219-223] and phytoestrogens combined with other agents.[224] Eight additional studies were reported in abstract form and are included only in the evidence table (Appendix 6-8).[225-232]

Soy isoflavones—dietary. Dietary forms of soy isoflavones were compared to placebo in 10 trials (Table 12) that included soy powder,[203,204,211,213] cereal,[205] drink,[206,212] diet,[208,211] flour,[209] and tablets.[207,210] Of these, seven were rated fair-quality,[203,204,206,207,209-212] and three poor.[205,208,213] Outcomes included hot flashes, sleep, mood or depression, vaginal dryness, sexual symptoms, scores on symptoms scales, and single trials reporting palpitations, headaches, and general health.

Of the eight trials providing between group comparisons, one fair-quality and one poor-quality trial reported improved hot flashes with soy compared to placebo[203,204,213] and six reported no differences.[205,206,209-212] A fair-quality trial of soy powder reported improved hot flash frequency with soy compared to placebo (44 percent vs. 31 percent, $p<0.01$), but no differences between groups on the Kupperman Index.[203,204] A poor-quality trial of soy protein tablets indicated improved severity of hot flashes and improved hypoestrogenic symptoms score with soy, but no differences in number of hot flushes, night sweats, sleep disturbance, or general health score.[213] In most trials, hot flashes improved in both soy and placebo groups,[203,204,206,209-212] although in two trials rated poor-quality, the placebo group reported improved symptoms while the soy group did not.[205,208]

Soy isoflavones—extract. Soy isoflavone extracts were compared to placebo in five trials (Table 12), including four rated fair-quality,[214-216,218] and one poor.[217] Outcomes included hot flashes, cognitive tests, scores on the Greene Climacteric Index, and mood.

Of the three trials providing between group comparisons and hot flash outcomes, all reported improved hot flash frequency[216,217] or severity[218] with soy compared to placebo, and one trial reported no differences in frequency of night sweats.[218] The Greene Climacteric Scale score was improved with soy compared to placebo in one trial,[217] but not the other.[215] Performance on

cognitive tests, including tests of memory, improved with soy compared to placebo in the two trials evaluating this outcome.[214,215] Mood was not improved with soy in one trial.[215]

A trial reporting adverse effects of isoflavones indicated an increased rate of endometrial hyperplasia after five years of using 150 mg/day of isoflavone soy supplement.[233]

Other phytoestrogens. Phytoestrogens were compared to placebo in five trials (Table 12), including two rated fair-quality[221,223] and three poor.[219,220,222] Trials included diet,[219] topical cream,[220,222] and genistein tablets.[221,223] One trial included a comparison group using estradiol and noresthisterone.[221] Outcomes included hot flashes in all trials, vaginal dryness, scores on menopausal symptom scales, mood, sexual symptoms, and energy level.

Three of five trials providing between group comparisons and hot flash outcomes reported improved hot flash severity[219] or score[221,223] with phytoestrogen compared to placebo. Two trials reported no differences compared to placebo in frequency and severity of hot flashes[222] or Kupperman Index score,[223] and another indicated that the hot flash score was better with estradiol and noresthisterone than genistein.[221] Vaginal dryness was improved with phytoestrogen diet in one trial,[219] but there were no significant differences in overall symptom scores.[219] A trial of wild yam cream found no differences in mood, libido, or energy level.[222]

Combinations. A poor-quality trial of soy based isoflavones combined with *C. racemosa* (black cohosh) reported improved hot flush symptoms with treatment compared to placebo, as reported on a questionnaire.[224]

Complementary and Alternative Medicine

A total of 1,237 abstracts were identified and 28 randomized controlled trials met inclusion criteria (Table 13, Appendix 6-8). Trials used acupuncture,[234-236] Chinese herbs,[237-242] red clover,[243-248] black cohosh,[249] combinations,[250] other supplements,[251-259] manual therapies,[260] and energy therapies.[261] Four trials were reported in abstract form and are included only in the evidence table (Appendix 6-8).[227,231,262,263]

Acupuncture. Four small trials compared a series of acupuncture treatments specific to menopausal symptoms with alternate nonspecific acupuncture procedures (Table 13).[234-236,264] Of these, one trial was rated fair-quality[264] and three poor.[234-236] The fair-quality trial found no differences between groups in any measures,[236] while a poor-quality study reported improved mood in the treatment group, but no differences in menopausal symptoms or well-being.[235] A poor-quality trial compared acupuncture treatment specific to menopausal symptoms to both nonspecific acupuncture and estrogen and found a more pronounced improvement in hot flashes with estrogen than acupuncture.[264]

Chinese herbs. Three fair-quality trials[240-242] and three poor-quality trials[237-239] of Chinese herbs met criteria for this review. Five trials compared herbs against placebo[238-242] and two against CEE/MPA[237,242] (Table 13). Treatments included specific formulations of herbs,[237,238] ginseng,[239,241] dong quai,[240] and an herbal remedy (pueraria lobata) combined with isoflavone.[242] Outcomes included hot flashes and other vasomotor symptoms, mood and depression, well-being and quality of life, memory, somatic symptoms, sexual symptoms, and general health. Studies were small, had short durations, and included highly selected populations.

A fair-quality trial comparing ginseng with placebo reported significant improvements for depression, well-being, and health scores on the Psychological General Well Being Index, but no differences in hot flashes or scores on other instruments.[241] Results of two other fair-quality placebo controlled trials indicated no differences between groups for menopausal symptoms,[240,242] well-being,[240,242] or rate of learning.[242]

Red clover. Red clover isoflavone tablets (Promensil and Rimostil) were compared against placebo in six trials (Table 13) including one rated good-quality,[247] four fair,[243-245,248] and one poor.[246] Outcomes included hot flashes and other vasomotor symptoms including measures from the Greene Climacteric Scale. One of five trials reporting between group comparisons indicated improved hot flashes with treatment compared to placebo,[248] and no trials reported differences in scores on the Greene Climacteric Scale or symptom diary.[243,244,246-248]

A good-quality meta-analysis of 25 trials of phytoestrogens for treatment of menopausal symptoms included an analysis of red clover using five of the six studies in this review.[244-248] Results of the meta-analysis indicated no significant differences in hot flash frequency between treatment and placebo groups (weighted mean difference –0.60; 95 percent CI, -1.71 to 0.51).[18]

Black cohosh. One fair-quality trial compared *C. racemosa* preparation (black cohosh) with estrogen and placebo (Table 13).[249] Between group comparisons indicated improved hot flushes with estrogen vs. placebo only.

Combinations. A small poor-quality trial of a botanical formula (burdock root, licorice root, motherwort, dong quai, and wild yam) compared with placebo indicated no differences between groups in the number and severity of hot flashes (Table 13).[250] Results indicated a significant decrease in the total number of other types of symptoms after three months of therapy for the botanical formula group compared to placebo ($p<0.03$).[250]

Other supplements. Nine trials evaluated effects of other forms of supplements including melatonin,[251] vitamin E,[252] kavakava,[253] evening primrose oil with vitamin E,[254] guar gum,[255] vaginal moisturizer,[256,257] phospohlipid liposome injections,[258] and S-adenosyl-L-methionine[259] (Table 13). Of these, two trials were rated fair-quality[253,258] and seven poor.[251,252,254-257,259] Outcomes included hot flashes, mood or depression, vaginal dryness, and scores on symptom scales.

Between group differences for placebo controlled trials indicated improved symptoms with treatment compared to placebo for mood or depression (melatonin, S-adenosyl-L-methionine),[251,259] anxiety (kavakava, phospholipids liposomes),[253,258] and scores on symptom scales (phospholipid liposomes).[258] No differences between groups were found for hot flashes (guar gum),[255] mood or depression (kavakava),[253] and scores on symptom scales (kavakava).[253] In a poor-quality trial of evening primrose oil, hot flashes were significantly improved with placebo compared to treatment.[254] A poor-quality trial comparing vaginal moisturizer against dienoestrol vaginal cream reported improved vaginal dryness with dienoestrol.[256]

Manual therapies. A fair-quality trial of low force osteopathic manipulation of the pelvis, spine, and cranium was compared against sham low force touch in similar areas (Table 13).[260] After 10 weeks of therapy, results indicated improved hot flashes and nights sweats, urinary frequency, depression, and insomnia with treatment compared with placebo.[260]

Energy therapies. A poor-quality trial of women undergoing nine sessions of reflexology provided over 19 weeks resulted in no differences in severity of hot flashes and night sweats or measures of health and well-being compared to women receiving standard foot massages (Table 13).[261]

Behavioral Interventions

A total of 436 abstracts were identified and eight randomized controlled trials met inclusion criteria (Table 14, Appendix 6-8). Trials consisted of exercise,[265-267] relaxation, [268-270] low frequency sound wave audiotape,[271] and education interventions.[272] Of these, three trials were rated fair-quality,[265,267,272] and five poor.[266,268-271] One additional trial was reported in abstract form and is included only in the evidence table (Appendix 6-8).[226]

Exercise. Two fair-quality studies evaluated the effects of aerobic exercise using comparison groups that underwent stretching activities[265] or received usual care[267] (Table 14). Outcomes included hot flashes and other vasomotor symptoms, mood and depression, cognitive function, sleep, well-being, and quality of life. Results of one trial indicated no differences in outcomes in the exercise group compared to the stretching group.[265] A subset of women categorized as recently entering menopause showed improved memory in the aerobic vs. stretching group. [265] In a trial of exercise compared to usual care, exercisers showed significantly improved quality of life on the Nottingham Health Profile.[267]

Other Interventions. A fair-quality trial compared health education with usual care and found no differences between groups for measures of mood, health, vaginal dryness, or sexual relationships.[272] Knowledge of menopause increased in the intervention group, while the control group was more likely to attribute symptoms to menopause.[272] Other trials rated poor-quality due to limitations in methods and/or small numbers of subjects evaluated biofeedback, relaxation, paced respiration, and use of audiotapes (Table 14).

Summary

Results of trials of therapies providing between group comparisons are summarized in Table 15. Although benefits and adverse effects of therapies were equally important in this review, most trials did not report adverse effects or reported them incompletely. Studies of estrogen provided the most information. It is unclear how applicable the adverse effects reported from other larger estrogen trials, such as the Women's Health Initiative (WHI), are for younger, symptomatic women taking estrogen for brief periods.[104] For women in the WHI who reported having menopausal symptoms, strokes and coronary heat disease events were not significantly elevated.[273,274] Other important adverse outcomes, such as breast cancer, thrombosis, and gall bladder disease, have not been reported by age and symptom status in this trial.

Main findings from trials of therapies include:

- 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.

Key Question 4. Therapies for Women with Specific Characteristics

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

Bilateral Oophorectomy

A large number of studies reported data on women with bilateral oophorectomies, but did not stratify results by this characteristic.[142,144-148,150,163,165,169,173,181,188,192,193,195,197,217,242,256] Trials of estrogen that exclusively enrolled women with oophorectomies to take unopposed estrogen reported similar improvements in vasomotor symptoms as trials of women without oophorectomies taking opposed estrogen.[16]

Premature Ovarian Failure

Only one trial of soy isoflavones considered premature ovarian failure, but results were not reported specifically for women with this condition.[217]

Breast Cancer

A total of 200 abstracts were identified and 15 randomized controlled trials met inclusion criteria (Table 16, Appendix 6-9).[275-289] Of these, 3 trials were rated good-quality,[278,280,285] 10 fair,[275-277,279,281-284,287,288] and 2 poor.[286,289] Major limitations of trials include small size, lack of sufficient detail regarding recruitment and randomization, non blinding, and lack of intention-to-treat analyses. Two studies recruited women who either had a history of breast cancer or a perceived increased risk of breast cancer,[282,283] and all other trials included women who had prior diagnoses of breast cancer but no residual disease and who were no longer receiving chemotherapy or radiation. Most studies included women taking tamoxifen, although tamoxifen-users represented varying proportions of the study populations (31 percent to 100 percent). Results for tamoxifen-users were presented separately in only one trial,[276] and in three trials, all women were taking tamoxifen.[284-286] Study designs did not allow ascertainment of whether treatments were addressing a side effect of tamoxifen therapy[284-286] or vasomotor symptoms that occur naturally in women with a history of breast cancer. All studies recruited women from breast cancer clinics.

Trials used conventional and complementary/alternative medical treatments including venlafaxine,[282] fluoxetine,[283] clonidine,[284,285] megestrol acetate,[280] various preparations of soy/isoflavone products,[277-279,288] black cohosh,[276,286] magnets,[289] vitamin E,[275] and a polycarbonphil-based vaginal moisturizer.[281] All compared treatments with placebo or usual care. Outcomes included hot flashes, sleep disturbances, mood, somatic complaints, sexual dysfunction, vaginal dryness, quality of life, and overall menopausal symptoms. No trials evaluated cognitive symptoms, urinary symptoms, or uterine bleeding.

Clonidine, venlafaxine, and megestrol acetate were associated with significantly improved measures of hot flashes.[280,282,284,285] A good-quality trial of oral clonidine indicated a 38 percent decrease in hot flashes for clonidine (8 to 5 hot flashes/day) vs. 24 percent for placebo (7.4 to 5.7 hot flashes/day).[285] In a fair-quality trial of transdermal clonidine, hot flashes decreased 44 percent with clonidine (6.1 to 3.4 hot flashes/day) compared to 27 percent for placebo (7 to 5.1 hot flashes/day).[284] Megestrol acetate reduced hot flashes by 74 percent compared to 27 percent for placebo in a good-quality trial.[280] A fair-quality trial of venlafaxine reported a mean decrease in hot flashes of 30 percent to 58 percent for varying doses of venlafaxine vs. 19 percent for placebo.[282] Vitamin E, black cohosh, isoflavones, magnets, and fluoxetine alone did not reduce hot flashes.

Results for other outcomes were mixed. Sleep was improved in a fair-quality trial evaluating fluoxetine,[283] but not in a fair-quality trial using black cohosh.[276] None of the four fair-quality trials assessing mood (fluoxetine, venlafaxine, phytoestrogen and black cohosh) found them to be effective.[276,279,282,283] Of the trials evaluating somatic complaints (headaches, palpitations, excessive sweating, nausea, fatigue), the only benefit reported was from a single fair-quality trial using black cohosh showing improvement of excessive sweating.[276] Behavioral counseling with tailored therapies was effective at improving sexual functioning in one trial,[287] but a fair-quality trial of venlafaxine found no difference in libido.[282] The one trial evaluating polycarbophil-

based vaginal preparation found it no more effective than placebo in reducing vaginal dryness, but effective at improving dyspareunia scores.[281] Of the four trials evaluating quality of life, clonidine improved measures,[285]while fluoxetine, magnets, and behavioral counseling did not.[282,287,289] Three trials assessed overall menopausal symptoms, of which only behavioral counseling was effective.[287]

Adverse effects were reported in 12 of 15 trials.[275-285,289] Gastrointestinal adverse effects occurred more often among women using phytoestrogen products,[278,279] particularly a soy beverage preparation.[278] Two other trials reported no gastrointestinal adverse effects with soy preparations,[277,288] although one trial excluded all women with intolerance to soy prior to randomization. [288] Fluoxetine was associated with worse appetite, nausea, constipation and dry mouth than placebo.[283] The clonidine patch was associated with dry mouth, constipation, itchiness under the patch, and drowsiness.[284] Clonidine tablets were associated with a trend toward more difficulty sleeping than placebo.[285] Participants in the trial of magnets had difficulty with itching, redness, and perspiration at the site where magnets were affixed.[289] Polycarbophil-based vaginal preparation was associated with an undesirable "wetness sensation."[281]

Concurrent Use of Selective Estrogen Receptor Modulators (SERMs) and Other Agents

Patients using tamoxifen were enrolled in most of the trials of therapies in women with breast cancer.[275-279,282-287] One fair-quality study of black cohosh reported hot flash symptoms separately for tamoxifen users vs. non-users, but found no significant differences between groups.[276] Other studies of treatment of menopausal symptoms did not describe how concurrent use of SERMs affects therapy.

Lifestyle and Behavioral Factors

Few trials considered lifestyle and behavioral factors such as smoking, alcohol use, diet, or others,[161,162,169,170] and no trials reported results according to these factors.

Recent Discontinuation of Menopausal Hormone Therapy

Most trials required discontinuation of hormone therapy prior to enrollment, however, no results were specifically reported for women with recent discontinuation.

Very Low or Very High Body Mass Index (BMI)

Some trials specified a range of acceptable BMIs in their eligibility criteria thereby disallowing enrollment of women with very high or low BMI. No studies reported results according to BMI.

Summary

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

Key Question 5. Future Research on Therapies

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

Although many trials of several types of interventions have been published, results are consistent and conclusive only for estrogen agents for the treatment of vasomotor and urogenital symptoms. Despite this evidence, many questions remain about the benefits and adverse effects of estrogen for treating menopause related symptoms long-term. For nonestrogen therapies, larger, more rigorous, and more comprehensive trials are needed in order to determine benefits and adverse effects. Funding for nonindustry sponsored trials would enable trials of non drug therapies, including head-to-head trials comparing several types of drug and non drug interventions. Future research should include:

- 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, and outcomes so results can be compared across trials.

Chapter 4. Discussion

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 studies provide data on cognition and 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.

References

1. North American Menopause Society. Available at: www.menopause.org. Accessed 13 Dec, 2004.

2. Soules MR, Sherman S, Parrott E, et al. Executive summary: stages of reproductive aging workshop (STRAW) Park City, Utah, July 2001. Menopause 2001;8:402-7.

3. National Institutes of Health. Assessing and improving measures of hot flashes: summary of an NIH workshop. Bethesda, Maryland: Rose Li and Associates; January 20, 2004.

4. Greene JG. A factor analytic study of climacteric symptoms. Journal of Psychosomatic Research 1976;20(5):425-30.

5. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.

6. McNair DM, Lorr M. An analysis of mood in neurotics. Journal of Abnormal & Social Psychology 1964;69(6):620-27.

7. Fazio AF. A concurrent validational study of the NCHS General Well-Being schedule. Vital & Health Statistics, Series 2. No 73, Sep 1977, 53.: U Wisconsin, Milwaukee; 1977.

8. Taylor JF, Rosen RC, Leiblum SR. Self-report assessment of female sexual function: Psychometric evaluation of the Brief Index of Sexual Functioning for Women. Arch Sex Behav 1994;23(6):627-43.

9. Nathorst-Boos J, Wiklund I, Mattsson LA, et al. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. Acta Obstet Gynecol Scand 1993;72(8):656-60.

10. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: Development and psychometric properties. Maturitas 1996;24(3):161-75.

11. Wiklund I, Holst J, Karlberg J, et al. A new methodological approach to the evaluation of quality of life in postmenopausal women. Maturitas 1992;14(3):211-24.

12. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical Care 1992;30(6):473-83.

13. Slavin RE. Best practice synthesis: An alternative to meta-analytic and traditional reviews. Education Research 1986;15:5-11.

14. National Center for Complementary and Alternative Medicine. http://nccam.nih.gov/health/whatiscam/. Accessed 10 Dec., 2004.

15. Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. JAMA 2004;291(13):1610-20.

16. MacLennan AH, Broadbent JL, Lester S, et al. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2004.

17. Nelson HD, Nygren P, Freeman M, et al. Drug Class Review on Estrogens. Final report. http://www.ohsu.edu/drugeffectiveness/reports/documents/Estrogens%20Final%20Report%20u2.pdf 2004. Accessed 10 Jan. 2005.

18. Krebs EE, Ensrud KE, MacDonald R, et al. Phytoestrogens for treatment of menopausal symptoms: A systematic review. Obstet Gynecol 2004;104(4):824-36.

19. 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.

20. Avis NE, Brambilla D, McKinlay SM, et al. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. Ann Epidemiol. 1994;4(3):214-20.

21. Avis NE, Crawford SL, McKinlay SM. Psychosocial, behavioral, and health factors related to menopause symptomatology. Womens Health. 1997;3(2):103-20.

22. Avis NE, Stellato R, Crawford S, et al. Is there an association between menopause status and sexual functioning? Menopause. 2000;7(5):297-309.

23. McKinlay JB, McKinlay SM, Brambilla D. The relative contributions of endocrine changes and social circumstances to depression in mid-aged women. J Health Soc Behav. 1987;28(4):345-63.

24. McKinlay SM, McKinlay JB. The impact of menopause and social factors on health. In: Hammond CB, Haseltine FP, Schiff I, editors. Menopause: Evaluation, treatment, and health concerns. New York: Alan R. Liss; 1989. p. 137-61.

25. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas. 1992;14(2):103-15.

26. Mitchell ES, Woods NF. Symptom experiences of midlife women: observations from the Seattle Midlife Women's Health Study. Maturitas. 1996;25(1):1-10.

27. Mitchell ES, Fugate Woods N. Midlife women's attributions about perceived memory changes: Observations from the Seattle Midlife Women's Health Study. J Womens Health Gender Based Med 2001;10(4):351-62.

28. Woods NF, Mitchell ES. Pathways to depressed mood for midlife women: observations from the Seattle Midlife Women's Health Study. Res Nurs Health 1997;20(2):119-29.

29. Glazer G, Zeller R, Delumba L, et al. The Ohio Midlife Women's Study. Health Care Women Int 2002;23(6-7):612-30.

30. Busch CM, Zonderman AB, Costa PT. Menopausal transition and psychological distress in a nationally representative sample: Is menopause associated with psychological distress? J Aging Health 1994;6(2):209-28.

31. Sowers M, Luborsky J, Perdue C, et al. Thyroid stimulating hormone (TSH) concentrations and menopausal status in women at the mid-life: SWAN. Clin Endocrinol 2003;58(3):340-7.

32. Sowers M, Crawford SL, Sternfeld B, et al. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus R, editors. Menopause: Biology and pathobiology. San Diego, CA: Academic Press; 2000. p. 175-88.

33. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med 2001;52(3):345-56.

34. Avis NE, Ory M, Matthews KA, et al. Health-related quality of life in a multiethnic sample of middle-aged women: Study of Women's Health Across the Nation (SWAN). Medical Care. 2003;41(11):1262-76.

35. Bromberger JT, Meyer PM, Kravitz HM, et al. Psychologic distress and natural menopause: a multiethnic community study. Am J Public Health. 2001;91(9):1435-42.

36. Bromberger JT, Assmann SF, Avis NE, et al. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. Am J Epidemiol 2003;158(4):347-56.

37. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. Am J Epidemiol 2000;152(5):463-73.

38. Kravitz HM, Ganz PA, Bromberger J, et al. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause. 2003;10(1):19-28.

39. Randolph JF, Jr., Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88(4):1516-22.

40. Koch PB, Mansfield PK, Voda A. Predictors of sexual response changes in heterosexual midlife women. Health Values 1995;19(1):10-20.

41. Freeman EW, Sammel MD, Liu L, et al. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 2004;61(1):62-70.

42. Gracia CR, Sammel MD, Freeman EW, et al. Predictors of decreased libido in women during the late reproductive years. Menopause. 2004;11(2):144-50.

43. Rodstrom K, Bengtsson C, Lissner L, et al. A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. Menopause 2002;9:156-61.

44. Hallstrom T, Samuelsson S. Mental health in the climacteric. The longitudinal study of women in Gothenburg. Acta Obstet Gynecol Scand Suppl 1985;130:13-8.

45. Milsom I, Ekelund P, Molander U, et al. The influence of age, parity, oral contraception, hysterectomy and menopause on the prevalence of urinary incontinence in women. Journal of Urology. 1993;149(6):1459-62.

46. Brown WJ, Mishra GD, Dobson A. Changes in physical symptoms during the menopause transition. Int J Behav Med. 2002;9(1):53-67.

47. Mishra GD, Brown WJ, Dobson AJ. Physical and mental health: changes during menopause transition. Quality of Life Research. 2003;12(4):405-12.

48. Kuh DL, Wadsworth M, Hardy R. Women's health in midlife: the influence of the menopause, social factors and health in earlier life. Br J Obstet Gynaecol 1997;104(8):923-33.

49. Kuh D, Cardozo L, Hardy R. Urinary incontinence in middle aged women: childhood enuresis and other lifetime risk factors in a British prospective cohort. Journal of Epidemiology & Community Health 1999;53(8):453-8.

50. Kuh D, Hardy R, Rodgers B, et al. Lifetime risk factors for women's psychological distress in midlife. Soc Sci Med 2002;55(11):1957-73.

51. Hardy R, Kuh D. Change in psychological and vasomotor symptom reporting during the menopause. Soc Sci Med 2002;55(11):1975-88.

52. Dennerstein L, Dudley E, Burger H. Well-being and the menopausal transition. J Psychosom Obstet Gynaecol 1997;18(2):95-101.

53. Dennerstein L, Dudley EC, Hopper JL, et al. A prospective population-based study of menopausal symptoms. Obstet Gynecol. 2000;96(3):351-8.

54. Dennerstein L, Lehert P, Burger H, et al. Mood and the menopausal transition. J Nerv Ment Dis. 1999;187(11):685-91.

55. Dennerstein L, Lehert P, Dudley E, et al. Factors contributing to positive mood during the menopausal transition. Journal of Nervous & Mental Disease. 2001;189(2):84-9.

56. Sherburn M, Guthrie JR, Dudley EC, et al. Is incontinence associated with menopause? Obstet Gynecol. 2001;98(4):628-33.

57. Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? Fertil Steril 2001;76(3):456-60.

58. Dennerstein L, Randolph J, Taffe J, et al. Hormones, mood, sexuality, and the menopausal transition. Fertil Steril 2002;77(Suppl 4):S42-8.

59. Dennerstein L, Lehert P, Guthrie J. The effects of the menopausal transition and biopsychosocial factors on well-being. Archives of Women's Mental Health. 2002;5(1):15-22.

60. Dennerstein L, Smith AM, Morse C, et al. Menopausal symptoms in Australian women. Med J Aust 1993;159(4):232-6.

61. Dennerstein L, Smith AM, Morse CA, et al. Sexuality and the menopause. J Psychosom Obstet Gynaecol 1994;15(1):59-66.

62. Guthrie JR, Dennerstein L, Hopper JL, et al. Hot flushes, menstrual status, and hormone levels in a population-based sample of midlife women. Obstet Gynecol. 1996;88(3):437-42.

63. Kaufert PA, Gilbert P, Tate R. The Manitoba Project: a re-examination of the link between menopause and depression. Maturitas. 1992;14(2):143-55.

64. Koster A, Davidsen M. Climacteric complaints and their relation to menopausal development--a retrospective analysis. Maturitas. 1993;17(3):155-66.

65. Koster A, Garde K. Sexual desire and menopausal development. A prospective study of Danish women born in 1936. Maturitas. 1993;16(1):49-60.

66. Koster A, Eplov LF, Garde K. Anticipations and experiences of menopause in a Danish female general population cohort born in 1936. Archives of Women's Mental Health. 2002;5(1):9-13.

67. Maartens LW, Leusink GL, Knottnerus JA, et al. Climacteric complaints in the community. Family Practice. 2001;18(2):189-94.

68. Maartens LW, Knottnerus JA, Pop VJ. Menopausal transition and increased depressive symptomatology: a community based prospective study. Maturitas. 2002;42(3):195-200.

69. Hunter MS, Whitehead MI. Psychological experience of the climacteric and postmenopause. Progress in Clinical & Biological Research. 1989;320:211-24.

70. Avis NE, Kaufert PA, Lock M, et al. The evolution of menopausal symptoms. Baillieres Clin Endocrinol Metab 1993;7(1):17-32.

71. Bardel A, Wallander MA, Svardsudd K. Hormone replacement therapy and symptom reporting in menopausal women: a population-based study of 35-65-year-old women in mid-Sweden. Maturitas. 2002;41(1):7-15.

72. Bell ML. Attitudes toward menopause among Mexican American women. Health Care Women Int 1995;16(5):425-35.

73. Feldman BM, Voda A, Gronseth E. The prevalence of hot flash and associated variables among perimenopausal women. Res Nurs Health 1985;8(3):261-8.

74. Groeneveld FP, Bareman FP, Barentsen R, et al. The climacteric and well-being. J Psychosom Obstet Gynaecol 1993;14(2):127-43.

75. Hagstad A, Janson PO. The epidemiology of climacteric symptoms. Acta Obstet Gynecol Scand Suppl 1986;134:59-65.

76. Hammar M, Berg G, Fahraeus L, et al. Climacteric symptoms in an unselected sample of Swedish women. Maturitas. 1984;6(4):345-50.

77. Hording U, Pedersen KH, Sidenius K, et al. Urinary incontinence in 45-year-old women. An epidemiological survey. Scandinavian Journal of Urology & Nephrology. 1986;20(3):183-6.

78. Jaszmann L, Van Lith ND, Zaat JC. The age of menopause in the Netherlands. The statistical analysis of a survey. Int J Fertil. 1969;14(2):106-17.

79. Jansson C, Johansson S, Lindh-Astrand L, et al. The prevalence of symptoms possibly related to the climacteric in pre- and postmenopausal women in Linkoping, Sweden. Maturitas. 2003;45(2):129-35.

80. Keenan NL, Mark S, Fugh-Berman A, et al. Severity of menopausal symptoms and use of both conventional and complementary/alternative therapies. Menopause. 2003;10(6):507-15.

81. Li C, Wilawan K, Samsioe G, et al. Health profile of middle-aged women: The Women's Health in the Lund Area (WHILA) study. Human Reproduction. 2002;17(5):1379-85.

82. McKinlay SM, Jefferys M. The menopausal syndrome. Br J Prev Soc Med 1974;28(2):108-15.

83. O'Connor VM, Del Mar CB, Sheehan M, et al. Do psycho-social factors contribute more to symptom reporting by middle-aged women than hormonal status? Maturitas. 1995;20(2-3):63-9.

84. Olofsson AS, Collins A. Psychosocial factors, attitude to menopause and symptoms in Swedish perimenopausal women. Climacteric. 2000;3(1):33-42.

85. Porter M, Penney GC, Russell D, et al. A population based survey of women's experience of the menopause. Br J Obstet Gynaecol 1996;103(10):1025-8.

86. Rekers H, Drogendijk AC, Valkenburg HA, et al. The menopause, urinary incontinence and other symptoms of the genito-urinary tract. Maturitas. 1992;15(2):101-11.

87. Rybo G, Westerberg H. Symptoms in the postmenopause--a population study. A preliminary report. Acta Obstet Gynecol Scand Suppl 1971;9:Suppl(9):25.

88. Schwingl PJ, Hulka BS, Harlow SD. Risk factors for menopausal hot flashes. Obstet Gynecol 1994;84(1):29-34.

89. Slaven L, Lee C. A cross-sectional survey of menopausal status, symptoms and psychological distress in a community sample of Australian women. J Health Psychol 1998;3(1):117-23.

90. Thompson B, Hart SA, Durno D. Menopausal age and symptomatology in a general practice. J Biosoc Sci 1973;5(1):71-82.

91. Young T, Rabago D, Zgierska A, et al. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. Sleep. 2003;26(6):667-72.

92. Young T, Finn L, Austin D, et al. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003;167(9):1181-5.

93. Matthews KA, Wing RR, Kuller LH, et al. Influences of natural menopause on psychological characteristics and symptoms of middle-aged healthy women. J Consult Clin Psychol 1990;58(3):345-51.

94. Treloar AE. Menstrual cyclicity and the pre-menopause. Maturitas. 1981;3(3-4):249-64.

95. Treloar AE. Menarche, menopause, and intervening fecundability. Hum Biol 1974;46(1):89-107.

96. McKinlay SM, Bigano NL, McKinlay JB. Smoking and age at menopause. Ann Intern Med 1985;103:350-6.

97. Nilsson P, Moller L, Koster A, et al. Social and biological predictors of early menopause: a model for premature aging. J Intern Med 1997;242(4):299-305.

98. Cooper GS, Sandler DP, Bohlig M. Active and passive smoking and the occurrence of natural menopause. Epidemiology. 1999;10(6):771-3.

99. Kato I, Toniolo P, Akhmedkhanov A, et al. Prospective study of factors influencing the onset of natural menopause. J Clin Epidemiol 1998;51(12):1271-6.

100. Whelan EA, Sandler DP, McConnaughey DR, et al. Menstrual and reproductive characteristics and age at natural menopause. Am J Epidemiol 1990;131(4):625-32.

101. Sherman B, Wallace R, Bean J, et al. Relationship of body weight to menarcheal and menopausal age: implications for breast cancer risk. J Clin Endocrinol Metab 1981;52(3):488-93.

102. MacLennan AH, Henry D, Hills S, et al. Oral oestrogen replacement therapy versus placebo for hot flushes, Menstrual Disorders Module of the Cochrane Database of Systematic Reviews. Menstrual Disorders Module of the Cochrane Database Syst Rev 2000.

103. MacLennan A, Lester S, Moore V. Oral estrogen replacement therapy versus placebo for hot flushes: a systematic review. Climacteric. 2001;4(1):58-74.

104. Nelson HD. Postmenopausal estrogen for treatment of hot flashes: clinical applications. JAMA 2004;291(13):1621-25.

105. Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. Obstet Gynecol 2003;102:823-34.

106. Al-Azzawi F, Buckler HM. Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms. Climacteric. 2003;6(2):118-27.

107. Ayton RA, Darling GM, Murkies AL, et al. A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. Br J Obstet Gynaecol 1996;103(4):351-8.

108. Bachmann G, Notelovitz M, Nachtigall L, et al. A comparative study of a low-dose estradiol vaginal ring and conjugated estrogen cream for postmenopausal urogenital atrophy. Primary Care Update for Ob/Gyns 1997;4(3):109-15.

109. Rioux JE, Devlin C, Gelfand MM, et al. 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 2000;7(3):156-61.

110. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. Am J Obstet Gynecol 1993;168(3 Pt 1):824-30.

111. von Holst T, Salbach B. Efficacy and tolerability of a new 7-day transdermal estradiol patch versus placebo in hysterectomized women with postmenopausal complaints. Maturitas 2000;34(2):143-53.

112. Shulman LP, Yankov V, Uhl K. Safety and efficacy of a continuous once-a-week 17beta-estradiol/levonorgestrel transdermal system and its effects on vasomotor symptoms and endometrial safety in postmenopausal women: the results of two multicenter, double-blind, randomized, controlled trials. Menopause 2002;9(3):195-207.

113. Campbell S. Double blind psychometric studies on the effects of natural estrogens on post-menopausal women. In: Campbell S, editor. The Management of the Menopause and Post Menopausal Years. Lancaster: MTP; 1976.

114. Good WR, John VA, Ramirez M, et al. Comparison of Alora estradiol matrix transdermal delivery system with oral conjugated equine estrogen therapy in relieving menopausal symptoms. Climacteric 1999;2(1):29-36.

115. Polo-Kantola P, Erkkola R, Helenius H, et al. When does estrogen replacement therapy improve sleep quality? Am J Obstet Gynecol 1998;178(5):1002-9.

116. Hays J, Ockene J, Brunner R, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med 2003;348(19):1839-54.

117. Purdie DW, Empson JAC, Crichton C, et al. Hormone replacement therapy, sleep quality and psychological wellbeing. Br J Obstet Gynaecol 1995;102(9):735-39.

118. Soares CdN, Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: A double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2001;58(6):529-34.

119. Strickler R, Stovall DW, Merritt D, et al. Raloxifene and estrogen effects on quality of life in healthy postmenopausal women: a placebo-controlled randomized trial. Obstet Gynaecol 2000;96(3):359-65.

120. Voss S, Quail D, Dawson A, et al. A randomised, double-blind trial comparing raloxifene HCl and continuous combined hormone replacement therapy in postmenopausal women: effects on compliance and quality of life. BJOG 2002;109(8):874-85.

121. Khoo SK, Coglan M, Battistutta D, et al. Hormonal treatment and psychological function during the menopausal transition: an evaluation of the effects of conjugated estrogens/cyclic medroxyprogesterone acetate. Climacteric 1998;1(1):55-62.

122. Bech P, Munk-Jensen N, Obel E, et al. Combined versus sequential hormonal replacement therapy: A double-blind, placebo-controlled study on quality of life-related outcome measures. Psychother Psychosom 1998;67(4-5):259-65.

123. Saure A, Planellas J, Poulsen HK, et al. A double-blind, randomized, comparative study evaluating clinical effects of two sequential estradiol-progestogen combinations containing either desogestrel or medroxyprogesterone acetate in climacteric women. Maturitas. 2000;34(2):133-42.

124. Ditkoff EC, Crary WG, Cristo M, et al. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet Gynaecol 1991;78(6):991-5.

125. Furuhjelm M, Karlgren E, Carlstrom K. The effect of estrogen therapy on somatic and psychical symptoms in postmenopausal women. Acta Obstet Gynecol Scand 1984;63(7):655-61.

126. Hall G, Pripp U, Schenck-Gustafsson K, et al. Long-term effects of hormone replacement therapy on symptoms of angina pectoris, quality of life and compliance in women with coronary artery disease. Maturitas. 1998;28(3):235-42.

127. Klaiber EL, Broverman DM, Vogel W, et al. Individual differences in changes in mood and platelet monoamine oxidase (MAO) activity during hormonal replacement therapy in menopausal women. Psychoneuroendocrinology. 1996;21(7):575-92.

128. Gerdes LC, Sonnendecker EW, Polakow ES. Psychological changes effected by estrogen-progestogen and clonidine treatment in climacteric women. Am J Obstet Gynecol 1982;142(1):98-104.

129. Thomson J, Oswald I. Effect of oestrogen on the sleep, mood, and anxiety of menopausal women. BMJ 1977;2(6098):1317-9.

130. Wheatley D. Hormone replacement therapy in post menopausal depression and the female climacteric. Curr Med Res Opin 1977;4(SUP 3):37-45.

131. Wilklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. Am J Obstet Gynecol 1993;168:824-30.

132. Karlberg J, Mattsson LA, Wiklund I. A quality of life perspective on who benefits from estradiol replacement therapy. Acta Obstet Gynecol Scand 1995;74(5):367-72.

133. Skarsgard C, Berg GE, Ekblad S, et al. Effects of estrogen therapy on well-being in postmenopausal women without vasomotor complaints. Maturitas 2000;36(2):123-30.

134. Derman RJ, Dawood MY, Stone S. Quality of life during sequential hormone replacement therapy -- a placebo-controlled study. Int J Fertil Menopausal Stud 1995;40(2):73-8.

135. Rebar RW, Trabal J, Mortola J. Low-dose esterified estrogens (0.3 mg/day): long-term and short-term effects on menopausal symptoms and quality of life in postmenopausal women. Climacteric. 2000;3(3):176-82.

136. Hilditch JR, Lewis J, Ross AH, et al. A comparison of the effects of oral conjugated equine estrogen and transdermal estradiol-17betacombined with an oral progestin on quality of life in postmenopausal women. Maturitas 1996;24(3):177-84.

137. Wren BG, Champion SM, Willetts K, et al. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. Menopause 2003;10(1):13-8.

138. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. Obstet Gynaecol 1999;94(2):225-8.

139. de Wit H, Schmitt L, Purdy R, et al. Effects of acute progesterone administration in healthy postmenopausal women and normally-cycling women. Psychoneuroendocrinology 2001;26(7):697-710.

140. Morrison JC, Martin DC, Blair RA, et al. The use of medroxyprogesterone acetate for relief of climacteric symptoms. Am J Obstet Gynecol 1980;138(1):99-104.

141. Schiff I, Tulchinsky D, Cramer D, et al. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. JAMA 1980;244(13):1443-5.

142. Lobo RA, Rosen RC, Yang HM, et al. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79(6):1341-52.

143. Hickok LR, Toomey C, Speroff L. A comparison of esterified estrogens with and without methyltestosterone: effects on endometrial histology and serum lipoproteins in postmenopausal women. Obstet Gynaecol 1993;82(6):919-24.

144. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000;343(10):682-8.

145. Dobs AS, Nguyen T, Pace C, et al. Differential effects of oral estrogen versus oral estrogen-androgen replacement therapy on body composition in postmenopausal women. J Clin Endocrinol Metab 2002;87(4):1509-16.

146. Barrett-Connor E, Young R, Notelovitz M, et al. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. J Reprod Med 1999;44(12):1012-20.

147. Raisz LG, Wiita B, Artis A, et al. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. J Clin Endocrinol Metab 1996;81(1):37-43.

148. Watts NB, Notelovitz M, Timmons MC, et al. Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. Obstet Gynaecol 1995;85(4):529-37.

149. Simon J, Klaiber E, Wiita B, et al. Differential effects of estrogen-androgen and estrogen-only therapy on vasomotor symptoms, gonadotropin secretion, and endogenous androgen bioavailability in postmenopausal women. Menopause. 1999;6(2):138-46.

150. Floter A, Nathorst-Boos J, Carlstrom K, et al. Addition of testosterone to estrogen replacement therapy in oophorectomized women: effects on sexuality and well-being. Climacteric. 2002;5(4):357-65.

151. Penotti M, Sironi L, Cannata L, et al. Effects of androgen supplementation of hormone replacement therapy on the vascular reactivity of cerebral arteries. Fertil Steril 2001;76(2):235-40.

152. Braunstein G. Testosterone patches for the treatment of low sexual desire in surgically menopausal women. Menopause 2003;10:587 Abstract p-70.

153. Davis S, Rees M, Ribot C, et al. Efficacy and safety of testosterone patches for the treatment of low sexual desire in surgically menopausal women.[abstract]. Fertil Steril 2003;80:S76.

154. Barnhart KT, Freeman E, Grisso JA, et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. J Clin Endocrinol Metab 1999;84(11):3896-902.

155. Stomati M, Rubino S, Spinetti A, et al. Endocrine, neuroendocrine and behavioral effects of oral dehydroepiandrosterone sulfate supplementation in postmenopausal women. Gynecol Endocrinol 1999;13(1):15-25.

156. Lam PM, Cheung GW, Shek DT, et al. A randomized, placebo-controlled, crossover study of tibolone (Livial) on menopause symptoms, psychological well-being, and dyadic relationship of postmenopausal Chinese women and their spouses. Menopause 2004;11(4):416-22.

157. Meeuwsen IB, Samson MM, Duursma SA, et al. The influence of tibolone on quality of life in postmenopausal women. Maturitas. 2002;41(1):35-43.

158. Winkler UH, Altkemper R, Kwee B, et al. Effects of tibolone and continuous combined hormone replacement therapy on parameters in the clotting cascade: a multicenter, double-blind, randomized study. Fertil Steril 2000;74(1):10-9.

159. Hammar M, Christau S, Nathorst-Boos J, et al. A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. Br J Obstet Gynaecol 1998;105(8):904-11.

160. Huber J, Palacios S, Berglund L, et al. Effects of tibolone and continuous combined hormone replacement therapy on bleeding rates, quality of life and tolerability in postmenopausal women. BJOG 2002;109(8):886-93.

161. Lloyd G, McGing E, Cooper A, et al. A randomised placebo controlled trial of the effects of tibolone on blood pressure and lipids in hypertensive women. J Hum Hypertens 2000;14(2):99-104.

162. Ross LA, Alder EM, Cawood EH, et al. Psychological effects of hormone replacement therapy: a comparison of tibolone and a sequential estrogen therapy. J Psychosom Obstet Gynaecol 1999;20(2):88-96.

163. Baracat EC, Barbosa IC, Giordano MG, et al. A randomized, open-label study of conjugated equine estrogens plus medroxyprogesterone acetate versus tibolone: effects on symptom control, bleeding pattern, lipid profile and tolerability. Climacteric 2002;5(1):60-9.

164. Benedek-Jaszmann LJ. Long-term placebo-controlled efficacy and safety study of Org OD 14 in climacteric women. Maturitas. 1987;Suppl(1):25-33.

165. De Aloysio D, Fabiani AG, Mauloni M, et al. Use of Org OD 14 for the treatment of climacteric complaints. Maturitas. 1987;Suppl(1):49-65.

166. Egarter C, Huber J, Leikermoser R, et al. Tibolone versus conjugated estrogens and sequential progestogen in the treatment of climacteric complaints. Maturitas. 1996;23(1):55-62.

167. Hudita D, Posea C, Ceausu I, et al. Efficacy and safety of oral tibolone 1.25 or 2.5 mg/day vs. placebo in postmenopausal women. Eur Rev Med Pharmacol Sci 2003;7(5):117-25.

168. Landgren MB, Bennink HJ, Helmond FA, et al. Dose-response analysis of effects of tibolone on climacteric symptoms. BJOG 2002;109(10):1109-14.

169. Mendoza N, Suarez AM, Alamo F, et al. Lipid effects, effectiveness and acceptability of tibolone versus transdermic 17 beta-estradiol for hormonal replacement therapy in women with surgical menopause. Maturitas. 2000;37(1):37-43.

170. Mendoza N, Pison JA, Fernandez M, et al. Prospective, randomised study with three HRT regimens in postmenopausal women with an intact uterus. Maturitas. 2002;41(4):289-98.

171. Nathorst-Boos J, Hammar M. Effect on sexual life--a comparison between tibolone and a continuous estradiol-norethisterone acetate regimen. Maturitas 1997;26(1):15-20.

172. Palacios S, Menendez C, Jurado AR, et al. Changes in sex behaviour after menopause: effects of tibolone. Maturitas. 1995;22(2):155-61.

173. Volpe A, Facchinetti F, Grasso A, et al. Benefits and risks of different hormonal replacement therapies in post-menopausal women. Maturitas. 1986;8(4):327-34.

174. Wu MH, Pan HA, Wang ST, et al. Quality of life and sexuality changes in postmenopausal women receiving tibolone therapy. Climacteric. 2001;4(4):314-9.

175. Yang TS, Tsan SH, Chen CR, et al. Evaluation of conjugated estrogen plus medroxyprogesterone acetate versus tibolone in early postmenopausal Chinese women. Chung Hua i Hsueh Tsa Chih - Chin Med J 1999;62(5):308-15.

176. Dansuk R, Unal O, Turan C. Evaluation of the effect of tibolone and transdermal estradiol on triglyceride level in hypertriglyceridemic and normohypertriglyceridemic postmenopausal women (abstract). Climacteric 2002;5(Supplement 1).

177. Johannes E, Coelingh Bennink H, Engelen S, et al. Tibolone: Dose-Response Analysis of Effects on Climacteric Symptoms. Acta Obstet Gynecol Scand Suppl 1997;167:13, Abstract FC801.6.

178. Kokcu A, Cetinkaya MB, Yanik F, et al. The effects of tibolone and combined oestrogen plus progesterone therapy on the sexual performance of post-menopausal women. Hum Reprod 2000;15(A1):188, Abstract P233.

179. Yang TS, Ng HT. Preliminary Report of the Effects of HRT on the Chinese Early Postmenopausal Women: Conjugated Estrogen Plus Medroxyprogesterone Versus Tibolone. Acta Obstet Gynecol Scand Suppl 1997;167:58, Abstract P86.16.

180. Berning B, van Kuijk C, Bennink HJ, et al. Absent correlation between vaginal bleeding and oestradiol levels or endometrial morphology during tibolone use in early postmenopausal women. Maturitas. 2000;35(1):81-8.

181. Stearns V, Beebe KL, Iyengar M, et al. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003;289(21):2827-34.

182. Wesel S, Bourguignon RP, Bosuma WB. Veralipride versus conjugated oestrogens: a double-blind study in the management of menopausal hot flushes. Curr Med Res Opin 1984;8(10):696-700.

183. Evans ML, Pritts E, Vittinghoff E, et al. Management of postmenopausal hot flashes with Venlafaxine Hydrochloride: A randomized, controlled trial. Obstet Gynaecol 2005;105(1):161-66.

184. Melis GB, Gambacciani M, Cagnacci A, et al. Effects of the dopamine antagonist veralipride on hot flushes and luteinizing hormone secretion in postmenopausal women. Obstet Gynaecol 1988;72(5):688-92.

185. Zichella L, Falaschi P, Fioretti P, et al. Effects of different dopamine agonists and antagonists on post-menopausal hot flushes. Maturitas 1986;8(3):229-37.

186. David A, Don R, Tajchner G, et al. Veralipride: alternative antidopaminergic treatment for menopausal symptoms. Am J Obstet Gynecol 1988;158(5):1107-15.

187. Limouzin-Lamothe MA, Mairon N, Joyce CR, et al. Quality of life after the menopause: influence of hormonal replacement therapy. Am J Obstet Gynecol 1994;170(2):618-24.

188. Tarim E, Bagis T, Kilicdag E, et al. Moclobemide in the treatment of hot flashes in postmenopausal women. Adv Ther 2002;19(6):258-65.

189. Clayden JR, Bell JW, Pollard P. Menopausal flushing: double-blind trial of a non-hormonal medication. British Medical Journal 1974;1(905):409-12.

190. Bolli P, Simpson FO. Clonidine in menopausal flushing: a double-blind trial. New Zealand Medical Journal 1975;82(548):196-7.

191. Lindsay R, Hart DM. Failure of response of menopausal vasomotor symptoms to clonidine. Maturitas 1978;1(1):21-5.

192. Salmi T, Punnonen R. Clonidine in the treatment of menopausal symptoms. Int J Gynaecol Obstet 1979;16(5):422-6.

193. Edington RF, Chagnon JP, Steinberg WM. Clonidine (Dixarit) for menopausal flushing. CMAJ 1980;123(1):23-6.

194. Wren BG, Brown LB. A double-blind trial with clonidine and a placebo to treat hot flushes. Med J Aust 1986;144(7):369-70.

195. Nappi C, Petraglia F, de Chiara BM, et al. The effect of various drugs with neuroendocrine activity and transdermal estradiol on plasma gonadotropin concentrations after ovariectomy in reproductive-aged women. Acta Obstet Gynecol Scand 1991;70(6):435-9.

196. Sonnendecker EW, Polakow ES. Comparison of oestrogen-progestogen with clonidine in the climacteric syndrome. S Afr Med J 1980;58(19):753-56.

197. Nagamani M, Kelver ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. Am J Obstet Gynecol 1987;156(3):561-5.

198. Guttuso T, Jr., Kurlan R, McDermott MP, et al. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynaecol. 2003;101(2):337-45.

199. Andersen O, Engebretsen T, Solberg VM, et al. alpha-Methyldopa for climacteric hot flushes. A double-blind, randomized, cross-over study. Acta Obstet Gynecol Scand 1986;65(5):405-9.

200. Hammond MG, Hatley L, Talbert LM. A double blind study to evaluate the effect of methyldopa on menopausal vasomotor flushes. J Clin Endocrinol Metab 1984;58(6):1158-60.

201. Nesheim BI, Saetre T. Reduction of menopausal hot flushes by methyldopa. A double blind crossover trial. Eur J Clin Pharmacol 1981;20(6):413-6.

202. Bergmans MG, Merkus JM, Corbey RS, et al. Effect of Bellergal Retard on climacteric complaints: a double-blind, placebo-controlled study. Maturitas 1987;9(3):227-34.

203. Albertazzi P, Pansini F, Bonaccorsi G, et al. The effect of dietary soy supplementation on hot flushes. Obstet Gynaecol 1998;91(1):6-11.

204. Albertazzi P, Pansini F, Bottazzi M, et al. Dietary soy supplementation and phytoestrogen levels. Obstet Gynaecol 1999;94(2):229-31.

205. Balk JL, Whiteside DA, Naus G, et al. A pilot study of the effects of phytoestrogen supplementation on postmenopausal endometrium. J Soc Gynecol Investig 2002;9(4):238-42.

206. Burke GL, Legault C, Anthony M, et al. Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study. Menopause. 2003;10(2):147-53.

207. Han KK, Soares JM, Jr., Haidar MA, et al. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. Obstet Gynaecol 2002;99(3):389-94.

208. Dalais FS, Rice GE, Wahlqvist ML, et al. Effects of dietary phytoestrogens in postmenopausal women. Climacteric. 1998;1(2):124-9.

209. Murkies AL, Lombard C, Strauss BJ, et al. Dietary flour supplementation decreases post-menopausal hot flushes: effect of soy and wheat. Maturitas. 1995;21(3):189-95.

210. Penotti M, Fabio E, Modena AB, et al. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. Fertil Steril 2003;79(5):1112-7.

211. St. Germain A, Peterson CT, Robinson JG, et al. Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. Menopause 2001;8(1):17-26.

212. Knight DC, Howes JB, Eden JA, et al. Effects on menopausal symptoms and acceptability of isoflavone-containing soy powder dietary supplementation. Climacteric. 2001;4(1):13-8.

213. Washburn S, Burke GL, Morgan T, et al. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. Menopause. 1999;6(1):7-13.

214. Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, et al. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. Menopause 2003;10(3):196-202.

215. Duffy R, Wiseman H, File SE. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. Pharmacol Biochem Behav 2003;75(3):721-9.

216. Faure ED, Chantre P, Mares P. Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. Menopause. 2002;9(5):329-34.

217. Scambia G, Mango D, Signorile PG, et al. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. Menopause 2000;7(2):105-11.

218. Upmalis DH, Lobo R, Bradley L, et al. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. Menopause. 2000;7(4):236-42.

219. Brzezinski AAHSRRASATVS, et al. Short term effects of phytoestrogen-rich diet on postmenopausal women. Menopause 1997;4(2):89-94.

220. Carranza-Lira S, Barahona OF, Ramos D, et al. Changes in symptoms, lipid and hormone levels after the administration of a cream with phytoestrogens in the Climacteric--preliminary report. Int J Fertil Womens Med 2001;46(6):296-9.

221. Crisafulli A, Marini H, Bitto A, et al. Effects of genistein on hot flushes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study. Menopause 2004;11(4):400-4.

222. Komesaroff PA, Black CV, Cable V, et al. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. Climacteric. 2001;4(2):144-50.

223. Sammartino A, Di Carlo C, Mandato VD, et al. Effects of genistein on the endometrium: ultrasonographic evaluation. Gynecol Endocrinol 2003;17(1):45-9.

224. Russo R, Corosu R. The clinical use of a preparation based on phyto-oestrogens in the treatment of menopausal disorders. Acta Biomed Ateneo Parmense 2003;74(3):137-43.

225. Lewis JE. The effect of dietary soy and flax on menopause quality of life. Menopause 2002;9(6):P-37.

226. Hyde LW. Relaxation training and biofeedback conditioning and the relief of menopausal symptoms: Florida Inst of Technology, 1.; 1983.

227. Boblitz N, Freudenstein J. Fixed combined herbal drug for therapy of menopausal complaints - a placebo-controlled randomized trial. Focus on Alternative and Complementary Therapies 2003;8(4):481-2.

228. Yoles I. Phytoestrogens: A time-tested solution for menopausal symptoms revisited (abstract). Obstet Gynaecol 2002;99:S58.

229. Rao A, Steels E, Seipel T. The effect of a natural transdermal preparation in the treatment of symptoms associated with menopause. Focus on Alternative and Complementary Therapies 2003;8(4):531-2.

230. Valente M. Phytoestrogens: a real alternative to HRT in menopause? (abstract). Gynecol Endocrinol 2000;14(Supplement 2):121.

231. Leonetti HB, Anasti JN. Natural progesterone cream improves the vasomotor symptoms of the menopause. Fertil Steril 1998;70(3):S284.

232. Hochanadel G. Soy isoflavones (phytoestrogens) in the treatment of the cognitive and somatic symptoms of menopause. Proceedings of the 47th Annual Meeting of the Pacific Coast Reproductive Society, Carlsbad, CA, April 16, 1999. 1999.

233. Unfer V, Casini ML, Costabile L, et al. Endometrial effects of long-term treatment with phytoestrogens: a randomized double-blind, placebo-controlled study. Fertil Steril 2004;82(1):145-48.

234. Cohen SM, Rousseau ME, Carey BL. Can acupuncture ease the symptoms of menopause? Holist Nurs Pract 2003;17(6):295-9.

235. Sandberg M, Wijma K, Wyon Y, et al. Effects of electro-acupuncture on psychological distress in postmenopausal women. Complement Ther Med 2002;10(3):161-9.

236. Wyon Y, Lindgren R, Lundeberg T, et al. Effects of acupuncture on climacteric vasomotor symptoms, quality of life, and urinary excretion of neuropeptides among postmenopausal women. Menopause 1995;2(1):3-12.

237. Chen JK. Menopause: Western and Traditional Chinese Medicine Perspectives, Part II. Acupuncture Today 2002;3(5):22-23.

238. Davis SR, Briganti EM, Chen RQ, et al. The effects of Chinese medicinal herbs on postmenopausal vasomotor symptoms of Australian women. A randomised controlled trial. Med J Aust 2001;174(2):68-71.

239. Hartley DE, Heinze L, Elsabagh S, et al. Effects on cognition and mood in postmenopausal women of 1-week treatment with Ginkgo biloba. Pharmacol Biochem Behav 2003;75(3):711-20.

240. Hirata JD, Swiersz LM, Zell B, et al. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. Fertil Steril 1997;68(6):981-6.

241. Wiklund IK, Mattsson LA, Lindgren R, et al. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group. Int J Clin Pharmacol Res 1999;19(3):89-99.

242. Woo J, Lau E, Ho SC, et al. Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause. Menopause. 2003;10(4):352-61.

243. Atkinson C, Warren RM, Sala E, et al. Red-clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial [ISRCTN42940165]. Breast Cancer Research 2004;6(3).

244. Baber RJ, Templeman C, Morton T, et al. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. Climacteric. 1999;2(2):85-92.

245. Jeri AR. The use of an isoflavone supplement to relieve hot flashes. Female Patient 2002;27:35-7.

246. Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. Climacteric. 1999;2(2):79-84.

247. Tice JA, Ettinger B, Ensrud K, et al. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. JAMA 2003;290(2):207-14.

248. van de Weijer PH, Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. Maturitas. 2002;42(3):187-93.

249. Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas. 2003;44(Suppl 1):S67-77.

250. Hudson TS, Standish L, Breed C, et al. Clinical and endocrinological effects of a menopausal botanical formula. Journal of Naturopathic Medicine Issue 1998;7:73-7.

251. Bellipanni G, Bianchi P, Pierpaoli W, et al. Effects of melatonin in perimenopausal and menopausal women: a randomized and placebo controlled study. Exp Gerontol 2001;36(2):297-310.

252. Blatt MHG, Wiesbader H, Kupperman HS. Vitamin E and climacteric syndrome: failure of effective control as measured by menopausal index. Arch Intern Med 1953;91:792-6.

253. Cagnacci A, Arangino S, Renzi A, et al. Kava-Kava administration reduces anxiety in perimenopausal women. Maturitas. 2003;44(2):103-9.

254. Chenoy R, Hussain S, Tayob Y, et al. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. BMJ 1994;308(6927):501-3.

255. Makkonen M, Simpanen AL, Saarikoski S, et al. Endocrine and metabolic effects of guar gum in menopausal women. Gynecol Endocrinol 1993;7(2):135-41.

256. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996;23(3):259-63.

257. Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women. Fertil Steril 1994;61(1):178-80.

258. Rachev E, Nalbansky B, Kolarov G, et al. Efficacy and safety of phospholipid liposomes in the treatment of neuropsychological disorders associated with the menopause: a double-blind, randomised, placebo-controlled study. Curr Med Res Opin 2001;17(2):105-10.

259. Salmaggi P, Bressa GM, Nicchia G, et al. Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women. Psychother Psychosom 1993;59(1):34-40.

260. Cleary C, Fox JP. Menopausal symptoms: an osteopathic investigation. Complement Ther Med 1994;2(4):181-6.

261. Williamson J, White A, Hart A, et al. Randomised controlled trial of reflexology for menopausal symptoms. BJOG 2002;109(9):1050-5.

262. Nassef A, Mostafa M, Khattar N, et al. Role of phytoestrogens in managing menopausal symptoms among Egyptian women (abstract). Climacteric 2002;5(Supplement 1):105.

263. Thompson Coon J, Pittler M, Ernst E. The role of red clover (Trifolium pratense) isoflavones in women's reproductive health: a systematic review and meta-analysis of randomized clinical trials. Focus on Alternative and Complementary Therapies 2003;8(4):544.

264. Wyon Y, Wijma K, Nedstrand E, et al. A comparison of acupuncture and oral estradiol treatment of vasomotor symptoms in postmenopausal women. Climacteric 2004;7(2):153-64.

265. Aiello EJ, Yasui Y, Tworoger SS, et al. Effect of a yearlong, moderate-intensity exercise intervention on the occurrence and severity of menopause symptoms in postmenopausal women. Menopause 2004;11(4):382-8.

266. Lindh-Astrand L, Nedstrand E, Wyon Y, et al. Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. Maturitas 2004;48(2):97-105.

267. Teoman N, Ozcan A, Acar B. The effect of exercise on physical fitness and quality of life in postmenopausal women. Maturitas. 2004;47(1):71-7.

268. Freedman RR, Woodward S, Brown B, et al. Biochemical and thermoregulatory effects of behavioral treatment for menopausal hot flashes. Menopause 1995;2(4):211-18.

269. Irvin JH, Domar AD, Clark C, et al. The effects of relaxation response training on menopausal symptoms. J Psychosom Obstet Gynaecol 1996;17(4):202-7.

270. Germaine LM, Freedman RR. Behavioral treatment of menopausal hot flashes: evaluation by objective methods. J Consult Clin Psychol 1984;52(6):1072-9.

271. Rankin M. Effect of low frequency sound on menopausal symptoms. J Holist Nurs 1989;7(1):34-41.

272. Hunter M, O'Dea I. An evaluation of a health education intervention for mid-aged women: five year follow-up of effects upon knowledge, impact of menopause and health. Patient Educ Couns 1999;38(3):249-55.

273. Manson J, Hsia J, Johnson K, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349(6):523-34.

274. Wassertheil-Smoller S, Hendrix S, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. JAMA 2003;289(20):2673-84.

275. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 1998;16:495-500.

276. Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19(10):2739-45.

277. Quella SK, Loprinzi CL, Sloan JA, et al. Long term use of megestrol acetate by cancer survivors for the treatment of breast cancer. Cancer 2000;82(9):1784-88.

278. Van Patten CL, Olivotto IA, Chambers GK, et al. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. J Clin Oncol 2002;20(6):1449-55.

279. Nikander E, Kilkkinen A, Metsa-Heikkila M, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. Obstet Gynecol 2003;101(6):1213-20.

280. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. N Engl J Med 1994;331(6):347-52.

281. Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. J Clin Oncol 1997;15:969-73.

282. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356(9247):2059-63.

283. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002;20(6):1578-83.

284. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. J Clin Oncol 1994;12(1):155-8.

285. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Ann Intern Med 2000;132(10):788-93.

286. Hernandez Munoz G, Pluchino S. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. Maturitas. 2003;44(Suppl 1):S59-65.

287. Ganz PA, Greendale GA, Petersen L, et al. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. J Natl Cancer Inst 2000;92(13):1054-64.

288. Secreto G, Chiechi LM, Amadori A, et al. Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study. Maturitas. 2004;47(1):11-20.

289. Carpenter JS, Johnson D, Wagner L, et al. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. Oncol Nurs Forum 2002;29(3):E16-25

List Of Excluded Studies

1. Adams J. Exploring yoga to relieve menopausal symptoms. Holist Nurs Pract. 2003;17(3):166-167.

2. Adamson DL, Webb CM, Collins P. Esterified estrogens combined with methyltestosterone improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms.[see comment]. Menopause. 2001;8(4):233-238.

3. Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. Fertil Steril. 1994;62:20-.

4. Adena MA, Gallagher HG. Cigarette smoking and the age at menopause. Annals of Human Biology. 1982;9(2):121-130.

5. Akahoshi M, Soda M, Nakashima E, et al. The effects of body mass index on age at menopause. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 2002;26(7):961-968.

6. Aksel S, Schomberg DW, Tyrey L, Hammond CB. Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause. Am J Obstet Gynecol. 1976;126(2):165-169.

7. Albertazzi P, Bottazzi M, Purdie DW. Gabapentin for the management of hot flushes: a case series. Menopause. 2003;10(3):214-217.

8. Albertazzi P, Natale V, Barbolini C, Teglio L, Di Micco R. The effect of tibolone versus continuous combined norethisterone acetate and oestradiol on memory, libido and mood of postmenopausal women: A pilot study. Maturitas. 2000;36(3):223-229.

9. Alcoff JM, Campbell D, Tribble D, Oldfield B, Cruess D. Double-blind, placebo-controlled, crossover trial of propranolol as treatment for menopausal vasomotor symptoms. Clinical Therapeutics. 1981;3(5):356-364.

10. Altshuler LL, Cohen LS, Moline ML, et al. The Expert Consensus Guideline Series. Treatment of depression in women. Postgraduate Medicine. 2001(Spec No):1-107.

11. Altshuler LL, Cohen LS, Moline ML, et al. Treatment of depression in women: A summary of the expert consensus guidelines. Journal of Psychiatric Practice. 2001;7(3):185-208.

12. American College of O, Gynecologists Committee on Practice B-G. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Use of botanicals for management of menopausal symptoms. Obstetrics & Gynecology. 2001;97(6):suppl 1-11.

13. Amigoni S, Morelli P, Chatenoud L, Parazzini F. Cross-sectional study of determinants of menopausal age and hormone replacement therapy use in Italian women. Climacteric. 2000;3(1):25-32.

14. Amundsen DW, Diers CJ. The age of menopause in classical Greece and Rome. Human Biology. 1970;42(1):79-86.

15. Anarte M, Cuadros J, Herrera J. Hormonal and psychological treatment: Therapeutic alternative for menopausal women? Maturitas. 1998;29(3):203-213.

16. Anasti J, Leonetti H, Wilson KJ. Topical progesterone cream has antiproliferative effect on estrogen-stimulated endometrium. Obstetrics & Gynecology. 2001;97(4supp1):S10.

17. Andersen FS, Transbol I, Christiansen C. Is cigarette smoking a promotor of the menopause? Acta Medica Scandinavica. 1982;212(3):137-139.

18. Andersen J, Poulsen HS. Immunohistochemical analysis of estrogen receptors (ER) using formalin-fixed paraffin-embedded breast cancer tissue: correlation with clinical endocrine response. Journal of Steroid Biochemistry. 1988;30(1-6):337-339.

19. Anderson D, Posner N. Relationship between psychosocial factors and health behaviours for women experiencing menopause. International Journal of Nursing Practice. 2002;8(5):265-273.

20. Andreen L, Bixo M, Nyberg S, Sundstrom-Poromaa I, Backstrom T. Progesterone effects during sequential hormone replacement therapy. European Journal of Endocrinology. 2003;148(5):571-577.

21. Andreyko JL, Monroe SE, Marshall LA, Fluker MR, Nerenberg CA, Jaffe RB. Concordant suppression of serum immunoreactive luteinizing hormone (LH), follicle-stimulating hormone, alpha subunit, bioactive LH, and testosterone in postmenopausal women by a potent gonadotropin releasing hormone antagonist (detirelix). J Clin Endocrinol Metab. 1992;74(2):399-405.

22. Anonymous. Clonidine in treatment of menopausal flushing. Acta Obstet Gynecol Scand Suppl. 1985;132:1-35.

23. Anonymous. What determines the age at the menopause? BMJ. 1991;302(6791):1540.

24. Anonymous. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer.[see comment][erratum appears in Lancet 1997 Nov 15;350(9089):1484]. Lancet. 1997;350(9084):1047-1059.

25. Anonymous. Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 6: Executive summary and consensus statement. Proceedings of a conference held at Boar's Head Inn, Charlottesville, Virginia, September 21-23, 1997. Oncology (Huntington). 1999;13(6):859-861, 865-856, 871-852 passim.

26. Anonymous. Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 1: Defining the problem. Proceedings of a conference held at the Boar's Head Inn Charlottesville, Virginia. September 21-23, 1997. Oncology (Huntington). 1999;13(1):109-115, 119-120, 123-104 passim.

27. Anonymous. Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 2: Hormone replacement therapy and breast cancer. Oncology (Huntington). 1999;13(2):245-248, 251-244, 257 passim.

28. Anonymous. Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 4: Urogenital atrophy, vasomotor instability, sleep disorders, and related symptoms. Oncology (Huntington). 1999;13(4):551-554, 557-560, 563 passim.

29. Anonymous. Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 5: Selective estrogen receptor modulators and hormone replacement therapy. Proceedings of a conference. Charlottesville, Virginia, USA. September 21-23, 1997. Oncology (Huntington). 1999;13(5):721-724, 727-728, 731-722 passim.

30. Anonymous. Million Women Study Collaborators. Breast cancer, hormone replacement therapy in the Million Women Study. Lancet. 2003;362:419-422.

31. Anonymous. Isoflavone supplements no better than placebo for reducing hot flushes. Pharmaceutical Journal. 2003;271(7258):76.

32. Argyroudis EM, Iatrakis G, Kourkoubas A, et al. Tibolone in the treatment of psychosomatic symptoms in menopause. Clinical & Experimental Obstetrics & Gynecology. 1997;24(3):167-168.

33. Arpels JC. The female brain hypoestrogenic continuum from the premenstrual syndrome to menopause. A hypothesis and review of supporting data. J Reprod Med. 1996;41(9):633-639.

34. Avis NE, McKinlay SM. A longitudinal analysis of women's attitudes toward the menopause: results from the Massachusetts Women's Health Study. Maturitas. 1991;13(1):65-79.

35. Avis NE, McKinlay SM. The Massachusetts Women's Health Study: an epidemiologic investigation of the menopause. Journal of the American Medical Womens Association. 1995;50(2):45-49, 63.

36. Aygen E, Ekmekcioglu O, Serin S. The relationship between the duration of menopause and lower urinary tract symptoms in women aged 40 to 59. Int J Fertil Womens Med. 2001;46(1):16-22.

37. Bachmann GA, Leiblum SR. The impact of hormones on menopausal sexuality: a literature review. Menopause. 2004;11(1):120-130.

38. Bachmann GA, Timmons MC, Abernethy WD. Breakthrough bleeding patterns in two continuous combined estrogen/progestogen hormone replacement therapies, one of which included androgens. Journal of Women's Health. 1996;5(3):205-212.

39. Baird DD, Umbach DM, Lansdell L, et al. Dietary intervention study to assess estrogenicity of dietary soy among postmenopausal women. J Clin Endocrinol Metab. 1995;80(5):1685-1690.

40. Baker A, Simpson S, Dawson D. Sleep disruption and mood changes associated with menopause. Journal of Psychosomatic Research. 1997;43(4):359-369.

41. Ballinger C. Subjective sleep disturbance at the menopause. Journal of Psychosomatic Research. 1976;20(5):509-513.

42. Ballinger C. Psychiatric aspects of the menopause. British Journal of Psychiatry. 1990;156:773-787.

43. Ballinger CB. Psychiatric morbidity and the menopause; screening of general population sample. British Medical Journal. 1975;3(5979):344-346.

44. Ballinger S. Stress as a factor in lowered estrogen levels in the early postmenopause. Annals of the New York Academy of Sciences. 1990;592:95-113; discussion 123-133.

45. Ballinger S. Stress as a factor in lowered estrogen levels in the early postmenopause. Flint, Marcha (Ed); Kronenberg, Fredi (Ed); et al (1990) Multidisciplinary perspectives on menopause Annals of the New York Academy of Sciences, Vol 592 (pp 95-113) xii, 488pp; 1990.

46. Barentsen R, van de Weijer PH, van Gend S, Foekema H. Climacteric symptoms in a representative Dutch population sample as measured with the Greene Climacteric Scale. Maturitas. 2001;38(2):123-128.

47. Barlow DH, Grosset KA, Hart H, Hart DM. A study of the experience of Glasgow women in the climacteric years. Br J Obstet Gynaecol. 1989;96(10):1192-1197.

48. Barnhart KT, Freeman E, Grisso JA, Neslter J. The effect of DHEA replacement on well being and perimenopausal symptoms. Fertil Steril. 1998;70(3).

49. Barrett-Connor E, Kritz-Silverstein D. Gender differences in cognitive function with age: The Rancho Bernardo Study. Journal of the American Geriatrics Society. 1999;47(2):159-164.

50. Barrett-Connor E, Timmons C, Young R, Wiita B. Interim safety analysis of a two-year study comparing oral estrogen-androgen and conjugated estrogens in surgically menopausal women. Journal of Women's Health. 1996;5(6):593-602.

51. Barrett-Connor E, von Muehlen D, Laughlin GA, Kripke A. Endogenous levels of dehydroepaindrosterone sulfate, but no other sex hormones are associated with depressed mood in older women: The Rancho Bernardo Study. Journal of the American Geriatrics Society. 1999;47(6):685-691.

52. Barton D, La VB, Loprinzi C, Novotny P, Wilwerding MB, Sloan J. Venlafaxine for the control of hot flashes: results of a longitudinal continuation study. Oncol Nurs Forum. 2002;29(1):33-40.

53. Barton D, Loprinzi C, Wahner-Roedler D. Hot flashes: aetiology and management. Drugs & Aging. 2001;18(8):597-606.

54. Barton DL. Pilot evaluations of newer antidepressants for hot flashes. Proc Am Soc Clin Oncol. 2002;21:366a.

55. Barton DL. Pilot evaluation of citalopram for the relief of hot flashes. J Support Oncol. 2003;1:47-52.

56. Barton DL, Loprinzi C, Gostout B. Current management of menopausal symptoms in cancer patients. Oncology (Huntington). 2002;16(1):67-72, 74; discussion 75-66, 79-80.

57. Basaria S, Nguyen T, Rosenson RS, Dobs AS. Effect of methyl testosterone administration on plasma viscosity in postmenopausal women. Clin Endocrinol. 2002;57(2):209-214.

58. Beal MW. Women's use of complementary and alternative therapies in reproductive health care. Journal of Nurse-Midwifery. 1998;43(3):224-234.

59. Beardsworth SA, Kearney CE, Purdie DW. Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year randomised controlled trial. Br J Obstet Gynaecol. 1999;106(7):678-683.

60. Bebbington P, Dunn G, Jenkins R, et al. The influence of age and sex on the prevalence of depression conditions: Report from the National Survey of Psychiatric Morbidity. Psychol Med. 1998;28(1):9-19.

61. Bebbington P, Dunn G, Jenkins R, et al. The influence of age and sex on the prevalence of depressive conditions: A report from the National Survey of Psychiatric Morbidity. International Review of Psychiatry. 2003;15(1-2):74-83.

62. Belsey EM, Pinol AP. Menstrual bleeding patterns in untreated women. Task Force on Long-Acting Systemic Agents for Fertility Regulation. Contraception. 1997;55(2):57-65.

63. Bengtsson C, Lindquist O, Redvall L. Menstrual status and menopausal age of middle-aged Swedish women. A population study of women in Goteborg 1968--69 and 1974--75. Acta Obstet Gynecol Scand. 1981;60(3):269-275.

64. Berendsen HH. The role of serotonin in hot flushes. Maturitas. 2000;36(3):155-164.

65. Berg JA. The perimenopausal transition of Filipino American midlife women: Biopsychosociocultural dimensions. Nursing Research. 1999;48(2):71-77.

66. Berg JA, Taylor DL. Symptom experience of Filipino American midlife women.[see comment]. Menopause. 1999;6(2):105-114.

67. Berg JA, Taylor DL. Symptom responses of midlife Filipina Americans.[see comment]. Menopause. 1999;6(2):115-121.

68. Bernhard LA, Sheppard L. Health, symptoms, self-care, and dyadic adjustment in menopausal women. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing. 1993;22(5):456-461.

69. Berning B, Kuijk CV, Kuiper JW, Bennink HJ, Kicovic PM, Fauser BC. Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: a two-year randomized, placebo-controlled study. Bone. 1996;19(4):395-399.

70. Berning B, van Kuijk C, Kuiper JW, Coelingh Bennink HJ, Fauser BC. Increased loss of trabecular but not cortical bone density, 1 year after discontinuation of 2 years hormone replacement therapy with Tibolone. Maturitas. 1999;31(2):151-159.

71. Bertelli G, Venturini M, Del Mastro L, al. e. Depot intramuscular medroxyprogesterone acetate (MAP) Vs. oral megestrol acetate (MA) for the treatment of hot flashes in breast cancer survivors: results of GONO (Gruppo Oncologico Nord Ovest) MIG-4 Phase III Trial. American Society of Clinical Oncology. 1999:abst 2286.

72. Beser E, Aydemir V, Bozkaya H. Body mass index and age at natural menopause. Gynecologic & Obstetric Investigation. 1994;37(1):40-42.

73. Beyene Y. Cultural significance and physiological manifestations of menopause. A biocultural analysis. Culture, Medicine & Psychiatry. 1986;10(1):47-71.

74. Bider D, Mashiach S, Serr DM, Ben-Rafael Z. Endocrinological basis of hot flushes. Obstetrical & Gynecological Survey. 1989;44(7):495-499.

75. Biglia N, Cozzarella M, Cacciari F, et al. Menopause after breast cancer: a survey on breast cancer survivors. Maturitas. 2003;45(1):29-38.

76. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer.[see comment]. J Clin Oncol. 1996;14(5):1718-1729.

77. Biron-Shental T, Tepper R, Fishman A, Shapira J, Cohen I. Recurrent endometrial polyps in postmenopausal breast cancer patients on tamoxifen. Gynecol Oncol. 2003;90(2):382-386.

78. Bjarnason NH, Bjarnason K, Haarbo J, Rosenquist C, Christiansen C. Tibolone: prevention of bone loss in late postmenopausal women.[comment]. J Clin Endocrinol Metab. 1996;81(7):2419-2422.

79. Bjorn I, Bixo M, Nojd KS, et al. The impact of different doses of medroxyprogesterone acetate on mood symptoms in sequential hormonal therapy. Gynecol Endocrinol. 2002;16(1):1-8.

80. Bjorn I, Bixo M, Nojd KS, Nyberg S, Backstrom T. Negative mood changes during hormone replacement therapy: a comparison between two progestogens. Am J Obstet Gynecol. 2000;183(6):1419-1426.

81. Bloedon LT, Jeffcoat AR, Lopaczynski W, et al. Safety and pharmacokinetics of purified soy isoflavones: single-dose administration to postmenopausal women. American Journal of Clinical Nutrition. 2002;76(5):1126-1137.

82. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: quality of life of young breast cancer survivors. Psycho-Oncology. 2004;13(3):147-160.

83. Blumenthal JA, Fredrikson M, Matthews KA, et al. Stress reactivity and exercise training in premenopausal and postmenopausal women. Health Psychology. 1991;10(6):384-391.

84. Blumenthal JA, Matthews K, Fredrikson M, et al. Effects of exercise training on cardiovascular function and plasma lipid, lipoprotein, and apolipoprotein concentrations in premenopausal and postmenopausal women. Arteriosclerosis & Thrombosis. 1991;11(4):912-917.

85. Bodnar S, Catterill T. Amitriptyline in emotional states associated with the climacteric. Psychosomatics. 1972;13(2):117-119.

86. Boldsen JL, Jeune B. Distribution of age at menopause in two Danish samples. Human Biology. 1990;62(2):291-300.

87. Borrelli F, Mascolo N, Russo A, Capasso R, Ernst E. Cimicifuga racemosa: a systematic review of its clinical and pharmacological effects. Focus on Alternative and Complementary Therapies. 2002;7(1):86.

88. Bosworth HB, Bastian LA, Kuchibhatla MN, et al. Depressive symptoms, menopausal status, and climacteric symptoms in women at midlife. Psychosomatic Medicine. 2001;63(4):603-608.

89. Botsis D, Kalogirou D, Kassanos D, Antoniou G, Kalogirou O. Clinical Trial of Vaginally Administered Conjugated Estrogens and Tibolone in Postmenopausal Women. 8th International Congress on the Menopause.96.

90. Boulot P, Viala JL. [A multicenter comparison of veralipride versus placebo in the vasomotor flushes of menopause. An evaluation of the prolonged effect]. [French]. Revue Francaise de Gynecologie et d Obstetrique. 1988;83(12):823-827.

91. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol. 2000;18(4):743-753.

92. Brambilla DJ, McKinlay SM. A prospective study of factors affecting age at menopause.[erratum appears in J Clin Epidemiol 1990;43(5):537]. J Clin Epidemiol. 1989;42(11):1031-1039.

93. Brambilla DJ, McKinlay SM, Johannes CB. Defining the perimenopause for application in epidemiologic investigations. Am J Epidemiol. 1994;140(12):1091-1095.

94. Brejnak C. Mechanisms of menopausal hot flashes: The role of catechol estrogens and diet, Wayne State U, US, 1.; 1999.

95. Brett KM, Cooper GS. Associations with menopause and menopausal transition in a nationally representative US sample. Maturitas. 2003;45(2):89-97.

96. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE. Sexual functioning in long-term breast cancer survivors treated with adjuvant chemotherapy. Breast Cancer Research & Treatment. 2002;75(3):241-248.

97. Bromberger JT, Matthews KA. A longitudinal study of the effects of pessimism, trait anxiety, and life stress on depressive symptoms in middle-aged women. Psychology & Aging. 1996;11(2):207-213.

98. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol. 1997;145(2):124-133.

99. Buckler HM, Evans CA, Mamtora H, Burger HG, Anderson DC. Gonadotropin, steroid, and inhibin levels in women with incipient ovarian failure during anovulatory and ovulatory rebound cycles. J Clin Endocrinol Metab. 1991;72(1):116-124.

100. Buckler HM, McElhone K, Durrington PN, Mackness MI, Ludlam CA, Wu FC. The effects of low-dose testosterone treatment on lipid metabolism, clotting factors and ultrasonographic ovarian morphology in women.[see comment]. Clin Endocrinol. 1998;49(2):173-178.

101. Bullock JL, Massey FM, Gambrell RD, Jr. Use of medroxyprogesterone acetate to prevent menopausal symptoms. Obstetrics & Gynecology. 1975;46(2):165-168.

102. Bungay GT, Vessey MP, McPherson CK. Study of symptoms in middle life with special reference to the menopause. British Medical Journal. 1980;281(6234):181-183.

103. Burger H, Hailes J, Nelson J, Menelaus M. Effect of combined implants of oestradiol and testosterone on libido in postmenopausal women. British Medical Journal Clinical Research Ed.. 1987;294(6577):936-937.

104. Burger HG, Hailes J, Menelaus M, Nelson J, Hudson B, Balazs N. The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid and hormonal results. Maturitas. 1984;6(4):351-358.

105. Burstein HJ, Winer EP. Primary care for survivors of breast cancer.[see comment]. N Engl J Med. 2000;343(15):1086-1094.

106. Busch H, Barth-Olofsson AS, Rosenhagen S, Collins A. Menopausal transition and psychological development. Menopause. 2003;10(2):179-187.

107. Cagnacci A, Melis GB, Paoletti AM, Soldani R, Fioretti P. Interaction between veralipride and the endogenous opioid system in the regulation of body temperature in postmenopausal women. Life Sciences. 1988;42(5):547-553.

108. Cagnacci A, Neri I, Tarabusi M, Volpe A, Facchinetti F. Effect of long-term local or systemic hormone replacement therapy on post-menopausal mood disturbances. Influences of socio-economic and personality factors. Maturitas. 1999;31(2):111-116.

109. Cairney J, Wade TJ. The influence of age on gender differences in depression: further population-based evidence on the relationship between menopause and the sex difference in depression. Social Psychiatry & Psychiatric Epidemiology. 2002;37(9):401-408.

110. Calvaresi E, Bryan J. Symptom experience in Australian men and women in midlife. Maturitas. 2003;44(3):225-236.

111. Carpenter JS, Andrykowski MA. Menopausal symptoms in breast cancer survivors. Oncol Nurs Forum. 1999;26(8):1311-1317.

112. Carranza-Lira S, Cortes-Fuentes E. Modification of vasomotor symptoms after various treatment modalities in the postmenopause. Int J Gynaecol Obstet. 2001;73(2):169-171.

113. Castelo-Branco C, Casals E, Figueras F, et al. Two-year prospective and comparative study on the effects of tibolone on lipid pattern, behavior of apolipoproteins AI and B. Menopause. 1999;6(2):92-97.

114. Castelo-Branco C, Vicente JJ, Figueras F, et al. Comparative effects of estrogens plus androgens and tibolone on bone, lipid pattern and sexuality in postmenopausal women. Maturitas. 2000;34(2):161-168.

115. Celentano E, Galasso R, Berrino F, et al. Correlates of age at natural menopause in the cohorts of EPIC-Italy. Tumori. 2003;89(6):608-614.

116. Celik H, Ayar A, Tug N, Cikim G, Kilic N, Parmaksiz C. Effects of tibolone on plasma homocysteine levels in postmenopausal women. Fertil Steril. 2002;78(2):347-350.

117. Chaby L, Grinsztein A, Weitzman JJ, de Bodinat C, Dagens V. [Anxiety-related and depressive disorders in women during the premenopausal and menopausal period. Study of the efficacy and acceptability of tianeptine versus maprotiline]. [French]. Presse Medicale. 1133;22(24):1133-1138.

118. Chakravarti S, Collins WP, Forecast JD, Newton JR, Oram DH, Studd JW. Hormonal profiles after the menopause. British Medical Journal. 1976;2(6039):784-787.

119. Chavez ML, Spitzer MF. Herbals and other dietary supplements for premenstrual syndrome and menopause. Psychiatric Annals. 2002;32(1):61-71.

120. Chen LC, Tsao YT, Yen KY, Chen YF, Chou MH, Lin MF. A pilot study comparing the clinical effects of Jia-Wey Shiau-Yau San, a traditional Chinese herbal prescription, and a continuous combined hormone replacement therapy in postmenopausal women with climacteric symptoms. Maturitas. 2003;44(1):55-62.

121. Chen YC, Chen GD, Hu SW, Lin TL, Lin LY. Is the occurrence of storage and voiding dysfunction affected by menopausal transition or associated with the normal aging process? Menopause. 2003;10(3):203-208.

122. Cherrington A, Lewis CE, McCreath HE, Herman CJ, Richter DL, Byrd T. Association of complementary and alternative medicine use, demographic factors, and perimenopausal symptoms in a multiethnic sample of women: The ENDOW study. Family & Community Health. 2003;26(1):74-83.

123. Chiazze L, Jr., Brayer FT, Macisco JJ, Jr., Parker MP, Duffy BJ. The length and variability of the human menstrual cycle. JAMA. 1968;203(6):377-380.

124. Chiechi LM, Putignano G, Guerra V, Schiavelli MP, Cisternino AM, Carriero C. The effect of a soy rich diet on the vaginal epithelium in postmenopause: a randomized double blind trial. Maturitas. 2003;45(4):241-246.

125. Chlebowski RT, Kim JA, Col NF. Estrogen deficiency symptom management in breast cancer survivors in the changing context of menopausal hormone therapy. Seminars in Oncology. 2003;30(6):776-788.

126. Chlebowski RT, McTiernan A. Elements of informed consent for hormone replacement therapy in patients with diagnosed breast cancer. J Clin Oncol. 1999;17(1):130-142.

127. Chopin Lucks B. The Vitex agnus castus dilemma: ethical management of a double-edged oil. Aromatheraphy Today. 2003;27:24-27.

128. Christodoulakos GE, Lambrinoudaki IV, Vourtsi AD, Panoulis KP, Kelekis DA, Creatsas GC. Mammographic changes associated with raloxifene and tibolone therapy in postmenopausal women: a prospective study.[comment]. Menopause. 2002;9(2):110-116.

129. Cicinelli E, Petruzzi D, Scorcia P, Resta L. Effects of progesterone administered by nasal spray on the human postmenopausal endometrium. Maturitas. 1993;18(1):65-72.

130. Cittadini J, Ben J, Badano AR, et al. [Use of a new steroid (Org OD 14) in the climacteric syndrome]. [Spanish]. Reproduccion. 1982;6(2):69-79.

131. Clayden JR. Effect of clonidine on menopausal flushing. Lancet. 1972;2(7791):1361.

132. Clayden JR, Bell JW. Control of menopausal flushes. British Medical Journal. 1973;4:44.

133. Cobleigh M. Estrogen replacement therapy in breast cancer surviviors. JAMA. 1994;272:540-545.

134. Colacurci N, Fornaro F, De Franciscis P, Palermo M, del Vecchio W. Effects of different types of hormone replacement therapy on mammographic density. Maturitas. 2001;40(2):159-164.

135. Colacurci N, Mele D, De Franciscis P, Costa V, Fortunato N, De Seta L. Effects of tibolone on the breast. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 1998;80(2):235-238.

136. Collins A, Landgren BM. Reproductive health, use of estrogen and experience of symptoms in perimenopausal women: a population-based study. Maturitas. 1994;20(2-3):101-111.

137. Conboy L, Domar A, O'Connell E. Women at mid-life: symptoms, attitudes, and choices, an internet based survey. Maturitas. 2001;38(2):129-136.

138. Cooke D, Greene J. Types of life events in relation to symptoms at the climacterium. Journal of Psychosomatic Research. 1981;25(1):5-11.

139. Cooper A, Spencer C, Whitehead MI, Ross D, Barnard GJ, Collins WP. Systemic absorption of progesterone from Progest cream in postmenopausal women. [Letter]. Lancet. 1998;351:1255-1256.

140. Cooper GS, Baird DD, Darden FR. Measures of menopausal status in relation to demographic, reproductive, and behavioral characteristics in a population-based study of women aged 35-49 years. Am J Epidemiol. 2001;153(12):1159-1165.

141. Cooper GS, Baird DD, Weinberg CR, Ephross SA, Sandler DP. Age at menopause and childbearing patterns in relation to mortality. Am J Epidemiol. 2000;151(6):620-623.

142. Cooper GS, Sandler DP. Age at natural menopause and mortality. Annals of Epidemiology. 1998;8(4):229-235.

143. Coppen A, Bishop M, Beard RJ, Barnard GJ, Collins WP. Hysterectomy, hormones, and behaviour. A prospective study. Lancet. 1981;1(8212):126-128.

144. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstetrics & Gynecology. 1986;67(4):604-606.

145. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol. 1995;13(11):2737-2744.

146. Cowan MM, Gregory LW. Responses of pre- and post-menopausal females to aerobic conditioning. Medicine & Science in Sports & Exercise. 1985;17(1):138-143.

147. Cramer DW, Xu H. Predicting age at menopause. Maturitas. 1996;23(3):319-326.

148. Creidi P, Faivre B, Agache P, Richard E, Haudiquet V, Sauvanet JP. Effect of a conjugated oestrogen (Premarin) cream on aging facial skin. A comparative study with a placebo cream. Maturitas. 1994;19(3):211-223.

149. Crona N, Samsioe G, Lindberg UB, Silfverstolpe G. Treatment of climacteric complaints with Org OD 14: a comparative study with oestradiol valerate and placebo. Maturitas. 1988;9(4):303-308.

150. Cummings, S R, Duong, et al. Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA. 2002;287(2):216-220.

151. Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. Menopause. 2002;9(4):253-263.

152. Cutler WB, Garcia CR, McCoy N. Perimenopausal sexuality. Archives of Sexual Behavior. 1987;16(3):225-234.

153. Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M. Measuring the impact of menopausal symptoms on quality of life.[see comment]. BMJ. 1993;307(6908):836-840.

154. Daly RC, Danaceau MA, Rubinow DR, Schmidt PJ. Concordant Restoration of Ovarian Function and Mood in Perimenopausal Depression. Am J Psychiatry. 2003;160(10):1842-1846.

155. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. Chest. 2001;120(1):151-155.

156. Danforth DR, Arbogast LK, Mroueh J, et al. Dimeric inhibin: a direct marker of ovarian aging. Fertil Steril. 1998;70(1):119-123.

157. Davis JM, Sargent RG, Brayboy TD, Bartoli WP. Thermogenic effects of pre-prandial and post-prandial exercise in obese females. Addictive Behaviors. 1992;17(2):185-190.

158. Davis MC, Matthews KA, Meilahn EN, Kiss JE. Are job characteristics related to fibrinogen levels in middle-aged women? Health Psychology. 1995;14(4):310-318.

159. Davis R. Physiatry -- The Practice of Physical Therapy by a Physician. Dynamic Chiropractic. 1993;11(25).

160. Davis S. Testosterone and sexual desire in women. Journal of Sex Education & Therapy. 2000;25(1):25-32.

161. Davis SR. The clinical use of androgens in female sexual disorders. Journal of Sex & Marital Therapy. 1998;24(3):153-163.

162. Davis SR. Menopause: new therapies. Med J Aust. 2003;178(12):634-637.

163. Davis SR, Goldstat R, Newman A, et al. Differing effects of low-dose estrogen-progestin therapy and pravastatin in postmenopausal hypercholesterolemic women. Climacteric. 2002;5(4):341-350.

164. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas. 1995;21(3):227-236.

165. Davis SR, Walker KZ, Strauss BJ. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. Menopause. 2000;7(6):395-401.

166. de Aloysio D, Fabiani AG, Mauloni M, Bottiglioni F. Analysis of the climacteric syndrome.[erratum appears in Maturitas 1989 Jun;11(2):169]. Maturitas. 1989;11(1):43-53.

167. de Beer F, Smelt AH, van Vark LC, Hoogerbrugge N, Havekes LM, Gevers Leuven JA. The effect of tibolone on the lipoprotein profile of postmenopausal women with type III hyperlipoproteinemia. J Intern Med. 2002;251(2):148-155.

168. de Novaes Soares C, Almeida OP. Depression during the perimenopause. Arch Gen Psychiatry. 2001;58(3):306.

169. de Vries E, den Tonkelaar I, van Noord PA, van der Schouw YT, te Velde ER, Peeters PH. Oral contraceptive use in relation to age at menopause in the DOM cohort. Human Reproduction. 2001;16(8):1657-1662.

170. Deeks AA, McCabe MP. Well-being and menopause: an investigation of purpose in life, self- acceptance and social role in premenopausal, perimenopausal and postmenopausal women. Qual Life Res. 2004;13(2):389-398.

171. Demetrio FN, Reno J, Jr., Goncves MA, et al. Conjugated estrogens therapy and mood in postmenopausal women: Preliminary results. Revista de Psiquiatria Clinica. 2001;28(2):89-93.

172. den Tonkelaar I, te Velde ER, Looman CW. Menstrual cycle length preceding menopause in relation to age at menopause. Maturitas. 1998;29(2):115-123.

173. Denham A, Green J, Hawkey S, Ingram J. Choice of an outcome measure for a pilot randomized controlled trial into the treatment by herbal practitioners of symptoms associated with the menopause. Focus on Alternative and Complementary Therapies. 2003;8(4):493.

174. Dennerstein L. Depression in the menopause. Obstetrics & Gynecology Clinics of North America. 1987;14(1):33-48.

175. Dennerstein L, Burrows GD. Hormone replacement therapy and sexuality in women. Clinics in Endocrinology & Metabolism. 1982;11(3):661-679.

176. Dennerstein L, Dudley EC, Guthrie JR. Predictors of declining self-rated health during the transition to menopause. Journal of Psychosomatic Research. 2003;54(2):147-153.

177. Dennerstein L, Lehert P, Burger H, Dudley E. Factors affecting sexual functioning of women in the mid-life years. Climacteric. 1999;2(4):254-262.

178. Desgor J. Menopause. Homeopath Int. 1989;3(2):14.

179. Dias R, Kerr-Correa F, Moreno RA, et al. Hrt with androgen as a strategy to treat postmenopausal depression: preliminary results. International Journal of Neuropsychopharmacology. 2002;5(Suppl 1).

180. Diers CJ. Historical trends in the age at menarche and menopause. Psychological Reports. 1974;34(3):931-937.

181. Dixon JM. Hormone replacement therapy and the breast. Surgical Oncology. 2003;12(4):251-263.

182. Do KA, Treloar SA, Pandeya N, et al. Predictive factors of age at menopause in a large Australian twin study. Human Biology. 1998;70(6):1073-1091.

183. Dog T, Riley D, Carter T. An integrative approach to menopause. Alternative Therapies in Health and Medicine. 2001;7(4):45-55; quiz 56-47.

184. Doren M, Rubig A, Coelingh Bennink HJ, Holzgreve W. Impact on uterine bleeding and endometrial thickness: tibolone compared with continuous combined estradiol and norethisterone acetate replacement therapy. Menopause. 1999;6(4):299-306.

185. Doren M, Rubig A, Coelingh Bennink HJ, Holzgreve W. Differential effects on the androgen status of postmenopausal women treated with tibolone and continuous combined estradiol and norethindrone acetate replacement therapy. Fertil Steril. 2001;75(3):554-559.

186. Dow MG, Hart DM, Forrest CA. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. Br J Obstet Gynaecol. 1983;90(4):361-366.

187. Dowsett M, Cantwell B, Lal A, Jeffcoate SL, Harris AL. Suppression of postmenopausal ovarian steroidogenesis with the luteinizing hormone-releasing hormone agonist goserelin. J Clin Endocrinol Metab. 1988;66(4):672-677.

188. Duffy C, Cyr M. Phytoestrogens: potential benefits and implications for breast cancer survivors. Journal of Women's Health. 2003;12(7):617-631.

189. Dunn LB, Damesyn M, Moore AA, Reuben DB, Greendale GA. Does estrogen prevent skin aging? Results from the First National Health and Nutrition Examination Survey (NHANES I). Arch Dermatol. 1997;133:339-342.

190. Eden JA. Oestrogen and the breast. 2. The management of the menopausal woman with breast cancer. Med J Aust. 1992;157(4):247-250.

191. Egarter C, Eppel W, Vogel S, Wolf G. A pilot study of hormone replacement therapy with tibolone in women with mastopathic breasts. Maturitas. 2001;40(2):165-171.

192. Egarter C, Sator M, Huber J. Effects of tibolone on cell adhesion molecules in postmenopausal women. Menopause. 2003;10(3):218-221.

193. Engel NS. Menopausal stage, current life change, attitude toward women's roles, and perceived health status. Nursing Research. 1987;36(6):353-357.

194. Ernst E, White A. Life-threatening adverse reactions after acupuncture? A systematic review. Pain. 1997;71:123-126.

195. Everson RB, Sandler DP, Wilcox AJ, Schreinemachers D, Shore DL, Weinberg C. Effect of passive exposure to smoking on age at natural menopause. British Medical Journal Clinical Research Ed.. 1986;293(6550):792.

196. Everson SA, Matthews KA, Guzick DS, Wing RR, Kuller LH. Effects of surgical menopause on psychological characteristics and lipid levels: the Healthy Women Study. Health Psychology. 1995;14(5):435-443.

197. Facchinetti F, Nappi RE, Tirelli A, Polatti F, Nappi G. Hormone supplementation differently affects migraine in postmenopausal women. Headache. 2002;42(9):924-929.

198. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Human Reproduction. 1992;7(10):1342-1346.

199. Farish E, Barnes JF, Fletcher CD, Ekevall K, Calder A, Hart DM. Effects of tibolone on serum lipoprotein and apolipoprotein levels compared with a cyclical estrogen/progestogen regimen. Menopause. 1999;6(2):98-104.

200. Ferrell BR, Grant MM, Funk B, Otis-Green S, Garcia N. Quality of life in breast cancer survivors as identified by focus groups. Psycho-Oncology. 1997;6(1):13-23.

201. Finck G, Barton DL, Loprinzi CL, Quella SK, Sloan JA. Definitions of hot flashes in breast cancer survivors. Journal of Pain & Symptom Management. 1998;16(5):327-333.

202. Finset A, Overlie I, Holte A. Musculo-skeletal pain, psychological distress, and hormones during the menopausal transition. Psychoneuroendocrinology. 2004;29(1):49-64.

203. Fistonic I, Srecko C, Marina F, Ivan S. Menopause in Croatia. Socio-demographic characteristics, women's attitudes and source of information, compliance with HRT. Maturitas. 2004;47(2):91-98.

204. Fitzpatrick LA, Santen RJ. Hot flashes: the old and the new, what is really true?[comment]. Mayo Clinic Proceedings. 2002;77(11):1155-1158.

205. Flint M, Kronenberg F, Utian W, eds. Multidisciplinary perspectives on menopause: (1990). xii, 488pp.; 1990. Annals of the New York Academy of Sciences, Vol 592.

206. Force USPST. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale.[summary for patients in Ann Intern Med. 2002 Nov 19;137(10):I48; PMID: 12435233]. Ann Intern Med. 2002;137(10):834-839.

207. Foster DC, Palmer M, Marks J. Effect of vulvovaginal estrogen on sensorimotor response of the lower genital tract: a randomized controlled trial. Obstetrics & Gynecology. 1999;94(2):232-237.

208. Fraumeni JF, Jr., Lloyd JW, Smith EM, Wagoner JK. Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. J Natl Cancer Inst. 1969;42(3):455-468.

209. Freedman RR, Dinsay R. Clonidine raises the sweating threshold in symptomatic but not in asymptomatic postmenopausal women. Fertil Steril. 2000;74(1):20-23.

210. Freedman RR, Norton D, Woodward S, Cornelissen G. Core body temperature and circadian rhythm of hot flashes in menopausal women. J Clin Endocrinol Metab. 1995;80(8):2354-2358.

211. Freedman RR, Woodward S. Behavioral treatment of menopausal hot flushes: evaluation by ambulatory monitoring. Am J Obstet Gynecol. 1992;167(2):436-439.

212. Freedman RR, Woodward S, Sabharwal SC. Alpha 2-adrenergic mechanism in menopausal hot flushes. Obstetrics & Gynecology. 1990;76(4):573-578.

213. Freeman EW, Grisso JA, Berlin J, Sammel M, Garcia-Espana B, Hollander L. Symptom reports from a cohort of African American and white women in the late reproductive years. Menopause. 2001;8(1):33-42.

214. Freeman EW, Sammel MD, Grisso JA, Battistini M, Garcia-Espagna B, Hollander L. Hot flashes in the late reproductive years: risk factors for Africa American and Caucasian women. J Womens Health Gender Based Med. 2001;10(1):67-76.

215. Frey G. Oversights detract from CME article on menopause. Alternative Therapies in Health and Medicine. 2001;7(6):20-21.

216. Friebely JS, Shifren JL, Schiff I, Regestein QR. Preliminary observations on differing psychological effects of conjugated and esterified estrogen treatments. J Womens Health Gender Based Med. 2001;10(2):181-187.

217. Friedlander M, Thewes B. Counting the costs of treatment: the reproductive and gynaecological consequences of adjuvant therapy in young women with breast cancer. Internal Medicine Journal. 2003;33(8):372-379.

218. Fu SY, Anderson D, Courtney M. Cross-cultural menopausal experience: comparison of Australian and Taiwanese women. Nursing & Health Sciences. 2003;5(1):77-84.

219. Fuh JL, Wang SJ, Lu SR, Juang KD, Lee SJ. Alterations in cognitive function during the menopausal transition. Journal of the American Geriatrics Society. 2003;51(3):431-432.

220. Fuh J-L, Wang S-J, Lu S-R, Juang K-D, Lee S-J. Alterations in cognitive function during the menopausal transition. Journal of the American Geriatrics Society. 2003;51(3):431-432.

221. Gallagher JC, Baylink DJ, Freeman R, McClung M. Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies. J Clin Endocrinol Metab. 2001;86(10):4717-4726.

222. Gambacciani M, Ciaponi M, Cappagli B, et al. A longitudinal evaluation of the effect of two doses of tibolone on bone density and metabolism in early postmenopausal women. Gynecol Endocrinol. 2004;18(1):9-16.

223. Gannon L. Endocrinology of menopause. Formanek, Ruth (Ed) (1990) The meanings of menopause: Historical medical and clinical perspectives (pp 179-237) xxv, 322pp; 1990.

224. Gannon L, Hansel S, Goodwin J. Correlates of menopausal hot flashes. Journal of Behavioral Medicine. 1987;10(3):277-285.

225. Gannon L, Stevens J. Portraits of menopause in the mass media. Women & Health. 1998;27(3):1-15.

226. Ganz PA. Menopause and breast cancer: symptoms, late effects, and their management. Seminars in Oncology. 2001;28(3):274-283.

227. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol. 2003;21(22):4184-4193.

228. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol. 1998;16(2):501-514.

229. Garcia Fantini M, Saavedra J, Garcia Alba M, Garcia M. Lipoprotein (A) and homocysteine after 12 months treatment with tibolone compared to raloxifene and no treatment in postmenopausal women (abstract). Climacteric. 2002;5(Supplement 1).

230. Garnett T, Studd J, Watson N, Savvas M, Leather A. The effects of plasma estradiol levels on increases in vertebral and femoral bone density following therapy with estradiol and estradiol with testosterone implants. Obstetrics & Gynecology. 1992;79(6):968-972.

231. Garrido-Latorre F, Lazcano-Ponce EC, Lopez-Carrillo L, Hernandez-Avila M. Age of natural menopause among women in Mexico City. Int J Gynaecol Obstet. 1996;53(2):159-166.

232. Gath D, Osborn M, Bungay G, et al. Psychiatric disorder and gynaecological symptoms in middle aged women: a community survey. British Medical Journal Clinical Research Ed.. 1987;294(6566):213-218.

233. Genazzani AR, Petraglia F, Facchinetti F, et al. Effects of Org OD 14 on pituitary and peripheral beta-endorphin in castrated rats and post-menopausal women. Maturitas. Suppl. 1987;1:35-48.

234. Georgiadis AE, Siganos E, Papadimitrou G, Megapanos E. Comparison of tibolone and estrogens on their effect on postmenopausal bone loss over 5 years. Acta Obstet Gynecol Scand. 1997;76(Suppl 167(3).

235. Gigliotti B, Multinu A, Lai VR. Role of pivagabine in the treatment of climacteric syndrome. Arzneimittel-Forschung. 1997;47(11A):1317-1321.

236. Ginsberg J. What determines the age at the menopause?[see comment]. BMJ. 1991;302(6788):1288-1289.

237. Gitlin MJ, Pasnau RO. Psychiatric syndromes linked to reproductive function in women: a review of current knowledge.[see comment]. Am J Psychiatry. 1989;146(11):1413-1422.

238. Gitlin N, Korner P, Yang HM. Liver function in postmenopausal women on estrogen-androgen hormone replacement therapy: a meta-analysis of eight clinical trials. Menopause. 1999;6(3):216-224.

239. Glass S, Shapiro M. Androgen-Estrogen Treatment in the Menopause. GP: General Practitioner. 1951;3(3):39-42.

240. Glazier MG, Bowman MA. A review of the evidence for the use of phytoestrogens as a replacement for traditional estrogen replacement therapy. Arch Intern Med. 2001;161(9):1161-1172.

241. Gokdeniz R, Taskin O, Atmaca R, Burak F, Wheeler JM. The impact of Hormone Replacement Therapy (HRT) and tibolone (OD) on urodynamic function in postmenopausal women: a randomized controlled study. Fertil Steril. 1999;72(Supplement 1).

242. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001;153(9):865-874.

243. Goodman MJ, Grove JS, Gilbert F, Jr. Age at menopause in relation to reproductive history in Japanese, Caucasian, Chinese and Hawaiian women living in Hawaii. Journal of Gerontology. 1978;33(5):688-694.

244. Goodman MJ, Stewart CJ, Gilbert F, Jr. Patterns of menopause: a study of certain medical and physiological variables among Caucasian and Japanese women living in Hawaii. Journal of Gerontology. 1977;32(3):291-298.

245. Gosden RG. Follicular status at the menopause. Hum Reprod. 1987;2(7):617-621.

246. Gottlieb N. Nonhormonal agents show promise against hot flashes. J Natl Cancer Inst. 2000;92(14):1118-1120.

247. Gougeon A, Ecochard R, Thalabard JC. Age-related changes of the population of human ovarian follicles: increase in the disappearance rate of non-growing and early-growing follicles in aging women. Biol Reprod. 1994;50(3):653-663.

248. Graf MC, Geller PA. Treating hot flashes in breast cancer survivors: a review of alternative treatments to hormone replacement therapy. Clinical Journal of Oncology Nursing. 2003;7(6):637-640.

249. Grattarola R. Androgens in breast cancer. I. Atypical endometrial hyperplasia and breast cancer in married premenopausal women. Am J Obstet Gynecol. 1973;116(3):423-428.

250. Greenblatt RB, Barfield WE, Garner JF, Calk GL, Harrod JP. Evaluation of an estrogen, androgen, estrogen-androgen combination and a placebo in the treatment of the menopause. J Clin Endocrinol. 1950;10:1547-1558.

251. Greenblatt RB, Bruneteau DW. Menopausal headaches--psychogenic or metabolic? Journal of the American Geriatrics Society. 1974;22(4):186-190.

252. Greendale GA, Judd HL. The menopause: health implications and clinical management. Journal of the American Geriatrics Society. 1993;41(4):426-436.

253. Greendale GA, Lee NP, Arriola ER. The menopause. Lancet. 1999;353(9152):571-580.

254. Greendale GA, Petersen L, Zibecchi L, Ganz PA. Factors related to sexual function in postmenopausal women with a history of breast cancer. Menopause. 2001;8(2):111-119.

255. Greene JG, Cooke DJ. Life stress and symptoms at the climacterium. British Journal of Psychiatry. 1980;136:486-491.

256. Grisso JA, Freeman EW, Maurin E, Garcia-Espana B, Berlin JA. Racial differences in menopause information and the experience of hot flashes. Journal of General Internal Medicine. 1999;14(2):98-103.

257. Groeneveld F, Bareman F, Barentsen R, Dokter H. Vasomotor symptoms and well-being in the climacteric years. Maturitas. 1996;23(3):293-299.

258. Grube B, Walper A, Wheatley D. St. John's Wort extract: efficacy for menopausal symptoms of psychological origin. Adv Ther. 1999;16(4):177-186.

259. Gruber DM, Sator MO, Kirchengast S, Joura EA, Huber JC. Effect of percutaneous androgen replacement therapy on body composition and body weight in postmenopausal women. Maturitas. 1998;29(3):253-259.

260. Guidozzi F. Estrogen replacement therapy in breast cancer survivors. Int J Gynaecol Obstet. 1999;64(1):59-63.

261. Haarbo J, Hassager C, Jensen SB, Riis BJ, Christiansen C. Serum lipids, lipoproteins, and apolipoproteins during postmenopausal estrogen replacement therapy combined with either 19-nortestosterone derivatives or 17-hydroxyprogesterone derivatives. Am J Med. 1991;90(5):584-589.

262. Hackbert L, Heiman JR. Acute dehydroepiandrosterone (DHEA) effects on sexual arousal in postmenopausal women. J Womens Health Gender Based Med. 2002;11(2):155-162.

263. Haggans CJ, Hutchins AM, Olson BA, Thomas W, Martini MC, Slavin JL. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. Nutrition & Cancer. 1999;33(2):188-195.

264. Hagstad A. Gynecology and sexuality in middle-aged women. Women & Health. 1988;13(3-4):57-80.

265. Hahn PM, Wong J, Reid RL. Menopausal-like hot flashes reported in women of reproductive age. Fertil Steril. 1998;70(5):913-918.

266. Hahn RA, Eaker E, Rolka H. Reliability of reported age at menopause.[erratum appears in Am J Epidemiol 1999 Jan 15;149(2):201]. Am J Epidemiol. 1997;146(9):771-775.

267. Hale GE, Hughes CL, Robboy SJ, Agarwal SK, Bievre M. A double-blind randomized study on the effects of red clover isoflavones on the endometrium. Menopause. 2001;8(5):338-346.

268. Hammar M, Berg G. Clonidine in the treatment of menopausal flushing. A review of clinical studies. Acta Obstet Gynecol Scand Suppl. 1985;132:29-31.

269. Hammar M, Berg G, Lindgren R. Does physical exercise influence the frequency of postmenopausal hot flushes? Acta Obstet Gynecol Scand. 1990;69(5):409-412.

270. Hanggi W, Lippuner K, Jaeger P, Birkhauser MH, Horber FF. Differential impact of conventional oral or transdermal hormone replacement therapy or tibolone on body composition in postmenopausal women. Clin Endocrinol. 1998;48(6):691-699.

271. Hanggi W, Lippuner K, Riesen W, Jaeger P, Birkhauser MH. Long-term influence of different postmenopausal hormone replacement regimens on serum lipids and lipoprotein(a): a randomised study. Br J Obstet Gynaecol. 1997;104(6):708-717.

272. Harbour KE. The use of medroxyprogesterone acetate versus micronized progesterone in postmenopausal women: Neuropsychological and psychological implications, California School Of Professional Psychology - Berkeley/Alameda, US, 1.; 1999.

273. Hardy R, Kuh D, Wadsworth M. Smoking, body mass index, socioeconomic status and the menopausal transition in a British national cohort. International Journal of Epidemiology. 2000;29(5):845-851.

274. Harlow BL, Cohen LS, Otto MW, Spiegelman D, Cramer DW. Prevalence and predictors of depressive symptoms in older menopausal women: The Harvard study of moods and cycles. Arch Gen Psychiatry. 1999;56(5):418-424.

275. Harlow BL, Cramer DW, Annis KM. Association of medically treated depression and age at natural menopause. Am J Epidemiol. 1995;141(12):1170-1176.

276. Harlow BL, Signorello LB. Factors associated with early menopause. Maturitas. 2000;35(1):3-9.

277. Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry. 2003;60(1):29-36.

278. Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA. Prevalence and treatment of menopausal symptoms among breast cancer survivors. Journal of Pain & Symptom Management. 2002;23(6):501-509.

279. Harrison RF. Ethamsylate in the treatment of climacteric flushing. Maturitas. 1981;3(1):31-37.

280. Hee J, MacNaughton J, Bangah M, Burger HG. Perimenopausal patterns of gonadotrophins, immunoreactive inhibin, oestradiol and progesterone. Maturitas. 1993;18(1):9-20.

281. Hemminki E, Topo P, Kangas I. Experience and opinions of climacterium by Finnish women. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 1995;62(1):81-87.

282. Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology. 2000;54(2):295-301.

283. Heudens-Mast H. Hot flashes. New England Journal of Homeopathy. 1994;3(4):11.

284. Heuser I. Depression, endocrinologically a syndrome of premature aging? Maturitas. 2002;41(Suppl 1):S19-23.

285. Hlatky MA, Boothroyd D, Vittinghoff E, et al. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial.[see comment]. JAMA. 2002;287(5):591-597.

286. Hoda D, Perez DG, Loprinzi CL. Hot flashes in breast cancer survivors. Breast Journal. 2003;9(5):431-438.

287. Hoegler N. St. John's Wort Relieves Menopause Symptoms. Herbalgram. 2000;50:27-28.

288. Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience. 2000;101(3):485-512.

289. Holte A. Influences of natural menopause on health complaints: a prospective study of healthy Norwegian women.[see comment]. Maturitas. 1992;14(2):127-141.

290. Holte A, Mikkelsen A. Psychosocial determinants of climacteric complaints. Maturitas. 1991;13(3):205-215.

291. Holte A, Mikkelsen A. The menopausal syndrome: a factor analytic replication. Maturitas. 1991;13(3):193-203.

292. Huerta R, Mena A, Malacara JM, de Leon JD. Symptoms at the menopausal and premenopausal years: their relationship with insulin, glucose, cortisol, FSH, prolactin, obesity and attitudes towards sexuality. Psychoneuroendocrinology. 1995;20(8):851-864.

293. Huerta R, Mena A, Malacara JM, Diaz de Leon J. Symptoms at perimenopausal period: Its association with attitudes toward sexuality, life-style, family function, and FSH levels. Psychoneuroendocrinology. 1995;20(2):135-148.

294. Hulka BS, Meirik O. Research on the menopause. Maturitas. 1996;23(2):109-112.

295. Hunskar S, Brugio K, Diokno A, Herzog AR, Hjalmas K, Lapitan MC. Epidemiology and natural history of urinary incontinence in women. Urology. 2003;62(4 Suppl 1):16-23.

296. Hunter A. Cimicifuga racemosa: pharmacology, clinical trials and clinical use. European Journal of Herbal Medicine. 1999;5(1):19-25.

297. Hunter M. The south-east England longitudinal study of the climacteric and postmenopause.[see comment]. Maturitas. 1992;14(2):117-126.

298. Hunter M, Battersby R, Whitehead M. Relationships between psychological symptoms, somatic complaints and menopausal status. Maturitas. 1986;8(3):217-228.

299. Hunter MS. Psychological and somatic experience of the menopause: a prospective study. Psychosomatic Medicine. 1990;52(3):357-367.

300. Huntley A. Complementary therapies for the relief of menopausal symptoms. Focus on Alternative and Complementary Therapies. 2002;7(2):121-125.

301. Huntley A. Complementary therapies for menopausal symptoms. Focus on Alternative and Complementary Therapies. 2003;8(1):143.

302. Huntley A, Ernst E. A systematic review of plant-based products for the treatment of menopausal symptoms. Focus on Alternative and Complementary Therapies. 2002;7(1):96.

303. Huntley A, Ernst E. A Systematic Review of Plant-Based Products for the Treatment of Menopausal Symptoms. Journal of Herbal Pharmacotherapy. 2003;3/1:33-34.

304. Irvin JHA. The effects of relaxation response training on the frequency and intensity of menopausal hot flash symptoms: Dissertation Abstracts International: Section B: the Sciences & Engineering. Vol 55(6-B), 1994, 2391, US: Univ Microfilms International., U Kentucky, KY, US, 1.; 1994.

305. Jackson BB, Taylor J, Pyngolil M. How age conditions the relationship between climacteric status and health symptoms in African American women. Res Nurs Health. 1991;14(1):1-9.

306. Jacobs PA, Hyland ME, Ley A. Self-rated menopausal status and quality of life in women aged 40-63 years. British Journal of Health Psychology. 2000;5(Part4):395-411.

307. Janson PO, Dennefors B, Hamberger L. The ageing ovary. Acta Obstet Gynecol Scand Suppl. 1981;106:7-9.

308. Ji P, Ma RH, Wang ZX. Body acupuncture plus ear pressing in the treatment of menopausal syndrome. International Journal of Clinical Acupuncture. 1998;9(4):471-473.

309. Jiroutek MR, Chen MH, Johnston CC, Longcope C. Changes in reproductive hormones and sex hormone-binding globulin in a group of postmenopausal women measured over 10 years. Menopause. 1998;5(2):90-94.

310. Joffe H, Hall JE, Soares CN, et al. Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care.[see comment]. Menopause. 2002;9(6):392-398.

311. Johnston SL. Associations with age at natural menopause in Blackfeet women. American Journal of Human Biology. 2001;13(4):512-520.

312. Johnston SL. Menopause in Blackfeet women--a life span perspective. Collegium Antropologicum. 2003;27(1):57-66.

313. Jokinen K, Rautava P, Makinen J, Ojanlatva A, Sundell J, Helenius H. Experience of climacteric symptoms among 42-46 and 52-56-year-old women. Maturitas. 2003;46(3):199-205.

314. Jones CR, Czajkowski L. Evaluation and management of insomnia in menopause. Clinical Obstetrics & Gynecology. 2000;43(1):184-197.

315. Judd HL, Judd GE, Lucas WE, Yen SS. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab. 1974;39(6):1020-1024.

316. Judd HL, Shamonki IM, Frumar AM, Lagasse LD. Origin of serum estradiol in postmenopausal women. Obstetrics & Gynecology. 1982;59(6):680-686.

317. Kaleli B, Yildirim B, Demir S, Alatas E. Effects of low-dose 17-beta-estradiol plus norethisterone acetate and tibolone on fasting plasma homocysteine levels in postmenopausal women. Acta Obstet Gynecol Scand. 2003;82(12):1107-1111.

318. Kapetanakis E, Dmowski WP, Auletta F, Scommegna A. Endocrine and clinical effects of estradiol and testosterone pellets used in long-term replacement therapy. Int J Gynaecol Obstet. 1982;20(5):387-399.

319. Kaufert PA, Gilbert P. The context of menopause: psychotropic drug use and menopausal status. Soc Sci Med. 1986;23(8):747-755.

320. Kemeter P, Feichtinger W. Prednisolone supplementation to Clomid and/or gonadotropin stimulation for in-vitro fertilization - A prospective randomized trial. Hum Reprod. 1986;1(7):441-444.

321. Kerr MM. Amitriptyline in emotional states at the menopause. New Zealand Medical Journal. 1970;72(461):243-245.

322. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. Journal of Affective Disorders. 1993;29(2-3):85-96.

323. Kicovic PM, Cortes-Prieto J, Luisi M, Milojevic S, Franchi F. Placebo-controlled cross-over study of effects of Org OD 14 in menopausal women. Reproduction. 1982;6(2):81-91.

324. Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss H. Randomized, placebo-controlled study of sertraline (Zoloft TM) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. Proc Am Soc Clin Oncol. 2001;20(397a):abst 1585.

325. Kirkham C, Hahn PM, Van Vugt DA, Carmichael JA, Reid RL. A randomized, double-blind, placebo-controlled, cross-over trial to assess the side effects of medroxyprogesterone acetate in hormone replacement therapy. Obstetrics & Gynecology. 1991;78(1):93-97.

326. Klein NA, Illingworth PJ, Groome NP, McNeilly AS, Battaglia DE, Soules MR. Decreased inhibin B secretion is associated with the monotropic FSH rise in older, ovulatory women: a study of serum and follicular fluid levels of dimeric inhibin A and B in spontaneous menstrual cycles. J Clin Endocrinol Metab. 1996;81(7):2742-2745.

327. Klein P, Versi E, Herzog A. Mood and the menopause. Br J Obstet Gynaecol. 1999;106(1):1-4.

328. Knobf MT. The menopausal symptom experience in young mid-life women with breast cancer. Cancer Nursing. 2001;24(3):201-210; quiz 210-201.

329. Koninckx PR, Lauweryns JM, Cornillie FJ. Endometrial effects during hormone replacement therapy with a sequential oestradiol valerate/cyproterone acetate preparation. Maturitas. 1993;16(2):97-110.

330. Kopernik G, Shoham Z. Tools for making correct decisions regarding hormone therapy. Part II. Organ response and clinical applications. Fertil Steril. 2004;81(6):1458-1477.

331. Kornstein SG, Schatzberg AF, Thase ME, et al. "Gender differences in treatment response to sertraline versus imipramine in chronic depression": Reply. Am J Psychiatry. 2001;158(9):1532-1533.

332. Koster A. Change-of-life anticipations, attitudes, and experiences among middle-aged Danish women. Health Care Women Int. 1991;12(1):1-13.

333. Kotsopoulos D, Dalais FS, Liang YL, McGrath BP, Teede HJ. The effects of soy protein containing phytoestrogens on menopausal symptoms in postmenopausal women.[see comment]. Climacteric. 2000;3(3):161-167.

334. Kraft K, Coulon S. Acupuncture may temporarily relieve climacteric symptoms (Der Einflub einer standardisierten Akupunkturbehandlung auf Beschwerden, Blutdruck und Serumlipide hypertensiver, postmenopausaler Frauen.). Forsch Komplementarmed. 1999;6:74-79.

335. Krailo MD, Pike MC. Estimation of the distribution of age at natural menopause from prevalence data. Am J Epidemiol. 1983;117(3):356-361.

336. Kratz KE. The cognitive effects of DHEA supplementation in postmenopausal women, Fuller Theological Seminary, School Of Psychology, US, 1.; 2000.

337. Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women. JAMA. 2004;292(1):65-74.

338. Kritz-Silverstein D, Goldani Von Muhlen D, Barrett-Connor E. Prevalence and clustering of menopausal symptoms in older women by hysterectomy and oophorectomy status. J Womens Health Gender Based Med. 2000;9(7):747-755.

339. Kroboth PD, McAuley JW. Progesterone: Does it affect response to drug? Psychopharmacology Bulletin. 1997;33(2):297-301.

340. Kronenberg F. Hot flashes: epidemiology and physiology. Annals of the New York Academy of Sciences. 1990;592:52-86; discussion 123-133.

341. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials.[see comment]. Ann Intern Med. 2002;137(10):805-813.

342. Kudielka BM, Schmidt-Reinwald AK, Hellhammer DH, Kirschbaum C. Psychological and endocrine responses to psychosocial stress and dexamethasone/corticotropin-releasing hormone in healthy postmenopausal women and young controls: the impact of age and a two-week estradiol treatment. Neuroendocrinology. 1999;70(6):422-430.

343. Kuller LH, Matthews KA, Meilahn EN. Estrogens and women's health: interrelation of coronary heart disease, breast cancer and osteoporosis. Journal of Steroid Biochemistry & Molecular Biology. 2000;74(5):297-309.

344. Kuller LH, Simkin-Silverman LR, Wing RR, Meilahn EN, Ives DG. Women's Healthy Lifestyle Project: A randomized clinical trial: results at 54 months. Circulation. 2001;103(1):32-37.

345. Kurabayashi T, Okada M, Tanaka K. Eicosapentaenoic acid effect on hyperlipidemia in menopausal Japanese women. The Niigata Epadel Study Group. Obstetrics & Gynecology. 2000;96(4):521-528.

346. Kurpius SE, Nicpon MF, Maresh SE. Mood, marriage and menopause. Journal of Counseling Psychology. 2001;48(1):77-84.

347. Kuzuya F, Kono K. Pharmacotherapy in later life: Eastern principles. Bergener, Manfred (Ed); Hasegawa, Kazuo (Ed); et al (1992) Aging and mental disorders: International perspectives (pp 239-252) xv, 426pp; 1992.

348. Kwawukume EY, Ghosh TS, Wilson JB. Menopausal age of Ghanaian women. Int J Gynaecol Obstet. 1993;40(2):151-155.

349. Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric. 2001;4(1):28-41.

350. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997;82(8):2396-2402.

351. Labrie F, Diamond P, Cusan L, Gomez JL, Belanger A, Candas B. Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina, and endometrium in postmenopausal women. J Clin Endocrinol Metab. 1997;82(10):3498-3505.

352. Lagrelius A, Fredricsson B, Hirt M, Weintraub L. Clinical experience with a low-dose combination of estradiol valerate and levonorgestrel. Double-blind comparative study between SH D 386 F and Cyclabil. Effects on symptoms, lipids and endometrial condition. Acta Obstet Gynecol Scand Suppl. 1986;134:97-101.

353. Lamlertkittikul S, Chandeying V. Efficacy and safety of Pueraria mirifica (Kwao Kruea Khao) for the treatment of vasomotor symptoms in perimenopausal women: Phase II Study. Journal of the Medical Association of Thailand. 2004;87(1):33-40.

354. Larsson-Cohn U, Hammar M, Chirstau S, Nathorst-Boos J, Rud T, Garre K. A double-blind, randomized study comparing the effects of Livial and Kliogest in postmenopausal women with climacteric complaints. Paper presented at: British Menopause Society; 11.9.04, Exeter 1996.

355. Lasco A, Frisina N, Morabito N, et al. Metabolic effects of dehydroepiandrosterone replacement therapy in postmenopausal women. European Journal of Endocrinology. 2001;145(4):457-461.

356. Laufer LR, Erlik Y, Meldrum DR, Judd HL. Effect of clonidine on hot flashes in postmenopausal women. Obstetrics & Gynecology. 1982;60(5):583-586.

357. Lebherz TB, French L. Nonhormonal treatment of the menopausal syndrome. A double-blind evaluation of an autonomic system stabilizer. Obstetrics & Gynecology. 1969;33(6):795-799.

358. Ledesert B, Ringa V, Breart G. Menopause and perceived health status among the women of the French GAZEL cohort. Maturitas. 1994;20(2-3):113-120.

359. Lee J. Use of Pro-Gest cream in postmenopausal women. Lancet. 1998;352:905.

360. Leidy LE. Timing of menopause in relation to body size and weight change. Human Biology. 1996;68(6):967-982.

361. Lennon MC. The psychological consequences of menopause: The importance of timing of a strange life event. Journal of Health & Social Behavior. 1982;23(4):353-366.

362. Lennon MC. Is menopause depressing? An investigation of three perspectives. Sex Roles. 1987;17(1-2):1-16.

363. Lenton EA, Landgren BM, Sexton L, Harper R. Normal variation in the length of the follicular phase of the menstrual cycle: effect of chronological age. Br J Obstet Gynaecol. 1984;91(7):681-684.

364. Lerner J. TCM/Kampo therapy also efficacious for menopause. Alternative Therapies in Health and Medicine. 2001;7(6):21.

365. Levy T, Gurevitch S, Bar-Hava I, et al. Pharmacokinetics of natural progesterone administered in the form of a vaginal tablet. Hum Reprod. 1999;14(3):606-610.

366. Lewis JG, McGill H, Patton VM, Elder PA. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. Maturitas. 2002;41(1):1-6.

367. Li C, Samsioe G, Borgfeldt C, Lidfeldt J, Agardh CD, Nerbrand C. Menopause-related symptoms: what are the background factors? A prospective population-based cohort study of Swedish women (The Women's Health in Lund Area study). Am J Obstet Gynecol. 2003;189(6):1646-1653.

368. Liao KL, Hunter MS. Preparation for menopause: prospective evaluation of a health education intervention for mid-aged women. Maturitas. 1998;29(3):215-224.

369. Linzmayer L, Semlitsch HV, Saletu B, et al. Double-blind, placebo-controlled psychometric studies on the effects of a combined estrogen-progestin regimen versus estrogen alone on performance, mood and personality of menopausal syndrome patients. Arzneimittel-Forschung. 2001;51(3):238-245.

370. Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (Cimicifugae racemosae rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gender Based Med. 2002;11(2):163-174.

371. Liu P, He FF, Bai WP, et al. Menopausal depression: comparison of hormone replacement therapy and hormone replacement therapy plus fluoxetine. Chin Med J. 2004;117(2):189-194.

372. Longcope C, Jaffee W, Griffing G. Production rates of androgens and oestrogens in post-menopausal women. Maturitas. 1981;3(3-4):215-223.

373. Loprinzi C, Quella SK, Sloan J, al. e. Preliminary data from a randomized evaluation of fluoxetine (Prozac) for treating hot flashes in breast cancer survivors. Breast Cancer Research and Treatment. 1999;57:abstract.

374. Loprinzi CL, Kugler JW, Sloan J. Venlafaxine alleviates hot flashes: an NCCTG trial. Proc Am Soc Clin Oncol. 2000;19:abst 4.

375. Loprinzi CL, Peethambaram PP. Management of menopausal symptoms in breast cancer patients. Ann Med. 1995;27(6):653-656.

376. Loprinzi CL, Pisansky TM, Fonseca R, et al. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. J Clin Oncol. 1998;16(7):2377-2381.

377. Loprinzi L, Barton DL, Sloan JA, et al. Pilot evaluation of gabapentin for treating hot flashes.[see comment]. Mayo Clinic Proceedings. 2002;77(11):1159-1163.

378. Lovejoy JC, Bray GA, Bourgeois MO, et al. Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women--a clinical research center study. J Clin Endocrinol Metab. 1996;81(6):2198-2203.

379. Luciano AA, Miller BE, Sequenzia LC, Benadiva CA, Slade KL. The pharmacokinetics of the sublingual administration of micronized estradiol, progesterone and testosterone in postmenopausal women. Fertil Steril. 1998;70(3).

380. Luckas MJ, Gleeve T, Biljan MM, et al. The effect of progestagens on the carotid artery pulsatility index in postmenopausal women on oestrogen replacement therapy. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 1998;76(2):221-224.

381. Lucks B. Vitex agnus castus essential oil and menopausal balance: a research update [Complementary Therapies in Nursing and Midwifery 8 (2003) 148.154]. Complementary Therapies in Nursing & Midwifery. 2003;9(3):157-160.

382. Lucks BC. The Vitex agnus castus dilemma: ethical management of a double-edged oil. Aromatheraphy Today. 2003;27:24-27.

383. Lundstrom E, Christow A, Kersemaekers W, et al. Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. Am J Obstet Gynecol. 2002;186(4):717-722.

384. Lyritis GP, Karpathios S, Basdekis K, et al. Prevention of post-oophorectomy bone loss with Tibolone. Maturitas. 1995;22(3):247-253.

385. Maartens LW, Leusink GL, Knottnerus JA, Pop VJ. Hormonal substitution during menopause: what are we treating? Maturitas. 2000;34(2):113-118.

386. MacNaughton J, Banah M, McCloud P, Hee J, Burger H. Age related changes in follicle stimulating hormone, luteinizing hormone, oestradiol and immunoreactive inhibin in women of reproductive age. Clin Endocrinol. 1992;36(4):339-345.

387. Mahady GB, Fabricant D, Chadwick LR, Dietz B. Black cohosh: an alternative therapy for menopause? Nutrition in Clinical Care. 2002;5(6):283-289.

388. Mahavni V, Buller RE. Estrogen replacement therapy in endometrial and breast cancer survivors. Clinical Obstetrics & Gynecology. 1999;42(4):863-875.

389. Maheux R, Naud F, Rioux M, et al. A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness. Am J Obstet Gynecol. 1994;170(2):642-649.

390. Mansfield PK, Koch PB, Voda AM. Midlife women's attributions for their sexual response changes. Health Care Women Int. 2000;21(6):543-559.

391. Manzella D, Fornaro F, Carbonella M, Picardi C, Paolisso G, Colacurci N. Effect of tibolone administration on heart rate variability and free fatty acid levels in postmenopausal women. Fertil Steril. 2002;78(5):1005-1009.

392. Marchesoni D, Mozzanega B, Maggino T, Nardelli GB. Postmenopausal hot flushes: Endocrine correlations and progestinic treatment. Double blind crossed clinical trial using MPA versus placebo. Journal of Gynaecological Endocrinology. 1985;1(1-2):63-69.

393. Maresi MP, Baldi L, Balatresi L, et al. A non-hormonal therapeutic alternative in cervico-vaginal dystrophies. Annali di Ostetricia, Ginecologia, Medicina Perinatale. 1990;111(6):393-399.

394. Mariella AM. Longitudinal patterns of depressive symptoms in midlife women, U Washington, US, 1.; 2002.

395. Marsden J. The menopause, hormone replacement therapy and breast cancer. Journal of Steroid Biochemistry & Molecular Biology. 2002;83(1-5):123-132.

396. Martin PL, Burnier AM, Segre EJ, Huix FJ. Graded sequential therapy in the menopause: a double-blind study. Am J Obstet Gynecol. 1971;111(2):178-186.

397. Matthews KA, Kuller LH, Wing RR, Meilahn EN. Biobehavioral aspects of menopause: lessons from the Healthy Women Study. Exp Gerontol. 1994;29(3-4):337-342.

398. Matthews KA, Wing RR, Kuller LH, Meilahn EN, Plantinga P. Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. Arch Intern Med. 1994;154(20):2349-2355.

399. Mazer NA. Testosterone deficiency in women: etiologies, diagnosis, and emerging treatments. Int J Fertil Womens Med. 2002;47(2):77-86.

400. Mazer NA, Shifren JL. Transdermal testosterone for women: a new physiological approach for androgen therapy. Obstetrical & Gynecological Survey. 2003;58(7):489-500.

401. McCarthy T, Dramusic V, Carter R, Costales A, Ratnam SS. Randomized cross-over study of a 21-day versus a 28-day hormone replacement therapy (HRT). Maturitas. 1995;22(1):13-23.

402. McKinlay JB, McKinlay SM, Brambilla DJ. Health status and utilization behavior associated with menopause. Am J Epidemiol. 1987;125(1):110-121.

403. Meirow D. Reproduction post-chemotherapy in young cancer patients. Molecular & Cellular Endocrinology. 2000;169(1-2):123-131.

404. Meldrum DR, Davidson BJ, Tataryn IV, Judd HL. Changes in circulating steroids with aging in postmenopausal women. Obstetrics & Gynecology. 1981;57(5):624-628.

405. Melis GB, Cagnacci A, Bruni V, et al. Salmon calcitonin plus intravaginal estriol: An effective treatment for the menopause. Maturitas. 1996;24(1-2):83-90.

406. Mendoza N, Alamo F, Alvarez M, Hortas ML, Martinez L. Lipid Effects, Safety and Acceptability of Tibolone Versus Transdermic 17B-Estradiol for Hormone Replacement Therapy in Women with Surgical Menopause. Acta Obstet Gynecol Scand. 1997;76(Supplement).

407. Menkes DB, Thomas MC, Phipps RF. Moclobemide for menopausal flushing. Lancet. 1994;344(8923):691-692.

408. Messina M, Hughes C. Efficacy of soyfoods and soybean isoflavone supplements for alleviating menopausal symptoms is positively related to initial hot flush frequency. Journal of Medicinal Food. 2003;6(1):1-11.

409. Messina MJ, Loprinzi CL. Soy for breast cancer survivors: a critical review of the literature. Journal of Nutrition. 2001;131(11 Suppl):3095S-3108S.

410. Metcalf MG. The approach of menopause: a New Zealand study. New Zealand Medical Journal. 1988;101(841):103-106.

411. Metcalf MG, Livesay JH. Gonadotropin excretion in fertile women: effect of age and the onset of the menopausal transition. Journal of Endocrinology. 1985;105:357-.

412. Metzl JM, Angel J. Assessing the impact of SSRI antidepressants on popular notions of women's depressive illness. Soc Sci Med. 2004;58(3):577-584.

413. Miller BE, De Souza MJ, Slade K, Luciano AA. Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. Menopause. 2000;7(5):318-326.

414. Miller K, Corcoran C, Armstrong C, et al. Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: a pilot study. J Clin Endocrinol Metab. 1998;83(8):2717-2725.

415. Miller LG. Promising results of Piper methysticum on mood parameters in perimenopausal women. Focus on Alternative & Complementary Therapies. 2003;8(3):310-311.

416. Milner M, Kelly A, Harrison RF. Controlled Study of Metabolic Effects of Estrogen-Progestogen and Tibolone Over 2 Years on Postmenopausal Women. 8th International Congress on the Menopause.96.

417. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab. 2002;87(1):16-23.

418. Montgomery JC. Treatment of Decreased Libido in Climacteric Women: Effects of Oestradiol Implants Alone and in Combination with Testosterone. Journal of Obstetrics & Gynaecology. 1991;11(4).

419. Montgomery JC, Appleby L, Brincat M, et al. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. Lancet. 1987;1(8528):297-299.

420. Moore HC. Managing menopause after breast cancer: balancing risks and benefits. Cleveland Clinic Journal of Medicine. 2001;68(3):243-248.

421. Moore RA. Livial: a review of clinical studies. Br J Obstet Gynaecol. 1999;106(Suppl 19):1-21.

422. Morales AJ, Nolan JJ, Nelson JC, Yen SS. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age.[erratum appears in J Clin Endocrinol Metab 1995 Sep;80(9):2799]. J Clin Endocrinol Metab. 1360;78(6):1360-1367.

423. Mortimer JE. Hormone replacement therapy and beyond. The clinical challenge of menopausal symptoms in breast cancer survivors. Geriatrics. 2002;57(9):25-31.

424. Munster K, Schmidt L, Helm P. Length and variation in the menstrual cycle--a cross-sectional study from a Danish county. Br J Obstet Gynaecol. 1992;99(5):422-429.

425. Murray MJ, Meyer WR, Lessey BA, Oi RH, DeWire RE, Fritz MA. Soy protein isolate with isoflavones does not prevent estradiol-induced endometrial hyperplasia in postmenopausal women: a pilot trial. Menopause. 2003;10(5):456-464.

426. Myers LS, Dixen J, Morrissette D, Carmichael M, Davidson JM. Effects of estrogen, androgen, and progestin on sexual psychophysiology and behavior in postmenopausal women. J Clin Endocrinol Metab. 1990;70(4):1124-1131.

427. Nash HA, Alvarez-Sanchez F, Mishell DR, Jr., Fraser IS, Maruo T, Harmon TM. Estradiol-delivering vaginal rings for hormone replacement therapy. Am J Obstet Gynecol. 1999;181(6):1400-1406.

428. Nevinny-Stickel J. Double-blind cross-over study with Org OD 14 and placebo in postmenopausal patients. Archives of Gynecology. 1983;234(1):27-31.

429. Nguyen TT, Wisniewski AB, Dobs AS. Influence of estrogen with or without methyl-testosterone therapy on cognitive functions in post-menopausal women. Fertil Steril. 1999;72(Supplement 1).

430. Nguyen TV, Wong FW. The effects of Chinese medicinal herbs on postmenopausal vasomotor symptoms of Australian women. Med J Aust. 2001;175(4):230.

431. Nihira MA, Henderson N. Epidemiology of urinary incontinence in women. Current Women's Health Reports. 2003;3(4):340-347.

432. North American Menopause S. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause. 2004;11(1):11-33.

433. Obermeyer CM. Menopause across cultures: a review of the evidence. Menopause. 2000;7(3):184-192.

434. Obillo E, Eleazar J, Demeterio J. Maprotiline for Depression during Menopause: A Philippine Menopause Clinic Experience CONFERENCE ABSTRACT. XXth Collegium Internationale Neuro psychopharmacologicum Melbourne, Australia 23rd 27th June. 1996.

435. O'Bryant SE, Palav A, McCaffrey RJ. A review of symptoms commonly associated with menopause: implications for clinical neuropsychologists and other health care providers. Neuropsychology Review. 2003;13(3):145-152.

436. O'Connor AM, Tugwell P, Wells GA, et al. Randomized trial of a portable, self-administered decision aid for postmenopausal women considering long-term preventive hormone therapy. Medical Decision Making. 1998;18(3):295-303.

437. O'Connor AM, Wells GA, Tugwell P, Laupacis A, Elmslie T, Drake E. The effects of an 'explicit' values clarification exercise in a woman's decision aid regarding postmenopausal hormone therapy. Health Expectations. 1999;2(1):21-32.

438. Oldenhave A, Jaszmann LJ, Haspels AA, Everaerd WT. Impact of climacteric on well-being. A survey based on 5213 women 39 to 60 years old. Am J Obstet Gynecol. 1993;168(3 Pt 1):772-780.

439. Owens JF, Matthews KA. Sleep disturbance in healthy middle-aged women. Maturitas. 1998;30(1):41-50.

440. Ozsoy M, Oral B, Ozsoy D. Clinical equivalence of intranasal estradiol and oral estrogens for postmenopausal symptoms. Int J Gynaecol Obstet. 2002;79(2):143-146.

441. Palmer JR, Rosenberg L, Wise LA, Horton NJ, Adams-Campbell LL. Onset of natural menopause in African American women. American Journal of Public Health. 2003;93(2):299-306.

442. Paoletti AM, Floris S, Mannias M, et al. Evidence that cyproterone acetate improves psychological symptoms and enhances the activity of the dopaminergic system in postmenopause. J Clin Endocrinol Metab. 2001;86(2):608-612.

443. Papps FA. Therapeutic use and associated biochemistry of Cimicifuga racemosa in the treatment of menopausal symptoms. Australian Journal of Medical Herbalism. 2000;12(1):22-26.

444. Parazzini F, Colli E, Origgi G, et al. Risk factors for urinary incontinence in women. European Urology. 2000;37(6):637-643.

445. Parazzini F, Progretto Menopausa Italia Study G. Menopausal status, hormone replacement therapy use and risk of self-reported physician-diagnosed osteoarthritis in women attending menopause clinics in Italy. Maturitas. 2003;46(3):207-212.

446. Parker M, Bosscher J, Barnhill D, Park R. Ovarian management during radical hysterectomy in the premenopausal patient.[see comment]. Obstetrics & Gynecology. 1993;82(2):187-190.

447. Parlee MB. Psychological aspects of the climacteric in women. Psychiatric Opinion. 1978;15(10):36-40.

448. Parlee MB. Integrating biological and social scientific research on menopause. Flint, Marcha (Ed); Kronenberg, Fredi (Ed); et al (1990) Multidisciplinary perspectives on menopause Annals of the New York Academy of Sciences, Vol 592 (pp 379-389) xii, 488pp; 1990.

449. Parry BL. Reproductive factors affecting the course of affective illness in women. Psychiatric Clinics of North America. 1989;12(1):207-220.

450. Parry BL, Newton RP. Chronobiological basis of female-specific mood disorders. Neuropsychopharmacology. 2001;25(5 Suppl):S102-108.

451. Pasquali R, Casimirri F, Labate AM, et al. Body weight, fat distribution and the menopausal status in women. The VMH Collaborative Group. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 1994;18(9):614-621.

452. Pearce J, Hawton K, Blake F. Psychological and sexual symptoms associated with the menopause and the effects of hormone replacement therapy. British Journal of Psychiatry. 1995;167(2):163-173.

453. Pearce J, Hawton K, Blake F, et al. Psychological effects of continuation versus discontinuation of hormone replacement therapy by estrogen implants: a placebo-controlled study. Journal of Psychosomatic Research. 1997;42(2):177-186.

454. Pearlstein TB. Hormones and depression: what are the facts about premenstrual syndrome, menopause, and hormone replacement therapy? Am J Obstet Gynecol. 1995;173(2):646-653.

455. Penotti M, Fabio E, Rinaldi M, Omodei U, Bacchi Modena A. Effects of soy-derived isoflavones on hot flushes and vascular reactivity (abstract). Climacteric. 2002;5(Supplement 1):104.

456. Persky H, Dreisbach L, Miller WR, et al. The relation of plasma androgen levels to sexual behaviors and attitudes of women. Psychosomatic Medicine. 1982;44(4):305-319.

457. Petitti DB, Buckwalter J, Crooks VC, Chiu V. Prevalence of dementia in users of hormone replacement therapy as defined by prescription data. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2002;57A(8):M532-M538.

458. Petre-Quadens O. Hormones and sleep [proceedings]. Journal of Physiology. 1979;295:70P-71P.

459. Petropoulos P, Karayiannis V, Tzafettas J, Tsimas V, Petropoulou V, Mamopoulos M. A randomised trial comparing the effects of tibolone and the continuous administration of conjugated estrogens and MPA as HRT in postmenopausal women with menopausal symptoms (abstract). Gynecol Endocrinol. 2000;14(Supplement 2).

460. Pfeiffer E, Davis GC. Determinants of sexual behavior in middle and old age. Journal of the American Geriatrics Society. 1972;20(4):151-158.

461. Pham KT, Grisso JA, Freeman EW. Ovarian aging and hormone replacement therapy. Hormonal levels, symptoms, and attitudes of African-American and white women. Journal of General Internal Medicine. 1997;12(4):230-236.

462. Philip H. Hot flashes - a review of the literature on alternative and complementary treatment approaches. Alternative Medicine Review. 2003;8(3):284-302.

463. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology. 1992;17(5):485-495.

464. Pinto BM, Maruyama NC. Exercise in the rehabilitation of breast cancer survivors. Psycho-Oncology. 1999;8(3):191-206.

465. Pisani G, Facioni L, Fiorani F. Psychological and sexual disturbances in menopause: <ORIGINAL> PROBLEMATICHE PSICOSESSUALI IN MENOPAUSA. Minerva Ginecologica. 1998;50(3):77-81.

466. Pitt B. Depression in middle-aged women. British Journal of Hospital Medicine. 1987;38(1):26-28, 30, 32.

467. Pittler MH. Chinese medicinal herbs are no more effective than placebo in reducing vasomotor symptoms in postmenopausal women. Focus on Alternative & Complementary Therapies. 2001;6(2):117-118.

468. Plumb JM, Guest JF. Economic impact of tibolone compared with continuous-combined hormone replacement therapy. In the management of postmenopausal women with climacteric symptoms in the UK. Pharmacoeconomics. 2000;18(5):477-486.

469. Polis NS. Aerobic exercise: effects on selected health variables in menopausal women (women). Health Sciences Case Western Reserve University. 1989.

470. Polo-Kantola P, Erkkola R, Irjala K, Helenius H, Pullinen S, Polo O. Climacteric symptoms and sleep quality. Obstetrics & Gynecology. 1999;94(2):219-224.

471. Polo-Kantola P, Portin R, Koskinen T, Polo O, Irjala K, Erkkola R. Climacteric symptoms do not impair cognitive performances in postmenopause. Maturitas. 1997;27(1):13-23.

472. Pop VJ, Maartens LH, Leusink G, et al. Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab. 1998;83(9):3194-3197.

473. Pornel B. Efficacy and safety of Menorest in two positive-controlled studies. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 1996;64(Suppl):S35-37.

474. Porzio G, Trapasso T, Martelli S, et al. Acupuncture in the treatment of menopause-related symptoms in women taking tamoxifen. Tumori. 2002;88(2):128-130.

475. Prelevic GM, Bartram C, Wood J, Okolo S, Ginsburg J. Comparative effects on bone mineral density of tibolone, transdermal estrogen and oral estrogen/progestogen therapy in postmenopausal women. Gynecol Endocrinol. 1996;10(6):413-420.

476. Prior JC. The ageing female reproductive axis II: ovulatory changes with perimenopause. Novartis Foundation Symposium. 2002;242:172-186; discussion 186-192.

477. Pritchard KI, Khan H, Levine M, Steering Committee on Clinical Practice Guidelines for the C, Treatment of Breast C. Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. CMAJ. 2002;166(8):1017-1022.

478. Progetto Menopausa Italia Study G. Risk of low bone density in women attending menopause clinics in Italy. Maturitas. 2002;42(2):105-111.

479. Progetto Menopausa Italia Study G. Premature ovarian failure: frequency and risk factors among women attending a network of menopause clinics in Italy. BJOG. 2003;110(1):59-63.

480. Progetto Menopausa Italia Study G. Determinants of body mass index in women around menopause attending menopause clinics in Italy. Climacteric. 2003;6(1):67-74.

481. Quella SK, L. LC, Barton DL, Knost JA, Sloan JA, LaVasseur BI, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group trial. J Clin Oncol. 2000;18:1068-1074.

482. Quitkin FM, Stewart JW, McGrath PJ. "Gender differences in treatment response to sertraline versus imipramine in chronic depression": Comment. Am J Psychiatry. 2001;158(9):1531-1533.

483. Quitkin FM, Stewart JW, McGrath PJ, et al. Are there differences between women's and men's antidepressant responses? Am J Psychiatry. 2002;159(11):1848-1854.

484. Rabinerson D, Avrech O, Kaplan B, Braslavsky D, Goldman GA, Neri A. Endometrioma of the vagina in menopause. Acta Obstet Gynecol Scand. 1996;75(5):506-507.

485. Randolph JF, Jr., Sowers M, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. J Clin Endocrinol Metab. 2004;89(4):1555-1561.

486. Rannestad T, Eikeland O-J, Helland H, Qvarnstroem U. Are the physiologically and psychosocially based symptoms in women suffering from gynecological disorders alleviated by means of hysterectomy? J Womens Health Gender Based Med. 2001;10(6):579-587.

487. Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L. A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas. 1995;21(2):103-113.

488. Rasgon Natalie L, Dunkin J, Altshuler Lori L, Rapkin A. Estrogen-replacement therapy: cognition and depression in postmenopausal women. 155th Annual Meeting of the American Psychiatric Association. 2002.

489. Ravnikar V. Physiology and treatment of hot flushes. Obstetrics & Gynecology. 1990;75(4 Suppl):3S-8S; discussion 15S-17S.

490. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections.[see comment]. N Engl J Med. 1993;329(11):753-756.

491. Reay Jones NH, Healy JC, King LJ, Saini S, Shousha S, Allen-Mersh TG. Pelvic connective tissue resilience decreases with vaginal delivery, menopause and uterine prolapse. British Journal of Surgery. 2003;90(4):466-472.

492. Rebar RW, Spitzer IB. The physiology and measurement of hot flushes. Am J Obstet Gynecol. 1987;156(5):1284-1288.

493. Regestein QR, Friebely J, Shifren J, Schiff I. Neuropsychological effects of methyltestosterone in women using menopausal hormone replacement. J Womens Health Gender Based Med. 2001;10(7):671-676.

494. Reginster JY, Deroisy R, Paul I, Hansenne M, Ansseau M. Depressive vulnerability is not an independent risk factor for osteoporosis in postmenopausal women. Maturitas. 1999;33(2):133-137.

495. Reinhard-Hennch B. Phytoestrogenes in the menopause: A review Review. Schweizerische Zeitschrift fur Ganzheitsmedizin. 2004;16(3):164-167.

496. Resnick SM, Metter E, Zonderman AB. Estrogen replacement therapy and longitudinal decline in visual memory: A possible protective effect? Neurology. 1997;49(6):1491-1497.

497. Reti LL, Rome RM, Jr., Brown JB, Fortune DW. Urinary oestrogen and pregnanediol excretion, endometrial and ovarian pathology and body weight in women with postmenopausal bleeding. Br J Obstet Gynaecol. 1978;85(11):857-861.

498. Reyes FI, Winter JS, Faiman C. Pituitary-ovarian relationships preceding the menopause. I. A cross-sectional study of serum follice-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone levels. Am J Obstet Gynecol. 1977;129(5):557-564.

499. Reynolds F. Psychological responses to menopausal hot flushes: Implications of a qualitative study for counselling interventions. Counselling Psychology Quarterly. 1997;10(3):309-321.

500. Reynolds F. Some relationships between perceived control and women's reported coping strategies for menopausal hot flushes. Maturitas. 1999;32(1):25-32.

501. Reynolds F. Relationships between catastrophic thoughts, perceived control and distress during menopausal hot flushes: exploring the correlates of a questionnaire measure. Maturitas. 2000;36(2):113-122.

502. Reynolds F. Exploring self-image during hot flushes using a semantic differential scale: associations between poor self-image, depression, flush frequency and flush distress. Maturitas. 2002;42(3):201-207.

503. Reynolds F. Exploring the long-term experience of vasomotor instability: A 5 year follow-up study of distress, perceived control and catastrophizing. Counselling Psychology Quarterly. 2002;15(1):73-83.

504. Rice K, Morse C. Measuring cognition in menopause research: a review of test use. Climacteric. 2003;6(1):2-22.

505. Rice MM, Graves AB, McCurry SM, et al. Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive change in a cohort of older Japanese American women: The Kame Project. Arch Intern Med. 2000;160(11):1641-1649.

506. Richards M, Kuh D, Hardy R, Wadsworth M. Lifetime cognitive function and timing of the natural menopause. Neurology. 1999;53(2):308-314.

507. Richards-Kustan CJ, Kase NG. Diagnosis and management of perimenopausal and postmenopausal bleeding. Obstetrics & Gynecology Clinics of North America. 1987;14(1):169-189.

508. Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: evidence for accelerated loss and ultimate exhaustion. J Clin Endocrinol Metab. 1987;65(6):1231-1237.

509. Richelle M, Pridmore-Merten S, Bodenstab S, Enslen M, Offord EA. Hydrolysis of isoflavone glycosides to aglycones by beta-glycosidase does not alter plasma and urine isoflavone pharmacokinetics in postmenopausal women. Journal of Nutrition. 2002;132(9):2587-2592.

510. Richter DL, Corwin SJ, Rheaume CE, McKeown RE. Perceptions of alternative therapies available for women facing hysterectomy or menopause. Journal of Women & Aging. 2001;13(4):21-37.

511. Richters JM. Menopause in different cultures. J Psychosom Obstet Gynaecol. 1997;18(2):73-80.

512. Roberts J, Chambers LF, Blake J, Webber C. Psychosocial adjustment in post-menopausal women. Canadian Journal of Nursing Research. 1992;24(4):29-46.

513. Rock E, DeMichele A. Nutritional approaches to late toxicities of adjuvant chemotherapy in breast cancer survivors. Journal of Nutrition. 2003;133(11 Suppl 1):3785S-3793S.

514. Rodstrom K, Bengtsson C, Milsom I, Lissner L, Sundh V, Bjourkelund C. Evidence for a secular trend in menopausal age: a population study of women in Gothenburg. Menopause. 2003;10(6):538-543.

515. Rohr UD. The impact of testosterone imbalance on depression and women's health. Maturitas. 2002;41(Suppl 1):S25-46.

516. Rosner GL, Hargis JB, Hollis DR, et al. Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: results from cancer and leukemia group B study 8541. J Clin Oncol. 1996;14(11):3000-3008.

517. Rostom A, O'Connor A, Tugwell P, Wells G. A randomized trial of a computerized versus an audio-booklet decision aid for women considering post-menopausal hormone replacement therapy. Patient Educ Couns. 2002;46(1):67-74.

518. Rothert ML, Holmes-Rovner M, Rovner D, et al. An educational intervention as decision support for menopausal women. Res Nurs Health. 1997;20(5):377-387.

519. Rousseau M. Women's midlife health. Reframing menopause. Journal of Nurse-Midwifery. 1998;43(3):208-223.

520. Ryan N, Rosner A. Quality of life and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for nonhysterectomized, postmenopausal women. Clinical Therapeutics. 2001;23(7):1099-1115.

521. Ryhammer AM, Laurberg S, Djurhuus JC, Hermann AP. No relationship between subjective assessment of urinary incontinence and pad test weight gain in a random population sample of menopausal women. Journal of Urology. 1998;159(3):800-803.

522. Rymer J, Chapman M, Fogelman I, Wilson P. A study of the effect of tibolone on the vagina in postmenopausal women. Maturitas. 1994;18(2):127-133.

523. Rymer J, Chapman MG, Fogelman I. Effect of tibolone on postmenopausal bone loss. Osteoporosis International. 1994;4(6):314-319.

524. Rymer J, Robinson J, Fogelman I. Effects of 8 years of treatment with tibolone 2.5 mg daily on postmenopausal bone loss. Osteoporosis International. 2001;12(6):478-483.

525. Sammel MD, Grisso JA, Freeman EW, et al. Weight gain among women in the late reproductive years. Fam Pract. 2003;20(4):401-409.

526. Sanchez FE, Urdinola JM, Onatra WH, Posso HV, Sanchez JA, Alwers RC. Clinical manifestations in menopause with modifications to hormone replacement therapy. Multicentre Clinical trial comparing mixed hormones (conjugated estrogens plus medroxyprogesterone vs. estradiol valerate plus cyproterone acetate. Revista Colombiana de Obstetricia y Ginecologia. 1996;47(4):263-272.

527. Sands RH, Studd JW, Jones J, Alaghband-Zadeh J. Comparison of the biochemical effects of testosterone and estrogen on bone markers in surgically menopausal women. Gynecol Endocrinol. 2000;14(5):382-387.

528. Sands RH, Studd JWW, Catalan J, Alaghband Zadeh J. Effect of testosterone replacement therapy in surgically menopausal women. Fertil Steril. 1998;70(3).

529. Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab. 1495;81(4):1495-1501.

530. Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses. J Reprod Med. 1998;43(10):847-856.

531. Schindler BA. The psychiatric disorders of midlife. Medical Clinics of North America. 1987;71(1):71-85.

532. Schmidt PJ, Murphy JH, Haq N, Danaceau MA, St Clair L. Basal plasma hormone levels in depressed perimenopausal women. Psychoneuroendocrinology. 2002;27(8):907-920.

533. Schmidt PJ, Roca CA, Rubinow DR. Depression in the perimenopausal woman. 152nd Annual Meeting of the American Psychiatric Association Washington DC, USA. 1999.

534. Schmidt PJ, Rubinow DR. Menopause-related affective disorders: a justification for further study. Am J Psychiatry. 1991;148(7):844-852.

535. Schneider L, Small G, Clary C. Does Estrogen Replacement Therapy Augment Response To Sertraline In Depressed Elderly Women. XXIst Collegium Internationale Neuro psychopharmacologicum, Glasgow, Scotland 12th 16th July. 1998(ABSTRACT).

536. Schneider LS, Small GW, Clary CM. Estrogen Replacement Therapy Status and Antidepressant to Sertraline. 151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June. 1998(NR426).

537. Schneider LS, Small GW, Hamilton SH, et al. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Am J Geriatr Psychiatry. 1997;5:97-106.

538. Schouten JS, van den Ouweland FA, Valkenburg HA. Natural menopause, oophorectomy, hysterectomy and the risk of osteoarthritis of the dip joints. Scandinavian Journal of Rheumatology. 1992;21(4):196-200.

539. Seiden AM. Overview: research on the psychology of women. I. Gender differences and sexual and reproductive life. Am J Psychiatry. 1976;133(9):995-1007.

540. Seltzer VL, Benjamin F, Deutsch S. Perimenopausal bleeding patterns and pathologic findings. Journal of the American Medical Womens Association. 1990;45(4):132-134.

541. Shainess N. Menopause: midlife crisis or milestone-marker? Journal of the American Medical Womens Association. 1982;37(4):87-90.

542. Shangold M, Sherman C. Exercise and Menopause. A Time for Positive Changes. Physician and Sportsmedicine. 1998;26(12):45-50,52.

543. Shangold MM. Exercise in the menopausal woman. Obstetrics & Gynecology. 1990;75(4 Suppl):53S-58S; discussion 81S-83S.

544. Shangold MM. An Active Menopause: Using Exercise to Combat Symptoms. Physician and Sportsmedicine. 1996;24(7):30-36.

545. Shargil AA. Hormone replacement therapy in perimenopausal women with a triphasic contraceptive compound: a three-year prospective study. Int J Fertil. 1985;30(1):15-28.

546. Sharkey KM, Bearpark HM, Acebo C, Millman RP, Cavallo A, Carskadon MA. Effects of menopausal status on sleep in midlife women. Behavioral Sleep Medicine. 2003;1(2):69-80.

547. Shaver J, Giblin E, Lentz M, Lee K. Sleep patterns and stability in perimenopausal women. Sleep. 1988;11(6):556-561.

548. Shaver JL. Women and sleep. Nursing Clinics of North America. 2002;37(4):707-718.

549. Shaver JL, Giblin E, Paulsen VM. Sleep quality subtypes in midlife women. Sleep. 1991;14(1):18-23.

550. Shaver JL, Paulsen VM. Sleep, psychological distress, and somatic symptoms in perimenopausal women. Family Practice Research Journal. 1993;13(4):373-384.

551. Shaver JL, Zenk SN. Sleep disturbance in menopause. J Womens Health Gender Based Med. 2000;9(2):109-118.

552. Shepherd JE. Effects of estrogen on cognition, mood, and degenerative brain diseases. Journal of the American Pharmaceutical Association. 2001;41(2):221-228.

553. Sherman BM, Wallace RB, Bean JA, Chang Y, Schlabaugh L. The relationship of menopausal hot flushes to medical and reproductive experience. Journal of Gerontology. 1981;36(3):306-309.

554. Sherman R. Lifestyle Interventions in Menopause. Complementary Health Practice Review. 2003;8(1):82.

555. Sherman SL. Premature ovarian failure among fragile X premutation carriers: parent-of-origin effect?[comment]. Am J Hum Genet. 2000;67(1):11-13.

556. Sherwin B. Estrogen-androgen therapy may help after surgical menopause. American Family Physician. 1994;49(5):1209-1210.

557. Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. J Clin Endocrinol Metab. 1991;72(2):336-343.

558. Sherwin BB. Cognitive assessment of postmenopausal women and general assessment of their mental health. Psychopharmacology Bulletin. 1998;34(3):323-326.

559. Sherwin BB, Gelfand MM. Effects of parenteral administration of estrogen and androgen on plasma hormone levels and hot flushes in the surgical menopause. Am J Obstet Gynecol. 1984;148(5):552-557.

560. Sherwin BB, Gelfand MM. Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. Am J Obstet Gynecol. 1985;151(2):153-160.

561. Sherwin BB, Gelfand MM. Sex steroids and affect in the surgical menopause: a double-blind, cross-over study. Psychoneuroendocrinology. 1985;10(3):325-335.

562. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. Psychosomatic Medicine. 1985;47(4):339-351.

563. Sherwin BB, Gelfand MM, Schucher R, Gabor J. Postmenopausal estrogen and androgen replacement and lipoprotein lipid concentrations. Am J Obstet Gynecol. 1987;156(2):414-419.

564. Sherwin BB, Suranyi-Cadotte BE. Up-regulatory effect of estrogen on platelet 3H-imipramine binding sites in surgically menopausal women. Biological Psychiatry. 1990;28(4):339-348.

565. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy.[see comment]. N Engl J Med. 2000;343(10):682-688.

566. Shifren JL, Nahum R, Mazer NA. Incidence of sexual dysfunction in surgically menopausal women. Menopause. 1998;5(3):189-190.

567. Shwayder JM. Pathophysiology of abnormal uterine bleeding. Obstetrics & Gynecology Clinics of North America. 2000;27(2):219-234.

568. Sidani M, Campbell J. Gynecology: select topics. Primary Care; Clinics in Office Practice. 2002;29(2):297-321, vi.

569. Sievert LL, Espinosa-Hernandez G. Attitudes toward menopause in relation to symptom experience in Puebla, Mexico. Women & Health. 2003;38(2):93-106.

570. Silberstein SD. The role of sex hormones in headache. Neurology. 1992;42(3 Suppl 2):37-42.

571. Simkin-Silverman LR, Wing RR, Boraz MA, Kuller LH. Lifestyle intervention can prevent weight gain during menopause: Results from a 5-year randomized clinical trial. Ann Behav Med. 2003;26(3):212-220.

572. Simkin-Silverman LR, Wing RR, Plantinga P, Matthews KA, Kuller LH. Lifetime weight cycling and psychological health in normal-weight and overweight women. International Journal of Eating Disorders. 1998;24(2):175-183.

573. Slaven L, Lee C. Mood and symptom reporting among middle-aged women: the relationship between menopausal status, hormone replacement therapy, and exercise participation. Health Psychology. 1997;16(3):203-208.

574. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, LaVasseur BI, Windschitl HE. Methodological lessons learned from hot flash studies. J Clin Oncol. 2001;19(23):4280-4290.

575. Sluijmer AV, Heineman MJ, De Jong FH, Evers JL. Endocrine activity of the postmenopausal ovary: the effects of pituitary down-regulation and oophorectomy. J Clin Endocrinol Metab. 1995;80(7):2163-2167.

576. Small G, Kornstein S, Schneider L, Clary Cathryn M. Effect of ERT with and without progesterone on clinical response to sertraline in elderly depression. 14th Annual Meeting of the American Association for Geriatric Psychiatry. 2001.

577. Smith CA, McCleary CA, Murdock GA, et al. Lifelong estrogen exposure and cognitive performance in elderly women. Brain & Cognition. 1999;39(3):203-218.

578. Smith G, Waters WE. An epidemiological study of factors associated with perimenopausal hot flushes. Public Health. 1983;97(6):347-351.

579. Snieder H, MacGregor AJ, Spector TD. Genes control the cessation of a woman's reproductive life: a twin study of hysterectomy and age at menopause. J Clin Endocrinol Metab. 1998;83(6):1875-1880.

580. Snowdon DA, Kane RL, Beeson WL, et al. Is early natural menopause a biologic marker of health and aging? American Journal of Public Health. 1989;79(6):709-714.

581. Snyder GM, Sielsch EC, Reville B. The controversy of hormone-replacement therapy in breast cancer survivors. Oncol Nurs Forum. 1998;25(4):699-706; quiz 707-698.

582. Soules MR, Bremner WJ. The menopause and climacteric: endocrinologic basis and associated symptomatology. Journal of the American Geriatrics Society. 1982;30(9):547-561.

583. Sowers M, Pope S, Welch G, Sternfeld B, Albrecht G. The association of menopause and physical functioning in women at midlife. Journal of the American Geriatrics Society. 2001;49(11):1485-1492.

584. Sowers MR, La Pietra MT. Menopause: its epidemiology and potential association with chronic diseases. Epidemiologic Reviews. 1995;17(2):287-302.

585. Stadberg E, Mattsson LA, Milsom I. Womens attitudes and knowledge about the climacteric period and its treatment. A Swedish population-based study. Maturitas. 1997;27(2):109-116.

586. Stadberg E, Mattsson LA, Milsom I. The prevalence and severity of climacteric symptoms and the use of different treatment regimens in a Swedish population. Acta Obstet Gynecol Scand. 1997;76(5):442-448.

587. Stadberg E, Mattsson LA, Milsom I. Factors associated with climacteric symptoms and the use of hormone replacement therapy. Acta Obstet Gynecol Scand. 2000;79(4):286-292.

588. Stadel BV, Weiss N. Characteristics of menopausal women: a survey of King and Pierce counties in Washington, 1973-1974. Am J Epidemiol. 1975;102(3):209-216.

589. Staropoli CA, Flaws JA, Bush TL, Moulton AW. Predictors of menopausal hot flashes. Journal of Women's Health. 1998;7(9):1149-1155.

590. Stearns V, Hayes DF. Approach to menopausal symptoms in women with breast cancer. Current Treatment Options in Oncology. 2002;3(2):179-190.

591. Stearns V, Isaacs C, Rowland J, et al. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors.[see comment]. Ann Oncol. 2000;11(1):17-22.

592. Steffens DC, Norton MC, Plassman BL, et al. Enhanced cognitive performance with estrogen use in nondemented community-dwelling older women. Journal of the American Geriatrics Society. 1999;47(10):1171-1175.

593. Steger RW, Peluso JJ. Sex hormones in the aging female. Endocrinology & Metabolism Clinics of North America. 1987;16(4):1027-1043.

594. Steinberg KK, Thacker SB, Smith SJ, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer.[see comment][erratum appears in JAMA 1991 Sep 11;266(10):1362]. JAMA. 1991;265(15):1985-1990.

595. Stephens C, Ross N. The relationship between hormone replacement therapy use and psychological symptoms: no effects found in a New Zealand sample. Health Care Women Int. 2002;23(4):408-414.

596. Stevens JC, Beard CM, O'Fallon WM, Kurland LT. Conditions associated with carpal tunnel syndrome. Mayo Clinic Proceedings. 1992;67(6):541-548.

597. Stevenson DW, Delprato DJ. Multiple component self-control program for menopausal hot flashes. Journal of Behavior Therapy & Experimental Psychiatry. 1983;14(2):137-140.

598. Stewart DE, Boydell KM. Psychologic distress during menopause: associations across the reproductive life cycle. International Journal of Psychiatry in Medicine. 1993;23(2):157-162.

599. Stewart DE, Boydell KM, Derzko C, Marshall V. Psychologic distress during the menopausal years in women attending a menopause clinic. International Journal of Psychiatry in Medicine. 1992;22(3):213-220.

600. Stoll BA, Parbhoo S. Treatment of menopausal symptoms in breast cancer patients. Lancet. 1988;1(8597):1278-1279.

601. Stoll W. Phytopharmacon influences atrophic vaginal epithelium. Double-blind study, Cimicifuga vs. estrogenic substances. Therapeutikon. 1987;1:23-31.

602. Stone SC, Mickal A, Rye PH. Postmenopausal symptomatology, maturation index, and plasma estrogen levels. Obstetrics & Gynecology. 1975;45(6):625-627.

603. Streckfus CF, Baur U, Brown LJ, Bacal C, Metter J, Nick T. Effects of estrogen status and aging on salivary flow rates in healthy Caucasian women. Gerontology. 1998;44(1):32-39.

604. Studd JW, Thom MH. Ovarian failure and ageing. Clinics in Endocrinology & Metabolism. 1981;10(1):89-113.

605. Svartvik L, Lidfeldt J, Nerbrand C, Samsioe G, Schersten B, Nilsson PM. Dyslipidaemia and impaired well-being in middle-aged women reporting low Sense of Coherence. The Women's Health in the Lund Area (WHLA) Study. Scandinavian Journal of Primary Health Care. 2000;18(3):177-182.

606. Swift M, West J. Clinical effects of a standardized soy extract in postmenopausal women. [letter; comment]. Menopause. 2001;8(1):76-77.

607. Swyer GIM, Mortimer CH, Perry W. Skeletal effects of oestrogen and testosterone in postmenopausal women. British Medical Journal. 1988;297(6649):687-688.

608. Szklo M, Cerhan J, Diez-Roux AV, et al. Estrogen replacement therapy and cognitive functioning in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1996;144(11):1048-1057.

609. Taffe J, Dennerstein L. Time to the final menstrual period. Fertil Steril. 2002;78(2):397-403.

610. Taffe J, Garamszegi C, Dudley E, Dennerstein L. Determinants of self rated menopause status. Maturitas. 1997;27(3):223-229.

611. Tangney CC, Young JA, Murtaugh MA, Cobleigh MA, Oleske DM. Self-reported dietary habits, overall dietary quality and symptomatology of breast cancer survivors: a cross-sectional examination. Breast Cancer Research & Treatment. 2002;71(2):113-123.

612. Tax L, Goorissen EM, Kicovic PM. Clinical profile of Org OD 14. Maturitas. 1987;1:3-13.

613. Taylor M. Psychological consequences of surgical menopause. J Reprod Med. 2001;46(3 Suppl):317-324.

614. Tchen N, Juffs HG, Downie FP, et al. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J Clin Oncol. 2003;21(22):4175-4183.

615. Theroux R, Taylor K. Women's decision making about the use of hormonal and nonhormonal remedies for the menopausal transition. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2003;32(6):712-723.

616. Thewes B, Butow P, Girgis A, Pendlebury S. The psychosocial needs of breast cancer survivors; a qualitative study of the shared and unique needs of younger versus older survivors. Psycho-Oncology. 2004;13(3):177-189.

617. This P, De La Rochefordiere A, Clough K, Fourquet A, Magdelenat H, Breast Cancer Group of the Institut C. Phytoestrogens after breast cancer. Endocrine-Related Cancer. 2001;8(2):129-134.

618. Thompson E, Douglas D, Reilly D. The homoeopathic consultation plus remedy vs. placebo for menopausal symptoms in breast cancer survivors: a pilot randomized, double-blind, placebo-controlled trial. Focus on Alternative and Complementary Therapies. 2002;7(1):112.

619. Tode T, Kikuchi Y, Hirata J, Kita T, Nakata H, Nagata I. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet. 1999;67(3):169-174.

620. Torgerson DJ, Avenell A, Russell IT, Reid DM. Factors associated with onset of menopause in women aged 45-49. Maturitas. 1994;19(2):83-92.

621. Townsend JM, Carbone CL. Menopausal syndrome: illness or social role--a transcultural analysis. Culture, Medicine & Psychiatry. 1980;4(3):229-248.

622. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil. 1967;12(1 Pt 2):77-126.

623. Trevoux R, Dieulangard P, Blum A. Efficacy and safety of Org OD 14 in the treatment of climacteric complaints. Maturitas. 1983;5(2):89-96.

624. Trichopoulos D, Polychronopoulou A, Brown J, MacMahon B. Obesity, serum cholesterol, and estrogens in premenopausal women. Oncology. 1983;40(3):227-231.

625. Tsao LI. Relieving discomforts: the help-seeking experiences of Chinese perimenopausal women in Taiwan. Journal of Advanced Nursing. 2002;39(6):580-588.

626. Tsaras G, Ambrus J. Comparative clinical trial of chlordiazepoxide plus amitriptyline against maprotiline in depression with a component of anxiety. Revue Medicale de la Suisse Romande. 1981;101(6):483-486.

627. Tulandi T, Kinch RA, Guyda H, et al. Effect of methyldopa on menopausal flushes, skin temperature, and luteinizing hormone secretion. Am J Obstet Gynecol. 1984;150(6):709-712.

628. Tulandi T, Kinch RA, Lal S. Effect of guanfacine, an alpha-adrenergic agonist, on menopausal flushing. Maturitas. 1986;8(3):197-200.

629. Tulandi T, Lal S, Kinch RA. Effect of intravenous clonidine on menopausal flushing and luteinizing hormone secretion. Br J Obstet Gynaecol. 1983;90(9):854-857.

630. Tuunainen A, Kripke DF, Elliot JA, et al. Depression and endogenous melatonin in postmenopausal women. Journal of Affective Disorders. 2002;69(1-3):149-158.

631. Urban RJ, Veldhuis JD. A selective serotonin reuptake inhibitor, fluoxetine hydrochloride, modulates the pulsatile release of prolactin in postmenopausal women. Am J Obstet Gynecol. 1991;164(1 Pt 1):147-152.

632. Ushiroyama T, Ikeda A, Ueki M. Prevalence, incidence, and awareness in the treatment of menopausal urinary incontinence. Maturitas. 1999;33(2):127-132.

633. Ushiroyama T, Ikeda A, Ueki M. Evidence for attenuation of gonadotropin pulse frequency in hypergonadotropic women with estradiol secretion in the menopausal transition. Psychoneuroendocrinology. 1999;24(1):85-97.

634. Utian WH. Vaginal function in postmenopausal women. JAMA. 1983;249(2):194-195.

635. Utian WH. Overview on menopause. Am J Obstet Gynecol. 1987;156(5):1280-1283.

636. Utian WH, Boggs PP. The North American Menopause Society 1998 Menopause Survey. Part I: Postmenopausal women's perceptions about menopause and midlife. Menopause. 1999;6(2):122-128.

637. Utian WH, Lederman SA, Williams BM, Vega RY, Koltun WD, Leonard TW. Relief of hot flushes with new plant-derived 10-component synthetic conjugated estrogens. Obstetrics & Gynecology. 2004;103(2):245-253.

638. Van Hall EV, Verdel M, Van Der Velden J. "Perimenopausal" complaints in women and men: a comparative study. Journal of Women's Health. 1994;3:45-.

639. van Keep PA, Kellerhals JM. The impact of socio-cultural factors on symptom formation. Some results of a study on ageing women in Switzerland. Psychotherapy & Psychosomatics. 1974;23(1-6):251-263.

640. van Keep PA, Kellerhals JM. The ageing woman. About the influence of some social and cultural factors on the changes in attitude and behaviour that occur during and after the menopause. Acta Obstet Gynecol Scand Suppl. 1976(51):17-27.

641. van Lith ND, Motke JC. Opipramol in the climacteric syndrome. A double-blind, placebo-controlled trial. Maturitas. 1983;5(1):17-23.

642. van Lunsen RHW, Laan ETM, Everaerd AM. Postmenopausal sexual response and sexual functioning are not estrogen dependent and are improved by tibolone administration. Fertil Steril. 1998;70(3).

643. van Noord PA, Dubas JS, Dorland M, Boersma H, te Velde E. Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. Fertil Steril. 1997;68(1):95-102.

644. Vanwesenbeeck I, Vennix P, van de Wiel H. 'Menopausal symptoms': associations with menopausal status and psychosocial factors. J Psychosom Obstet Gynaecol. 2001;22(3):149-158.

645. Vassilopoulou-Sellin R, Klein MJ. Estrogen replacement therapy after treatment for localized breast carcinoma. Patient responses and opinions.[erratum appears in Cancer 1996 Feb 15;79(4):867]. Cancer. 1996;78(5):1043-1048.

646. Vassilopoulou-Sellin R, Klein MJ. Health care priorities for menopausal women with a history of breast cancer. Southern Medical Journal. 2002;95(11):1269-1275.

647. Verbeke K, Dhont K, al. e. Clinical and hormaonal effects of long-term veralipride treatment in post-menopausal women. Maturitas. 1988;10(3):225-230.

648. Vervest HA, Kiewiet de Jonge M, Vervest TM, Barents JW, Haspels AA. Micturition symptoms and urinary incontinence after non-radical hysterectomy. Acta Obstet Gynecol Scand. 1988;67(2):141-146.

649. Vestergaard P, Hermann AP, Stilgren L, et al. Effects of 5 years of hormonal replacement therapy on menopausal symptoms and blood pressure-a randomised controlled study. Maturitas. 2003;46(2):123-132.

650. Villarruel AM, Harlow SD, Lopez M, Sowers M. El cambio de vida: conceptualizations of menopause and midlife among urban Latina women. Research & Theory for Nursing Practice. 2002;16(2):91-102.

651. Vittinghoff E, Shlipak MG, Varosy PD, et al. Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study.[comment][summary for patients in Ann Intern Med. 2003 Jan 21;138(2):I10; PMID: 12529114]. Ann Intern Med. 2003;138(2):81-89.

652. Vollman RF. The menstrual cycle. Vol 7. Philadephia: W.B. Saunders Company; 1977.

653. Volpe A, Zirilli E, Baralti R, et al. Conjugated estrogens, estradiol valerate, estriol and tibolone (ORG OD14) in the control of the climacteric syndrome [abstract]. Archives of Gynecology. 1985;237(Suppl).

654. von Muehlen DG, Kritz-Silverstein D, Barrett-Connor E. A community-based study of menopause symptoms and estrogen replacement in older women. Maturitas. 1995;22(2):71-78.

655. Vrasti R, Schreppler D, Olteanu I. Prevalence of depression at menopause. Neurologia, Psihiatria, Neurochirurgia. 1986;31(1):47-52.

656. Wade C, Kronenberg F, Cushman L. Use of CAM Among U.S. Women: Preliminary Findings From a National Multi-Ethnic Survey. Complementary Health Practice Review. 2003;8(1):81.

657. Wakamatsu MM. What affects bladder function more: menopause or age?[comment]. Menopause. 2003;10(3):191-192.

658. Waldman TN. Menopause: when hormone replacement therapy is not an option. Part I. Journal of Women's Health. 1998;7(5):559-565.

659. Wang M. 42 cases of climacteric syndrome treated with auricular pellet pressure. Journal of Traditional Chinese Medicine. 1991;11(3):196-198.

660. Ware JC, McBrayer RH, Scott JA. Influence of sex and age on duration and frequency of sleep apnea events. Sleep. 2000;23(2):165-170.

661. Warnock JJK, Bundren J, Morris DW. Female hypoactive sexual desire disorder due to androgen deficiency: Clinical and psychometric issues. Psychopharmacology Bulletin. 1997;33(4):761-766.

662. Washio M. Kami-shoyo-san is usually used for women. Psychiatry & Clinical Neurosciences. 2003;57(3):345.

663. Waxman J, Zatzkis SM. Fibromyalgia and menopause. Examination of the relationship. Postgraduate Medicine. 1986;80(4):165-167, 170-161.

664. Weber D. The influence of an antidepressant drug on the factorial structure of intelligence scores in climacteric depressives. Universitaetsbibliothek Graz: II. 1977;367399.

665. Weel AE, Uitterlinden AG, Westendorp IC, et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. J Clin Endocrinol Metab. 1999;84(9):3146-3150.

666. Weissman MM, Klerman GL. Sex differences and the epidemiology of depression. Arch Gen Psychiatry. 1977;34(1):98-111.

667. Weitzner MA, Moncello J, Jacobsen PB, Minton S. A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. Journal of Pain & Symptom Management. 2002;23(4):337-345.

668. Welnicka-Jaskiewicz M, Jassem J. The risks and benefits of hormonal replacement therapy in healthy women and in breast cancer survivors. Cancer Treatment Reviews. 2003;29(5):355-361.

669. Wender MCO, Freitas FM, Castro JAS, Mattiello SS, Estery C. Effectiveness of Tibolone X Placebo in Postmenopausal Women. 8th International Congress on the Menopause.96.

670. Westlund Tam L, Parry BL. Does estrogen enhance the antidepressant effects of fluoxetine? Journal of Affective Disorders. 2003;77(1):87-92.

671. Wheatley D. Evaluation of psychotropic drugs in general practice. Proceedings of the Royal Society of Medicine. 1972;65(4):317-320.

672. White AR. Electro-acupuncture during the menopause altered mood but not vasomotor symptoms. Focus on Alternative & Complementary Therapies. 2003;8(2):212-214.

673. Whiteman MK, Staropoli CA, Langenberg PW, McCarter RJ, Kjerulff KH, Flaws JA. Smoking, body mass, and hot flashes in midlife women. Obstetrics & Gynecology. 2003;101(2):264-272.

674. Wiegand M. A Gentle Alternative in the Therapy of Perimenopausal Symptoms: Findings of a Multicentric Study with a Total of 657 Patients. Biological Therapy: Journal of Natural Medicine. 1994;XII(1):162-165.

675. Wijma K, Melin A, Nedstrand E, Hammar M. Treatment of menopausal symptoms with applied relaxation: A pilot study. Journal of Behavior Therapy & Experimental Psychiatry. 1997;28(4):251-261.

676. Wilbur J, Dan A, Hedricks C, Holm K. The relationship among menopausal status, menopausal symptoms, and physical activity in midlife women. Family & Community Health. 1990;13(3):67-78.

677. Wilbur J, Miller A, Montgomery A. The influence of demographic characteristics, menopausal status, and symptoms on women's attitudes toward menopause. Women & Health. 1995;23(3):19-39.

678. Wilbur J, Miller AM, Montgomery A, Chandler P. Sociodemographic characteristics, biological factors, and symptom reporting in midlife women. Menopause. 1998;5(1):43-51.

679. Williams CW. Clonidine in treatment of menopausal flushing. Lancet. 1973;1(7816):1388.

680. Williamson J, White A. A randomized control trial to evaluate the effects of reflexology on women experiencing menopausal symptoms. Focus on Alternative and Complementary Therapies. 2001;6(1):98.

681. Wilmoth MC, Sanders LD. Accept me for myself: African American women's issues after breast cancer. Oncol Nurs Forum. 2001;28(5):875-879.

682. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga P. Waist to hip ratio in middle-aged women. Associations with behavioral and psychosocial factors and with changes in cardiovascular risk factors. Arteriosclerosis & Thrombosis. 1991;11(5):1250-1257.

683. Wisniewski AB, Nguyen TT, Dobs AS. Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. Hormone Research. 2002;58(3):150-155.

684. Wolfe BM, Koval JJ, Nisker JA. Impact on postmenopausal symptoms of adding continuous C-21 versus C-19 progestin to estrogen. Maturitas. 1999;33(2):153-161.

685. Woods NF, Mariella A, Mitchell ES. Patterns of depressed mood across the menopausal transition: approaches to studying patterns in longitudinal data. Acta Obstet Gynecol Scand. 2002;81(7):623-632.

686. Woods NF, Mitchell ES. Patterns of depressed mood in midlife women; observations from the Seattle Midlife Women's Health Study. Res Nurs Health. 1996;19(2):111-123.

687. Woods NF, Mitchell ES, Adams C. Memory functioning among midlife women: observations from the Seattle Midlife Women's Health Study. Menopause. 2000;7(4):257-265.

688. Woodward S, Freedman RR. The thermoregulatory effects of menopausal hot flashes on sleep. Sleep. 1994;17(6):497-501.

689. Wool C, Cerutti R, Marquis P, Cialdella P, Hervie C, Life IISGoQo. Psychometric validation of two Italian quality of life questionnaires in menopausal women. Maturitas. 2000;35(2):129-142.

690. Wren BG, McFarland K, Edwards L. Micronised transdermal progesterone and endometrial response. Lancet. 1999;354(9188):1447-1448.

691. Wren BG, McFarland K, Edwards L, et al. Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women.[see comment]. Climacteric. 2000;3(3):155-160.

692. Wu L, Zhou X. 300 cases of menopausal syndrome treated by acupuncture. Journal of Traditional Chinese Medicine. 1998;18(4):259-262.

693. Wu X. [Comparative effectiveness of Chinese H3 and liu wei di huang wan in the treatment of the female climacteric syndrome]. Zhong Xi Yi Jie He Za Zhi. 1986;6(6):336-338, 323.

694. Wu X. Comparative effectiveness of Chinese H3 (CH3) and liu wei di huang wan (LWDHW) in female climacteric and their mechanism of action. Journal of Traditional Chinese Medicine. 1987;7(4):266-268.

695. Yarnell E, Abascal K. Herbal Medicine for Treating Menopausal Symptoms. Alternative & Complementary Therapies. 2003;9(6):299-306.

696. Ylikorkala O. Clonidine in the treatment of menopausal symptoms. Annales Chirurgiae et Gynaecologiae Fenniae. 1975;64(4):242-245.

697. Yoon BK, Kim DK, Kang Y, Kim JW, Shin MH, Na DL. Hormone replacement therapy in postmenopausal women with Alzheimer's disease: a randomized, prospective study. Fertil Steril. 2003;79(2):274-280.

698. Young E, Korszun A. Psychoneuroendocrinology of depression: Hypothalamic-pituitary-gonadal axis. Psychiatric Clinics of North America. 1998;21(2):309-323.

699. Young M, Denny G, Young T, Luquis R. Sexual satisfaction among married women age 50 and older. Psychological Reports. 2000;86(3 Pt 2):1107-1122.

700. Young RL, Kumar NS, Goldzieher JW. Management of menopause when estrogen cannot be used. Drugs. 1990;40(2):220-230.

701. Younus J, Simpson I, Collins A, Wang X. Mind control of menopause. Womens Health Issues. 2003;13(2):74-78.

702. Zibecchi L, Greendale GA, Ganz PA. Continuing education: Comprehensive menopausal assessment: an approach to managing vasomotor and urogenital symptoms in breast cancer survivors. Oncol Nurs Forum. 2003;30(3):393-407.

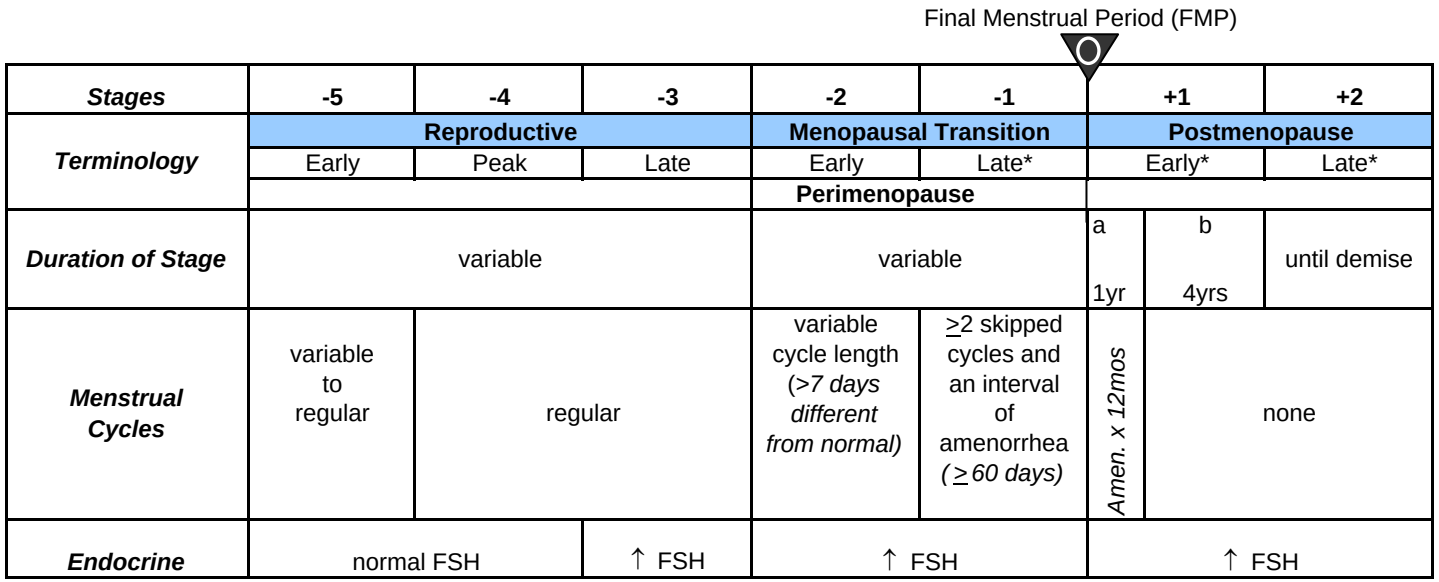
703. Zumoff B. Hormonal profiles in women with breast cancer. Obstetrics & Gynecology Clinics of North America. 1994;21(4):751-772.

704. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab. 1995;80(4):1429-1430.

705. Zwiens G, Sturm G, Eulenburg R. Treatment of climacteric disorders by low doses of clonidine [abstract]. Archives of Gynecology. 1985;237(Suppl): pp.252.

Figures

Figure 1. Normal reproductive aging in women



*Stages most likely to be characterized by vasomotor symptoms

Adapted from Menopause Practice: A Clinician's Guide available at: http://www.menopause.org/edumaterials/cliniciansguide/cliniciansguidetoc.htm

Figure 2. Analytic framework

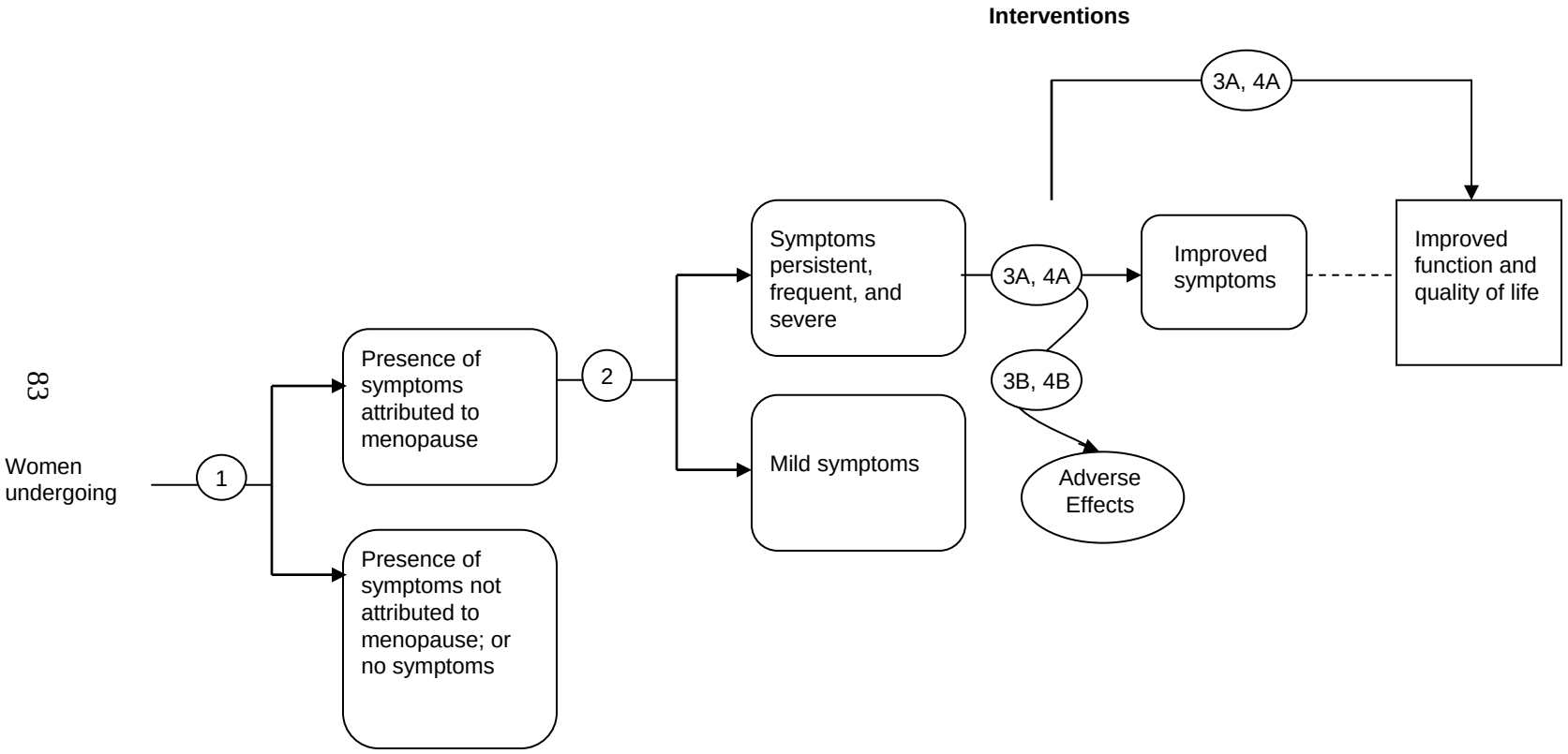


Figure 3. Quality rating criteria

Internal Validity of Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis, consideration of inception cohorts.
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
- Important differential loss to follow-up or overall high loss to follow-up.
- Measurements: equal, reliable, and valid (includes masking of outcome assessment).
- Clear definition of interventions.
- Important outcomes considered.
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.

Definition of ratings based on above criteria

Good: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

External Validity

Considerations

- Similarities of the populations studied and target population.
- Similarities of the test or intervention studied to those that would be routinely available or feasible.
- Clinical or social environmental circumstances in the studies that could modify the results from those expected in the target population.

Tables

Table 1. Measures of menopause related symptoms

Measure
Vasomotor symptoms/Global menopausal symptoms
Blatt Menopausal Index[191, 211, 252]
Climacteric Index[258]
Clinical Global Impression Improvement Scale (CGI-I) [181, 227, 259]
Daily Symptom Rating Calendar (DSR)[154]
General Health Questionnaire (GHQ)[156, 161]
Greene Climacteric Scale (GCS)[137, 156, 160, 162, 174, 175, 179, 181, 212, 217, 237, 238, 244, 246, 253, 288]
Hopkins Symptom Checklist[130]
Hot Flash Related Daily Interference Scale (HFRDIS)[289]
Kupperman Index[146, 148, 155, 203, 204, 220, 227, 236, 264]
Measure Yourself Medical Outcome Profile (MYMOP)[261, 263]
Menopausal Rating Scale[249]
Menopausal Symptom Index[276]
Menopausal Symptom Scale[263, 287]
Menopausal Symptoms Questionnaire (MSQ)[205, 219]
Menopause Representation Questionnaire (MRQ)[272]
Neugarten-Kraines Menopausal Index Scale[271]
Nottingham Health Profile (NHP)[126, 157, 267]
Patient Global Impression of Change Scale[198]
Short Form-36 Health Survey (SF36)[183, 198, 242, 287]
Symptom Check List-90 (SCL-90)[235, 266]
Visual Analogue Scales (VAS)[129, 151, 181, 199, 201, 235, 243, 261, 264, 266, 276, 279]
Women's Health Questionnaire (WHQ) [119, 120, 162, 187, 241, 261, 272]
Sleep disturbances
Epworth Sleepiness Scale[215, 238]
Pittsburgh Sleep Quality Index[198]
Sleep Dysfunction Test[236]
Sleep Problems Questionnaire[187]
Stanford Sleepiness Scale[215, 238]
Mood symptoms
Beck Anxiety Inventory II (BAI-II)[181]
Beck Depression Inventory (BDI)[124, 214, 282, 283]
Center of Epidemiological Studies Depression Scale (CES-D) [154]
Eysenck Personality Inventory[125]
Hamilton Anxiety Scale (HAMA)[129, 258]
Hamilton Depression Rating Scale (HAM-D)[129, 130, 154, 259]
Hospital Anxiety and Depression Scale[215, 238, 263]
Irritability, Depression, and Anxiety (IDA)[162]
Leckie-Withers Test of Liability to Depressive Illness [128]
Minnesota Multiphasic Personality Inventory (MMPI)[124, 259]
Personal Distress Scale (PDS)[153]
Profile of Mood Scale[154]

Table 1. Measures of menopause related symptoms (continued)

Measure
Mood symptoms (continued)
Profile of Mood States[198]
Psychological General Well-Being Index (PGWBI) [144, 150, 153, 160, 187, 241, 236]
Rome Depression Inventory (RDI)[259]
Sabbatsberg Distress Self-Rating Scale (SDS)[125]
Self-Evaluations Depression Scale[253]
South African Personality Questionnaire[128]
Spielberger State-trait Anxiety Inventory[253, 269]
Zung Self-Rating Depression Scale Questionnaire[138]
Cognitive disturbances
Auditory Serial Addition Test[215]
Boston Naming Test[242]
Buschke Immediate Recall and Delayed Recall Tests[154]
Digit Symbol Substitution Test[154]
Hong Kong List-Learning Test[242]
Logical Memory and Recall[214]
Mini-Biography Questionnaire[128]
Mini-Mental State Examination (MMSE)[214, 242]
National Adult Reading Test-Revised[238]
Neuropsychological Test Battery[214]
Symbol Copying Test[154]
Trail Making Test[242]
Wechsler Adult Intelligence Scales of Digit Span and Digit Symbol [124]
Weschler Memory Scale[215, 238]
Work Ability Index[279]
Sexual dysfunction
Bem Sex Role Inventory[128]
Brief Index of Sexual Function for Women (BISF-W) [142, 144, 145]
Local Urogenital Complaints Rating Scale (LUCRS)[160]
McCoy Sex Scale[150, 167, 171, 174]
Profile of Female Sexual Function (PFSF)[152, 153]
Sabbatsberg Revised Sexual Rating Scale (SRS)[145]
Sabbatsberg Sexual Self-Rating Scale (SSS)[125]
Sexual Activity Log (SAL)[152, 153]
Sexual Behavior Questionnaire[187]
Sexual Interest Questionnaire (SIQ)[142, 145]
Sexual Summary Scale[287]
Quality of life
Cancer Quality of Life Score (European Organization for Research and Treatment) [263]
Menopause Specific Quality of Life Questionnaire (MENQOL)[137, 225, 229, 238]
Quality of Life Menopause Scale (QUALMS)[145]
Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [160]
SmithKline Beecham Quality of Life Self Report Questionnaire[154]

Table 1. Measures of menopause related symptoms (continued)

Measure
Quality of life (continued)
Uniscale QOL instrument[282, 283]
Other
Collins and Landgren Rating Scale[168]
Dyadic Adjustment Scale (DAS)[156]
Finger Tapping Test[242]
Food Frequency Questionnaire[242]
Halstead-Reitan[214]
Heat Stress Test (HST)[270]
Karolinska Scale[158]
Kellner and Sheffield Rating Scale[191]
Profile of Adaptation to Life[124]
Sheehan Disability Scale[181]
Uken Motherliness Test[128]
Vaginal Dryness Index[256]
Vaginal Health Index[257]

Table 2. Descriptions of cohort studies

Cohort	Description	Number of publications included in evidence review
Australian Longitudinal Study on Women's Health	8,236 Australian women 45 to 50 years old in 1996.	2[46,47]
Copenhagen	630 women 40 years old in 1976 selected from 4 municipalities and served by one hospital in Copenhagen, Denmark. Women using postmenopausal hormone therapy or who underwent premature or surgical menopause were excluded.	3[64-66]
Eindhoven	8,503 women recruited based on responses to an osteoporosis screening study in Eindhoven, Netherlands. Women were excluded if non-Dutch White, had hysterectomy with or without oophorectomy, had bilateral oophorectomy, are using postmenopausal hormone therapy, or were noncompliant with one or more items in the questionnaire.	2[67,68]
Gothenburg	1,462 women 38 to 60 years old randomly selected in 1968-69 and followed for over 25 years in Gothenburg, Sweden. Measures were assessed through periodic medical exams and interviews.	3[43-45]
Manitoba Project on Women and Their Health in the Middle Years	A cross-sectional and longitudinal cohort study that enrolled 2,500 women aged 40-59 years old from the general population of Manitoba, Canada.	1[63]
Massachusetts Women's Health Study	2,500 premenopausal women from Massachusetts, U.S.	6[20-25]
Medical Research Council (MRC) National Survey for Health and Development	1,572 women identified from a socially stratified sample of all births in March 1943 in Britain.	4[48-51]
Melbourne Women's Midlife Health Project	Cross-sectional and longitudinal, community-based cohort that enrolled 2,000 women 45 to 55 years old from Melbourne, Australia. Longitudinal follow up of 492 women has been ongoing since 1991. The study assesses women's health during midlife and the menopause including well being, sexuality, symptoms, and bone density and their relationship to a range of variables including hormones, age, stress, lifestyle, and other health experiences.	11[52-62]
Minnesota/Tremin Trust Longitudinal Research Program on Women's Health	Longitudinal study that initially consisted of 2,350 University of Minnesota women. Between 1961-1963, a second group of 1,600 women was added, and in 1965, a third group of 1,000 native Alaskan women were added. Women in the study range from teens to mid-nineties and represent fifty states and twenty-five foreign countries.	1[40]

Table 2. Descriptions of cohort studies (continued)

Cohort	Description	Number of publications included in evidence review
National Health Examination Follow-up Study	Sample of 3,049 U.S. women 40 to 60 years old from the National Health and Nutrition Examination Survey (NHANES).	1[30]
Ohio Midlife Women's Study	208 women 40 to 60 years old, recruited with advertisements from a community in Ohio, U.S. Cohort includes 57% Caucasian, 43% African-American women.	1[29]
Pennsylvania Ovarian Aging Study	Population-based cohort of 436 women from Philadelphia County, Pennsylvania, 35-47 years old at baseline including 50% African American, 50% Caucasian. Ongoing longitudinal study.	2[41,42]
Seattle Midlife Women's Health Study	11,222 women from within Seattle, U.S. census tracts, 35 to 55 years old, including multiple ethnicities and income levels and followed for 3 years. All women had active menstrual periods at baseline and were excluded if pregnant, using postmenopausal hormones, or non-English reading/speaking.	3[26-28]
Study of Women's Health Across the Nation (SWAN)	U.S., community-based, multisite cross-sectional and longitudinal cohort study that enrolled 16,065 women 40 to 55 years old. Longitudinal follow up of 3,306 women has been ongoing since 1995. The goal of the study is to describe the chronology of the biological and psychosocial characteristics of the menopausal transition and its effects on health and risk factors for age-related chronic diseases.	8[31,32-39]

Table 3. Results of cohort studies of menopause related symptoms

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Vasomotor symptoms						
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Hot flashes, night sweats	Yes	Hot flashes: pre-peri, peri-peri and HT groups had significantly higher odds ratio vs. pre-pre. Night sweats: Significantly increased odds ratio for all groups.
Dennerstein, 2000[53]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	172	Hot flashes, night sweats	Yes	Increased in late peri- and post-menopause.
Hardy, 2002[51]	Medical Research Council (MRC)	Socially stratified sample of all births in 1 week in March 1943 in Britain.	1,572	Vasomotor symptoms	Yes	Increase
Mitchell, 1996[26]	Seattle	Pre- and perimenopausal women (35-55 years) identified by census tract in Seattle, including minorities.	301	Vasomotor	No	NA
Vaginal dryness						
Dennerstein, 2000[53]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	172	Vaginal dryness	Yes	Increased in late peri- and postmenopause.

Table 3. Results of cohort studies of menopause related symptoms (continued)

	Modifiers						
Study, year	**Age at onset**	**Body mass index**	**Race/ ethnicity**	**Smoking**	**Depression**	**Surgical menopause**	**Quality rating**
Vasomotor symptoms (continued)							
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Dennerstein, 2000[53]	NE	NR	NE	Yes, for hot flashes	NE	Excluded	Good
Hardy, 2002[51]	NR	NR	NR	NR	NR	NR	Good
Mitchell, 1996[26]	NA	NE	NE	NE	NE	Excluded	Fair
Vaginal dryness (continued)							
Dennerstein, 2000[53]	NE	NR	NE	NR, presumed not significant	NE	Excluded	Good

Table 3. Results of cohort studies of menopause related symptoms (continued)

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Sleep disturbance						
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Difficulty sleeping	Yes	Pre-peri, peri-peri, pre/peri-post and HT had significantly higher odds ratios vs. pre-pre; only post-post was not significant.
Dennerstein, 2000[53]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	172	Trouble sleeping	Yes	Increased gradually across menopausal stages.
Mitchell, 1996[26]	Seattle	Pre- and perimenopausal women (35-55 years) identified by census tract in Seattle, including minorities.	301	Insomnia	No	NA
Mood symptoms						
Avis, 1994[20]	Massachusetts Women's Health Study	Cohort of premenopausal women sampled from Massachusetts, USA (born 1926-36).	2,565	Depression	No	Increased odds ratio of depression (2.05; 95% CI 1.04-4.02) for peri-peri group. No other significant odds ratios with change in stage.
Busch, 1994[30]	National Health Examination Follow-up Study	U.S. women 40-60 years in NHANES.	573	Depression	No	NA
Dennerstein, 1999[54]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	354	Negative mood	No	NA
Dennerstein, 2001[55]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	267	Positive mood	No	NA

Table 3. Results of cohort studies of menopause related symptoms (continued)

Table 3. Results of cohort studies of menopause related symptoms (continued)

	Modifiers						
Study, year	**Age at onset**	**Body mass index**	**Race/ ethnicity**	**Smoking**	**Depression**	**Surgical menopause**	**Quality rating**
Sleep disturbance (continued)							
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Dennerstein, 2000[53]	NE	NR	NE	NR, presumed not significant	NE	Excluded	Good
Mitchell, 1996[26]	NA	NE	NE	NE	NE	Excluded	Fair
Mood symptoms (continued)							
Avis, 1994[20]	NR	NR	NR	NR	Yes	NR	Fair
Busch, 1994[30]	NR	NR	NR	NR	NR	No	Poor
Dennerstein, 1999[54]	NE	NE	NE	No	NE	Excluded	Good
Dennerstein, 2001[55]	NE	NS	NE	NS	NE	Excluded	Good

Table 3. Results of cohort studies of menopause related symptoms (continued)

Modifiers

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Mood symptoms (continued)						
Freeman, 2004[41]	Pennsylvania Ovarian Aging Study	Cohort of 436 African American and Caucasian women age 35-47 years from Pennsylvania, recruited by random digit dialing.	332	Depression	Yes	Increased odds of CES-D scores $\geq$16 in early and late transition. No increased odds of major depressive disorder.
Glazer, 2002[29]	Ohio Midlife Women's Study	Community population based on media recruitment; 40-60 years.	208	Anxiety	No	NA
Glazer, 2002[29]	Ohio Midlife Women's Study	Community population based on media recruitment; 40-60 years.	208	Depression	No	NA
Hallstrom, 1985[44]	Gothenburg	Systematic sampling of women age 38-60 years using Taxation Office Register; psychiatric sample selected from this group.	899	Development of mental disorder	No	NA
Hardy, 2002[51]	Medical Research Council (MRC)	Socially stratified sample of all births in 1 week in March 1943 in Britain.	1,572	Psychological symptoms (anxiety or depression)	No	NA
Kaufert, 1992[63]	Manitoba	Community population of Manitoba, Canada 45-55 years.	469	Depression	No	NA
Maartens, 2002[68]	Eindhoven	Women born between 1941-1947 living in Eindhoven, The Netherlands, participating in Eindhoven Perimenopausal Osteoporosis Study.	2,103	Depression	Yes	Increase from pre-peri and peri-postmenopause.
McKinlay, 1989[24]	Massachusetts Women's Health Study	Cohort of premenopausal women sampled from Massachusetts, USA (born 1926-36).	2,466	Depression	No	Increased depression for those within 3 months of hysterectomy.

Table 3. Results of cohort studies of menopause related symptoms (continued)

Study, year	Age at onset	Body mass index	Race/ ethnicity	Smoking	Depression	Surgical menopause	Quality rating
Mood symptoms (continued)							
Freeman, 2004[41]	NE	NS	Yes, increased odds of depression in African Americans vs. Caucasians	NR in multivariate model	Yes	NE	Good
Glazer, 2002[29]	NE	NE	NE	NE	Yes	Yes	Good
Glazer, 2002[29]	NE	NE	NE	NE	Yes	Yes	Good
Hallstrom, 1985[44]	NR	NR	NR	NR	NR	Excluded	Poor
Hardy, 2002[51]	NR	NR	NR	NR	NR	NR	Good
Kaufert, 1992[63]	NE	NE	NE	NE	NE	Increased odds of being depressed	Fair
Maartens, 2002[68]	NE	NE	NE	NE	NE	Excluded	Good
McKinlay, 1989[24]	NR	NR	NR	NR	NR	Yes	Poor

Table 3. Results of cohort studies of menopause related symptoms (continued)

	Modifiers

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Mood symptoms (continued)						
Mishra, 2003[47]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,623	General mental health (SF-36)	No	NA
Mitchell, 1996[26]	Seattle	Pre- and perimenopausal women (35-55 years) identified by census tract in Seattle, including minorities.	301	Dysphoric mood	No	NA
Woods, 1997[28]	Seattle	Pre- and perimenopausal women (35-55 years) identified by census tract in Seattle, including minorities.	347	Depressed mood	No	NA
Somatic complaints						
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Back pain	Yes	Only peri-peri had higher odds ratio than pre-pre, others not significant.
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Headache	No	All odds ratios not significant.

Study, year	Age at onset	Body mass index	Race/ ethnicity	Smoking	Depression	Surgical menopause	Quality rating
Mood symptoms (continued)							
Mishra, 2003[47]	NR	Adjusted for weight but NR	NR	Adjusted for but NR	NR	Excluded	Good
Mitchell, 1996[26]	NA	NE	NE	NE	NE	Excluded	Fair
Woods, 1997[28]	NE	NE	NE	NE	NE	Excluded	Fair
Somatic complaints (continued)							
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good

Table 3. Results of cohort studies of menopause related symptoms (continued)

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Somatic complaints (continued)						
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Severe tiredness	Yes	Severe tiredness: pre-peri, peri-peri, and HT groups had significantly higher odds ratios vs. pre-pre; others not significant.
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Stiff/painful joints	Yes	Pre-peri, peri-peri, HT groups had significantly higher odds ratios vs. pre-pre; others not significant.
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Constipation	No	Only HT group had significantly higher odds ratios than pre-pre; others not significant.
Dennerstein, 2000[53]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	172	Breast soreness	Yes	Decreased in late peri- and post-menopause.
Dennerstein, 2000[53]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	172	Somatic symptoms (other than breast soreness)	No	NA
Mishra, 2003[47]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,623	Bodily pain (SF-36)	Yes	Only peri-peri and HT groups had significantly worse scores for bodily pain vs. pre-pre.

Table 3. Results of cohort studies of menopause related symptoms (continued)

	Modifiers						
Study, year	**Age at onset**	**Body mass index**	**Race/ ethnicity**	**Smoking**	**Depression**	**Surgical menopause**	**Quality rating**
Somatic complaints (continued)							
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Dennerstein, 2000[53]	NE	NR	NE	NR	NE	Excluded	Good
Dennerstein, 2000[53]	NE	NR	NE	NR	NE	Excluded	Good
Mishra, 2003[47]	NR	Adjusted for weight change and weight at baseline, but contribution NR	NR	Adjusted for but NR	NR	Excluded	Good

Table 3. Results of cohort studies of menopause related symptoms (continued)

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Somatic complaints (continued)						
Mishra, 2003[47]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,623	General health perception (SF-36)	Yes	Only peri-peri and HT groups had significantly worse general health perceptions vs. pre-pre.
Mitchell, 1996[26]	Seattle	Pre- and perimenopausal women (35-55 years) identified by census tract in Seattle, including minorities.	301	Neuromuscular	No	NA
Mitchell, 1996[26]	Seattle	Pre- and perimenopausal women (35-55 years) identified by census tract in Seattle, including minorities.	301	Somatic	No	NA
Urinary complaints						
Brown, 2002[46]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,236	Leaking urine	Yes	Only per-peri had significantly higher odds ratio than pre-pre; others not significant.
Dennerstein, 2000[53]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	172	Urinary symptoms	No	NA
Sherburn, 2001[56]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	373	Urinary in-continence	No	NA
Sexual dysfunction						
Dennerstein, 2001[57]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	283	Sexual dysfunction	Yes	Increased

Table 3. Results of cohort studies of menopause related symptoms (continued)

	Modifiers						
Study, year	**Age at onset**	**Body mass index**	**Race/ ethnicity**	**Smoking**	**Depression**	**Surgical menopause**	**Quality rating**
Somatic complaints (continued)							
Mishra, 2003[47]	NR	Adjusted for weight change and weight at baseline but contribution NR	NR	Adjusted for but NR	NR	Excluded	Good
Mitchell, 1996[26]	NA	NE	NE	NE	NE	Excluded	Fair
Mitchell, 1996[26]	NA	NE	NE	NE	NE	Excluded	Fair
Urinary complaints (continued)							
Brown, 2002[46]	NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	Adjusted for but NR	NR	Good
Dennerstein, 2000[53]	NE	NR	NE	NR	NE	Excluded	Good
Sherburn, 2001[56]	NE	Yes	NE	Not significant	NE	Yes	Good
Sexual dysfunction (continued)							
Dennerstein, 2001[57]	NA	NA	NA	NA	NA	Excluded	Fair

Table 3. Results of cohort studies of menopause related symptoms (continued)

Study, year	Cohort	Population	N	Symptom	Associated with change in menopausal stage?	Direction of change with transition
Sexual dysfunction (continued)						
Dennerstein, 2002[58]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	226	Sexual dysfunction	Yes	Increased from early to late peri-menopause.
Reduced quality of life						
Busch, 1994[30]	National Health Examination Follow-up Study	U.S. women age 40-60 years in NHANES.	573	Quality of life	No	NA
Dennerstein, 1997[52]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	438	Quality of life	Yes	Decreased across menopausal categories
Dennerstein, 2002[59]	Melbourne Women's Midlife Health Project	Community-based cohort of 492 women (45-55 years) living in Melbourne, Australia.	226	Well-being	Yes	Increased from early to late peri- and post menopause.
Mishra, 2003[47]	Australian Longitudinal Study on Women's Health	Mid-age (45-50 years) cohort selected from 41,500 Australian women with national health insurance.	8,623	Quality of life	Yes, for peri-peri women only	Decreased

Abbreviations

CI=Confidence Interval
CES-D = Center for Epidemiologic Studies Depression Scale
HT=Hormone Replacement Therapy
NA=Not Applicable
NE=Not Examined
NR=Not Reported
Peri=Perimenopausal
Post=Postmenopausal
Pre=Premenopausal
SF-36=Short Form-36 Health Survey

Table 3. Results of cohort studies of menopause related symptoms (continued)

	Modifiers						
Study, year	**Age at onset**	**Body mass index**	**Race/ ethnicity**	**Smoking**	**Depression**	**Surgical menopause**	**Quality rating**
Sexual dysfunction (continued)							
Dennerstein, 2002[58]	NE	NE	NE	NE	NE	Excluded	Fair
Reduced quality of life (continued)							
Busch, 1994[30]	NR	NR	NR	NR	NR	No	Poor
Dennerstein, 1997[52]	NR	NR	NR	NR	NR	Excluded	Good
Dennerstein, 2002[59]	NE	NE	NE	NE	NE	Excluded	Good
Mishra, 2003[47]	NR	Similar body weight between groups	NR	NR	NR	Excluded	Good

Abbreviations

CI=Confidence Interval
CES-D = Center for Epidemiologic Studies Depression Scale
HT=Hormone Replacement Therapy
NA=Not Applicable
NE=Not Examined
NR=Not Reported
Peri=Perimenopausal
Post=Postmenopausal
Pre=Premenopausal
SF-36=Short Form-36 Health Survey

Table 4. Results of cross-sectional studies of menopause related symptoms

	Main Outcomes															
Study, year	Vaso-motor	Vaginal dryness	Sleep	Mood	Cogni-tive	Somatic	Urinary	Uterine bleeding	Sexual dysfunc-tion	Quality of life	Age at onset	Race/ ethnicity	BMI	Surgical/ natural menopause	Smo-king	Depres-sion
Data from study cohorts																
Avis, 1997[21]	X										X					
Avis, 2000[22]				X					X	X			X			
Avis, 2001[33]	X			X								x				
Avis, 2003[34]										X		X				
Bromberger, 2001[35]	X		X	X								X			X	
Bromberger, 2003[36]	X		X	X		X						X				
Busch, 1994[30]														X		
Dennerstein, 1993[60]	X		X	X	X		X									
Dennerstein, 1994[61]									X							
Gold, 2000[37]	X	X	X		X	X	X					X	X		X	
Gracia, 2004[42]									X			X	X			
Guthrie, 1996[62]	X														X	
Hunter, 1989[69]	X	X	X	X	X	X			X							
Kaufert, 1992[63]				X										X		
Koch, 1995[40]	X	X						X	X							
Koster, 1993[64]	X			X		X								X		
Koster, 1993[65]									X					X		
Koster, 2002[66]	X			X		X			X					X		
Kravitz, 2003[38]			X									X		X		
Kuh, 1997[48]	X	X	X	X	X	X	X		X					X	X	X
Kuh, 1999[49]							X					X				
Kuh, 2002[50]				X												
McKinlay, 1987[23]				X												
McKinlay, 1989[24]				X												
McKinlay, 1992[25]	X		X													
Milsom, 1993[45]							X							X		
Mitchell, 2001[27]					X											
Randolph, 2003[39]												X	X		X	
Sherburn, 2001[56]							X						X	X		

Table 4. Results of cross-sectional studies of menopause related symptoms (continued)

	Main Outcomes															
Study, year	Vaso-motor	Vaginal dryness	Sleep	Mood	Cogni-tive	Somatic	Urinary	Uterine bleeding	Sexual dysfunc-tion	Quality of life	Age at onset	Race/ ethnicity	BMI	Surgical/ natural menopause	Smo-king	Depres-sion
Data from other populations																
Avis, 1993[70]	X			X								X		X		
Bardel, 2002[71]	X	X				X	X									
Bell, 1995[72]	X	X		X		X						X		X		
Feldman, 1985[73]	X													X		
Groeneveld, 1993[74]	X	X								X			X		X	
Hagstad, 1986[75]	X	X					X									
Hammar, 1984[76]	X	X		X												
Hording, 1986[77]							X									
Jansson, 2003[79]	X		X													
Jaszmann, 1969[78]	X		X			X										
Keenan, 2003[80]	X	X	X	X	X			X						X		
Li, 2002[81]	X		X	X	X	X										
McKinlay, 1974[82]	X		X	X		X										
O'Connor, 1995[83]	X	X		X		X			X							
Olofsson, 2000[84]	X	X	X	X	X	X	X		X							
Porter, 1996[85]	X	X	X	X	X	X	X									
Reckers, 1992[86]							X		X					X		
Rybo, 1971[87]	X		X		X	X	X									
Schwingl, 1994[88]	X												X		X	
Slaven, 1998[89]	X				X	X			X					X		
Thompson, 1973[90]	X		X	X		X								X		
Young, 2003[92]			X										X		X	X

Key

X=statistically significant association between symptom and menopausal stage.

Table 5. Trials of estrogen for depression

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Bech, 1998[122]	151	Not reported	1. Estradiol 2 mg/day and NETA 1 mg/day 2. Estradiol 2 mg/day for 22 days, 1 mg/day for 6 days and NETA 1 mg/day for 10 days of cycle	Placebo	12 months	Improved scores on Beck Depression Inventory (12 & 21 item scales) with both estrogen groups vs. placebo (p<0.05).	Improved depression scores for estrogen groups.	Fair
Ditkoff, 1991[124]	36	53 (45-60)	1. CEE 0.625 mg/day days 1 to 25; cyclic 2. CEE 1.25 mg/day days 1 to 25; cyclic	Placebo	3 months	Not reported	Improved scores on Beck Depression Inventory and income management scale (p<0.05 for both) for both doses of CEE; no changes on other measures; (MMPI-168; Profile of Adaptation to Life, Wechsler Adult Intelligence Scales).	Fair
Furuhjelm, 1984[125]	58 (48 anal-yzed)	54 (44-64)	1. Estradiol 1-2 mg/day, estriol 0.5-2 mg/day, and norethisterone acetate 1 mg/day; cyclic 2. Estradiol 2-4 mg/day, estriol 0.5-2 mg/day, and norethisterone acetate 1 mg/day; cyclic 3. Estradiol 2 mg/day, estriol 1 mg/day All groups combined in analysis	Placebo	Cross-over; 4 2-month phases	Not reported	Improved measures of mental distress in estrogen groups (p<0.01); only women depressed at baseline had improved depression scores (p<0.001); (Sabbatsberg General Symptom Scale, Distress Self-rating Scale, Sexual Self-rating Scale, Eysenck Personality Inventory).	Poor

Table 5. Trials of estrogen for depression (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Gerdes, 1982[128]	38	Not reported	CEE 1.25 mg/day for 21 days and medrogestrone 5 mg/day from day 16 to 21 followed by 7 days of placebo; cyclic	1. Placebo 2. Clonidine 25 mcg twice daily	20 weeks	Improved cheerfulness, health, and energy with CEE vs. placebo (p<0.001); improved moodiness, feeling relaxed, feeling understood, and self-confidence with CEE vs. placebo (p<0.01). Improved depression score (p<0.01) (Mini-Biography Questionnaire) and less moodiness in CEE vs. clonidine group (p<0.05); no difference in moodiness with clonidine vs. placebo.		Poor
Hall, 1998[126]	60	44-75	1. CEE 0.625 mg/day and MPA 5 mg/day; cyclic 2. Estradiol 50 mcg patch and MPA 5 mg/day; cyclic	Placebo	1 year	Not reported	Improved measures of mood in all groups; improved depressed mood scores in CEE group (p=0.054) but not in estradiol or placebo groups.	Poor
Khoo, 1998[121]	105	46 (40-52)	CEE 0.625 mg/day and MPA 10 mg/day days 14 to 27; cyclic	Placebo	Cross-over; 6 months each phase	No differences between groups in depressive symptoms during first phase.		Fair
Klaiber, 1996[127]	38	53 (45-65)	Estropiate 1.5 mg/day and norethindrone 1 mg/day	Placebo	Cross-over; 56 days each phase	Improved mood symptoms while on estropiate only vs. placebo (anxiety p<0.001, depression and anger p<0.01); no differences while on estropiate and norethindrone.		Poor

Table 5. Trials of estrogen for depression (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Saure, 2000[123]	376	49	Estradiol 1.5 mg/day for 24 days and desogestrel 0.15 mg/day for 12 days each cycle	Estradiol valerate 2 mg/day for 21 days and MPA 10 mg/day for 10 days of cycle	6 months	No differences in mood disturbances between groups at end of study.	Improved mood disturbances (self report) in both groups.	Fair
Soares, 2001[118]	50	49 estra-diol, 50 placebo; (40-55)	Estradiol 100 mcg/day transdermal	Placebo	12 weeks	Improved depressive symptoms in depressed women using estradiol vs. placebo (p<0.001); (Montgomery-Asberg Depression Rating Scale.)	Improved depression scores in both groups at end of treatment.	Good
Strickler, 2000[119]	373	55 (47-60)	CEE 0.625 mg/day	1. Raloxifene 60 mg/day 2. Raloxifene 150 mg/day 3. Placebo	1 year	No differences in depressed mood between groups. Improved anxiety with raloxifene 60 mg/day vs. placebo (p=0.03), and raloxifene 60 mg/day vs. CEE (p=0.003). No differences with raloxifene 150 mg/day.		Good
Thomson, 1977[129]	42	49 (45-55)	Piperazin oestrone sulphate 1.5mg twice a day	Placebo	8 weeks	No difference in depression, anxiety or hot flashes. Improved sleep on estrogen (p<0.05).	Both groups had improvement in depression, anxiety, hot flashes and sleep	Poor
Voss, 2002[120]	1008	56	Estradiol 2 mg/day and norethisterone acetate 1 mg/day	1. Raloxifene 60 mg/day	6 months	Improved depressed mood with raloxifene vs. estradiol (p=0.004). No differences in anxiety or fears.		Good
Wheatley, 1977[130]	58	50 (45-60)	Piperazin oestrone sulphate 1.5 mg twice a day (with amitriptyline)	Placebo (with amitriptyline)	4 weeks	No difference in depression between groups.	Both groups had improvement in depression.	Poor

Abbreviations
CEE=Conjugated equine estrogens
MMPI=Minnesota Multiphasic Personality Inventory
MPA=Medroxyprogesterone acetate
NETA=Norethindrone acetate

Table 6. Trials of progestins

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main Results: Between group differences	Main Results: Within group differences	Quality
Progesterone								
de Wit, 2001[139]	10	50-72	Progesterone intramuscular injections 25, 50, or 100 mg weekly	Placebo	4 weeks	No differences in mood, cognition, or behavior. Higher rating of sluggishness in 100 mg group.	Not reported	Poor
Leonetti, 1998[231], 1999[138]	102	52	Progesterone transdermal cream 20 mg/day	Placebo cream	12 months in 4 month phases	Improved vasomotor symptoms with progesterone vs. placebo (p<0.001). No differences in depression scores.	Not reported	Fair
Wren, 2003[137]	80	54 (43-69)	Progesterone transdermal cream 32 mg/day	Placebo cream	12 weeks	No differences between groups on measures of vasomotor or somatic symptoms, mood, or sexual feelings.	Not reported	Good
Medroxyprogesterone acetate								
Morrison, 1980[140]	48	45 (27-59)	Medroxy-progesterone acetate injection 50 mg, 100 mg, or 150 mg weekly	Placebo injection	12 weeks	Improved number of hot flashes and subjective symptoms with MPA vs. placebo; higher satisfaction with MPA.	Not reported	Poor
Schiff, 1980[141]	27	50 (28-67)	Medroxy-progesterone acetate tablet 20 mg/day	Placebo	12 weeks	Improved hot flashes in MPA vs. placebo (p value not given).	Improved hot flashes in both MPA (74%) and placebo (26%) groups.	Poor

Abbreviations
MPA=Medroxyprogesterone acetate

Table 7. Trials of Androgens

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Testosterone								
Barrett-Connor, 1999[146]	311	45 (21-65)	1. Esterified estrogen 0.625 mg/day and MT 1.25 mg/day 2. Esterified estrogen 1.25 mg/day and MT 2.5 mg/day	1. CEE 0.625 mg/day 2. CEE 1.25 mg/day	2 years	Not reported	Improved hot flashes and vaginal dryness in all groups; non-significant trend toward greater improvement in well-being and sexual interest with MT/estrogen; no differences for somatic symptoms (Modified Kupperman Scale).	Fair
Dobs, 2002[145]	40	57 (41-76)	Esterified estrogen 1.25 mg/day and MT 2.5 mg/day	Esterified estrogen 1.25 mg/day	16 weeks	Not reported	Improved symptoms in both groups. Significant improvement with MT/estrogen in hot flashes (Quality of Life Menopause Scale), sexual functioning, and somatic symptoms; no changes in mood and cognition.	Fair
Floter, 2002[150]	50	54 (45-60)	Estradiol valerate 2 mg/day and testosterone undecanoate 40 mg/day	Estradiol valerate 2 mg/day	24 weeks cross over	Improved enjoyment of sex, satisfaction with frequency, interest in sex, and total McCoy Sex Scale score with testosterone/estrogen vs. estrogen. No significant different in psychological well-being.	Improved mood (Psychological General Well-Being Index), sexual symptoms (McCoy Sex Scale), and quality of life (Psychological General Well-Being Index) in both groups.	Poor
Hickok, 1993[143]	26	52 treatment; 50 comparison	Esterified estrogen 0.625 mg/day and MT 1.25 mg/day	Esterified estrogen 0.625 mg/day	6 months	No differences between groups in hot flash symptom severity, vaginal dryness, sleep problems (4-point menopausal symptom scale).	Improved hot flash symptom severity, vaginal dryness, sleep problems in both groups (4-point menopausal symptom scale).	Poor
Lobo, 2003[142]	218	53 (40-65)	Esterified estrogen 0.625 mg/day and MT 1.25 mg/day	Esterified estrogen 0.625 mg/day	4 months	Improved frequency sexual interest/desire, responsiveness and total Sexual Interest Questionnaire score with MT/ estrogen vs. estrogen, $p<0.02$.	Improved sexual interest/desire, responsiveness, and total Sexual Interest Questionnaire score in both groups, $p<0.05$.	Good

Table 7. Trials of Androgens (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Testosterone (continued)								
Penotti, 2001*,[151]	40	57 treatment; 55 comparison	Estradiol 50 mcg/day transdermal and MPA 10 mg/day for 12 days/month and testosterone undecanoate 40 mg/day	Estradiol 50 mcg/day transdermal and MPA 10 mg/day for 12 days/month	8 months	No differences between groups in sexual symptoms (Visual Analogue Scores).	Improved sexual desire and satisfaction on Visual Analogue Scale in both groups.	Poor
Raisz, 1996*,[147]	18	60 treatment; 66 comparison	Esterified estrogen 1.25 mg/day and MT 2.5 mg/day	CEE 1.25 mg/day	9 weeks	Not reported	Improved psychosomatic and psychological symptoms in MT/estrogen group. Improved hot flashes, vaginal dryness, and somatic symptoms in both groups. (Modified Kupperman with 0-3 scale).	Poor
Shifren, 2000[144]	75	47 (31-56)	1. Testosterone 150 mcg/day transdermal and CEE 2. Testosterone 300 mcg/day transdermal and CEE	CEE at various doses (0.625, 0.9, 1.25, 1.8, or 2.5 mg/day)	36 weeks cross over	Improved composite score (p=0.04), depressed mood (p=0.03), and positive well-being (p=0.04) (Psychological General Well-Being Index), and improved sexual symptoms (Brief Index of Sexual Function for Women) with testosterone 300 mcg/day vs. placebo (p=0.03)	Not reported	Fair
Simon, 1999[149]	93	54	1. Esterified estrogen 0.625 mg/day and MT 1.25 mg/day 2. Esterified estrogen 1.25 mg/day and MT 2.5 mg/day	1. Esterified estrogen 0.625 mg/day 2. Esterified estrogen 1.25 mg/day 3. Placebo	3 months	Not reported	Improved somatic symptoms, vaginal dryness, and hot flashes in all nonplacebo groups; no effect on sleep or mood (Kupperman Index). No treatment effect for psychosomatic or psychological scores.	Poor
Watts, 1995[148]	66	21-60	Esterified estrogen 1.25 mg/d + MT 2.5 mg/day	Esterified estrogen 1.25 mg/day	2 years	No differences between groups for hot flashes, vaginal dryness, or sleep (modified Kupperman Index with 0-7 scale).	Improved hot flashes, vaginal dryness and sleep in both groups (modified Kupperman Index with 0-7 scale).	Fair

Table 7. Trials of Androgens (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results		Quality
						Between group differences	Within group differences	
Dehydroepiandrosterone (DHEA)								
Barnhart, 1999[154]	60	48 (45-55)	DHEA 50 mg/day	Placebo	3 months	No differences between groups in hot flashes, vaginal dryness, sleep, mood, cognition, somatic symptoms, urinary symptoms, sexual symptoms, and quality of life	Improved total symptoms and health-related quality of life in both groups.	Fair
Stomati, 1999[155]	22	50-55	1. DHEAS 50 mg/day 2. DHEAS 50 mg/day and estradiol 50 mg/day transdermal	Estradiol 50 mg/day transdermal	3 months	Not reported	Similar improved Kupperman Index score with all groups ($p<0.01$).	Poor

Abbreviations

CEE=Conjugated equine estrogen
MT=Methyltestosterone
MPA=Medroxyprogesterone acetate

*Open label trial

Table 8. Trials of tibolone

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Baracat, 2002*, [163]	85	51 treatment; 53 comparison (45-65)	Tibolone 2.5 mg/day	CEE 0.625 mg/day and MPA 5 mg/day	12 months	No differences between groups in intensity and mean number hot flashes, sleep, mood, cognition, somatic complaints, and sexual symptoms.	Improved intensity and mean number hot flashes, sleep, mood, cognition, somatic complaints, and sexual symptoms in both groups.	Poor
Benedek-Jaszmann, 1987[164]	60	44-61	Tibolone 2.5 mg/day	Placebo	12 months	Improved hot flashes, irritability, and psychic instability with tibolone vs. placebo. No consistent differences between groups in depression, sleep, somatic complaints.	Not reported	Poor
De Aloysio, 1987*, [165]	168	Not reported	Tibolone 2.5 mg/day	1. Placebo injection 2. No treatment	4 months	Improved hot flashes with tibolone vs. placebo; no differences between groups for sleep and somatic symptoms.	"Spontaneous symptomatic improvement" of climacteric symptoms in all three groups (no p-value given).	Poor
Egarter, 1996*, [166]	129	54	Tibolone 2.5 mg/day	CEE 0.625 mg/day and medrogestone 10 mg/day for 12 days/month	6 months	No differences between groups in hot flashes, vaginal dryness, sleep, mood, somatic complaints, and sexual symptoms.	Improved hot flashes, vaginal dryness, sleep, mood, somatic complaints, and sexual symptoms in both groups (Kupperman Index).	Poor
Hammar, 1998[159]	437	55	Tibolone 2.5 mg/day	Estradiol 2 mg/day and NETA 1 mg/day	48 weeks	Improved hot flushes with estrogen/NETA vs. tibolone ($p<0.001$); no differences between groups in sweating episodes or vaginal dryness; tibolone group had less vaginal bleeding.	Improved hot flushes, sweating episodes, and vaginal dryness in both groups (5 point symptoms scale).	Fair
Huber, 2002[160]	501	55	Tibolone 2.5 mg/day	CEE 0.625 mg/day and MPA 5 mg/day	1 year	No difference between groups in total Greene Climacteric Score, or vaginal or urinary symptoms; vasomotor subscore slightly more improved with CEE/MPA vs. tibolone. Reduced vaginal bleeding and improved sexual interest, drive, and/or performance in tibolone group.	Improved total Greene Climacteric Score in both groups. Improvement in vaginal and urinary symptoms in both groups.	Fair

Table 8. Trials of tibolone (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Hudita, 2003[167]	162	56 (40-65)	1. Tibolone 1.25 mg/day 2. Tibolone 2.5 mg/day	Placebo	24 weeks	Improved hot flashes, vaginal dryness, and sexual symptoms with both doses of tibolone vs. placebo; greater improvement in hot flashes and vaginal dryness with 2.5 mg vs. 1.25 mg doses (Modified McCoy Sex Scale, menopausal symptoms scale). Increased bleeding with both doses of tibolone.	Improved hot flash and vaginal dryness in both tibolone groups, not in placebo.	Poor
Lam, 2004[156]	100	50	Tibolone 2.5 mg/day	Placebo	6 months in each arm	Improved somatic complaints in tibolone group. No difference in total Greene Climacteric Score or any other subscales.	Improved vasomotor, urogenital, and sexual subscores in both groups; improved mood and somatic complaints in tibolone group; (Greene Climacteric Scale, General Health Questionnaire, Dyadic Adjustment Scale). No change in psychological well-being in either group.	Good
Landgren, 2002[168]	775	52 (40-60)	1. Tibolone 0.625 mg/day 2. Tibolone 1.25 mg/day 3. Tibolone 2.5 mg/day 4. Tibolone 5 mg/day	Placebo	12 weeks	Improved frequency of hot flashes and sweating at 1.25 mg, 2.5 mg, and 5.0 mg doses of tibolone vs. placebo (Collins and Landgren Rating Scale). Dose related vaginal bleeding.	Not reported	Poor
Lloyd, 2000[161]	29	61	Tibolone 2.5 mg/day	Placebo	6 months	No differences between groups in quality of life (General Health Questionnaire).	Not reported	Fair

Table 8. Trials of tibolone (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Meeuwsen, 2002[157]	85	54	Tibolone 2.5 mg/day	Placebo	1 year	Improved hot flashes and sleep with tibolone vs. placebo (p<0.05); no differences between groups for mood, energy, pain, social isolation, urinary symptoms, or quality of life (Nottingham Health Profile). Increased vaginal bleeding with tibolone.	Not reported	Good
Mendoza, 2000*, [169]	76	<50	Tibolone 2.5 mg/day	Estradiol 50 mcg/day transdermal	1 year	No differences between groups in hot flashes, mood, and sexual symptoms (Kupperman Index).	Improved hot flashes, mood, and sexual symptoms in both groups (no p-values given for within group comparisons).	Poor
Mendoza, 2002*, [170]	165	50	Tibolone 2.5 mg/day	1. Estradiol 50 mcg/day transdermal and progesterone 200 mg twice weekly 2. Estradiol 50 mcg/day transdermal for 14 days, then Estradiol 50 mcg/day transdermal and NETA 0.25 mg/day for 14 days	1 year	No differences between groups for hot flashes, sleep, mood, cognition, somatic symptoms, and sexual symptoms.	Improved hot flashes in both groups (Modified Kupperman Index).	Poor
Nathorst-Böös, 1997[171]	437	>53	Tibolone 2.5 mg/day	Estradiol 2 mg/day and NETA 1 mg/day	48 weeks	Improved sexual frequency, satisfaction, and enjoyment with tibolone vs. estradiol/NETA (p<0.05); (McCoy Sex Scale; Swedish version).	Improved sexual frequency, pain, and vaginal dryness in both groups. Improvement in other sexual symptoms in tibolone.	Poor
Palacios, 1995*, [172]	28	50-60	Tibolone 2.5 mg/day	Calcium 500 mg/day	12 months	Improved sexual symptom score with tibolone vs. placebo (p<0.05) (10 item questionnaire scored on a 7 point scale).	Improved sexual symptom score in tibolone group.	Poor

Table 8. Trials of tibolone (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Ross, 1999[162]	36	52 (45-65)	Tibolone 2.5 mg/day	CEE 0.625 mg/day and norgestrol 150 mg/day for 12 days of cycle	3 months	No differences between groups for hot flashes, mood, cognition, somatic symptoms, uterine bleeding, and sexual symptoms (Women's Health Questionnaire, Irritability, Depression, and Anxiety, Greene Climacteric Scale).	Not reported	Fair
Volpe, 1986[173]	113	Not reported	Tibolone 2.5 mg/day	1. Placebo 2. CE 0.625 mg/day for 21 days/mo and NETA 5 mg/day for 10 days/mo 2. CE 0.625 mg/day for 21days/mo and CPA 12.5 mg/day for 10 days/mo 3. Estradiol valerate 2 mg/day for 21 days/mo and NETA 5 mg/day for 10 days/mo 4. Estradiol valerate 2 mg/day for 21 days/mo and CPA 12.5 mg/day for 10 days/mo 5. Estriol 2-4 mg/day	6 months	Not reported.	Improved hot flashes in all treatment groups (4 point scale).	Poor
Winkler, 2000[158]	60	54 (45-70)	Tibolone 2.5 mg/day	1. Estradiol 2 mg/day and Estriol 1 mg/day and NETA 1 mg/day	24 weeks	No differences between groups in hot flashes and vaginal dryness (Karolinska Scale).	Improved hot flashes and vaginal dryness in all treatment groups. (Karolinska Scale)	Good

Table 8. Trials of tibolone (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Wu, 2001*,[174]	48	51 (38-56)	Tibolone 2.5 mg/day	CEE 0.625 mg/day and MPA 5 mg/day	3 months	Improved sexuality with tibolone. No differences between groups in hot flashes, mood, and somatic complaints.	Climacteric symptoms, quality of life, and sexuality improved in (McCoy Sex Scale, Greene Climacteric Scale) both groups.	Poor
Yang, 1999*,[175]	40	51	Tibolone 2.5 mg/day	CEE 0.625 and MPA 5 mg/day 12 days/month	6 months	No differences between groups in hot flashes, mood, cognition, somatic complaints, and sexual symptoms.	Improved hot flashes, mood, cognition, somatic complaints, and sexual symptoms in both groups (Greene Climacteric Scale).	Poor

Abbreviations
CE=Conjugated estrogen
CEE =Conjugated equine estrogen
CPA=Cyproterone acetate
MPA=Medroxyprogesterone acetate
NETA=Norethidrone acetate

*Not a double-blind study (single blind or open).

Table 9. Trials of antidepressant drugs

						Main results	
Study, year	**N**	**Mean age (range)**	**Therapy**	**Comparison**	**Duration**	**Between group differences**	**Within group differences**	**Quality**
David, 1988[186]	50	32-81	Veralipride 100 mg/day	Placebo	Four 20 day courses	Not reported	Improved hot flash frequency and severity with veralipride (p=0.01).	Poor
Evans 2005[183]	80	51	Venlafaxine XR, 37.5mg/day for 1 week, then 75mg/day	Placebo	12 weeks	No difference in hot flash frequency or severity as measured by daily diaries. Greater reduction in "self-perceived hot flash score" in venlafaxine group. (p<0.001; single item on interference of hot flash with daily living). Greater improvement in mood and vitality in venlafaxine group (p=0.005; SF-36 scales).	Both groups noted to have improved hot flash severity scores. (No p-value reported.)	Fair
Limouzine-Lamothe, 1994*,[187]	499	Not reported	Veralipride 100 mg/day first 20 days of each month	Estraderm TTS 50 transdermal and chlormandinon first 12 days of each month	6 months	Improved numbers of hot flashes in estrogen vs. veralipride group (41% vs. 81%; p<0.001). Improved measures of quality of life, sleep, sexual function, depression, anxiety, general psychological well being, somatic complaints, cognitive difficulties, social life, family life, professional life, and vitality with estrogen vs. veralipride (Women's Health Questionnaire, Psychological General Well-Being Index, Sleep Problems Questionnaire, Sexual Behavior Questionnaire, symptom scale).	Not reported	Poor

Table 9. Trials of antidepressant drugs (continued)

						Main results		
Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Between group differences	Within group differences	Quality
Melis, 1988[184]	40	48-56	Veralipride 100 mg/day	Placebo	30 days	Improved hot flash composite score with veralipride vs. placebo (66% vs. 26%; p<0.5); more women noted improvement with veralipride vs. placebo (85% vs. 50%; p<0.05).	Both groups showed improvement in hot flash composite score (placebo p<0.05; veralipride p<0.01).	Poor
Stearns, 2003[181]	165	>35	Paroxetine 12.5 mg/day or 25 mg/day	Placebo	6 weeks	Improved mean hot flash frequency with paroxetine 25 mg and 12.5 mg vs. placebo (3.2 and 3.3 vs. 1.8; p=0.01); improved composite score with paroxetine vs. placebo (65% and 62% vs. 38%; p=0.03) (daily hot flash composite score, Greene Climacteric Scale 21). No differences in sleep, depression, anxiety, sexual interest, or disability (Visual Analogue Scale, Beck Anxiety Inventory II, Sheehan Disability Scale, Clinical Global Impression).	Not reported	Good
Tarim, 2002[188]	30	51 (35-55)	Moclobemide 150 mg/day or 300 mg/day	Placebo	5 weeks	Not reported	All groups had decreased hot flash composite scores (67% moclobemide 150 mg/day, 35% moclobemide 300 mg/day, 24% placebo).	Fair
Wesel, 1984[182]	43	40-60	Veralipride 100 mg/day	CEE 1.25 mg/day	20 days	No differences between groups in hot flash frequency or composite score.	Improved hot flash frequency and composite score in both groups.	Fair
Zichella, 1986[185]	75	45-55	Veralipride 100 mg/day	Placebo	20 days	Improved hot flash composite score with veralipride vs. placebo (-2.3 vs. -0.6; p<0.5).	Improved hot flash composite score with veralipride (p<0.001) and placebo (p<0.05)	Poor

Abbreviations
CEE=Conjugated equine estrogen

*Non blinded trial

Table 10. Trials of Clonidine

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Bolli, 1975[190†]	20	51	1. Clonidine tablet 0.0375 mg twice daily 2. Clonidine tablet 0.075 mg twice daily	Placebo crossover	2 weeks each phase	No differences between groups in mean number of hot flashes or subjective measures of severity and duration. Results same for both doses.	Reduction in number of hot flashes was significant in both the 0.075 mg twice daily (p<0.02) and the placebo (p<0.05) groups.	Poor
Clayden, 1974[189]	100	50 (41-62)	Clonidine tablet 0.025 mg twice daily; increased if needed to maximum 0.075 mg twice daily	Placebo crossover	4 weeks each phase	Prior to crossover: no differences between groups in mean change in number of hot flashes. After crossover: improved subjective scores of hot flash severity (p=0.05) and duration	Greater reduction in hot flashes while on clonidine first (p<0.05) or second (p<0.001). Improved subjective scores of hot flash severity (p=0.05) and duration (p=0.01) with	Fair
Edington, 1980[193†]	93	47 (27-71)	Clonidine tablet 0.05 mg twice daily	Placebo crossover	4 weeks each phase	Improved mean number of flushing episodes (averaged over all 4 trials) with clonidine vs. placebo (p<0.05).		Poor
Gerdes, 1982[128] (Same as Sonnendecker 1980)	38	Not reported	Clonidine tablet 0.050 mg twice daily for 28 days + placebo tablets for CEE and medrogestone	CEE 1.25 mg daily for 21 days + medrogestone 5 mg daily from day 16 to 21 + placebo for clonidine	20 weeks	Improved depression score (Mini-Biography Questionnaire, p<0.01) and moodiness (p<0.05) with CEE vs. clonidine; no difference in moodiness with clonidine vs. placebo.	Improved scores for depression and anxiety (p<0.05) in the estrogen group only.	Fair-Poor
Lindsay, 1978[191]	100	46 (35-60)	Clonidine tablet 0.050 mg twice daily; increased if needed to maximum of 0.05 mg three times daily	Placebo crossover	6 weeks each phase	No differences between groups in hot flashes (Blatt Menopausal Index, flushing attacks scale) or psychological symptoms (Kellner and Sheffield Scale).		Poor

Table 10. Trials of Clonidine (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Nagamani, 1987[197]	30	41 (25-58)	Clonidine transdermal 0.1 mg/day, patch changed weekly	Placebo	8 weeks	No differences between groups in mean reduction in hot flashes (diary) at weeks 4 and 8.* More women in the clonidine group reported improvement on subjective measures of frequency (p<0.04), severity (p<0.04), and duration (p<0.03).	Significant decrease in mean number of hot flashes for both clonidine (p=0.002) and placebo (p=0.04) at week 8.	Fair-Poor
Nappi, 1991[195]	35	44 (30-50)	Clonidine tablet 0.075 mg twice daily	1. Sodium valproate tablet 200 mg twice daily 2. Lisuride tablet 0.2 mg twice daily 3. Transdermal 17B estradiol 0.050 mg daily 4. Placebo	4 weeks	Improved hot flash frequency and intensity in the estradiol, clonidine, and lisuride vs. placebo groups (p<0.01).		Poor
Salmi, 1979[192]	40	51 (41-57)	Clonidine tablet 0.025 mg twice daily; increased if needed to maximum 0.075 mg twice daily	Placebo crossover	6 weeks each phase	No differences between groups in frequency of hot flushes, insomnia, depression or anxiety.		Fair-Poor
Sonnendecker, 1980[196]	38	Not reported	Clonidine tablet 0.050 mg twice daily for 28 days + placebo tablets for CEE and medrogestone	CEE 1.25 mg daily for 21 days + medrogestone 5 mg daily from day 16 to 21 + placebo for clonidine	20 weeks	No differences between groups in reduction of number of hot flashes.	Number of daily hot flashes decreased significantly in the CEE group (p<0.05) but not in the clonidine group.	Fair-Poor
Wren, 1986[194†]	19	51 (46-56)	Clonidine tablet 0.05 mg twice daily	Placebo crossover	4 weeks	No differences between groups in mean number of hot flashes.	No change in tiredness, insomnia, anxiety, panic and irritability with clonidine.	Fair-Poor

Abbreviations
CEE=Conjugated equine estrogen
*Calculated p-value; not reported in study

†Pre-crossover data not reported

Table 11. Trials of methyldopa, Bellergal, and gabapentin

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Andersen, 1986[199]	40	51 (46-60)	Methyldopa 375 mg nightly; increased by 1 tablet every 2 weeks as needed to maximum dose of 1,125 mg nightly	Placebo crossover	Up to 8 weeks each phase	No differences between groups in median number of hot flashes; women on methyldopa felt less troubled by hot flashes (Visual Analogue Scale) vs. placebo (p<0.05).	Number of hot flashes improved for both placebo (12/19) and methyldopa (14/17).	Poor
Bergmans, 1987[202]	71	Not reported	Bellergal Retard 1 tablet twice daily (0.6 mg ergotamine, 40 mg phenobarbital, 0.2 mg levorotatory alkaloids)	Placebo	8 weeks	No differences between groups at week 8 in mean number and severity of hot flashes, sweating, or any other symptom.	For both groups significant improvement was noted in hot flashes, sweating, insomnia, hyperirritability, and nervousness (p<0.05). Headache, paresthesia and dizziness improved on Bellergal and loss of libido improved on placebo (p<0.05).	Poor
Guttuso, 2003[198]	59	53	Gabapentin 300 mg three times daily	Placebo	12 weeks	Improved hot flash frequency at weeks 4 (p=0.03) and 12 (p=0.02), composite score at weeks 4 (p=0.01) and 12 (p=0.01), and sleep (Pittsburgh Sleep Quality Index) at week 4 (p=0.01) for gabapentin vs. placebo group. No differences between groups in Profile of Mood States score, quality of life (Short Form-36 Health Survey), or Patient Global Impression of Change Scale.		Good
Hammond, 1984[200]	10	46 (36-54)	Methyldopa 250 mg twice daily; increased after one week to 3 times daily	Placebo crossover	4 weeks each phase	No difference between placebo and methyldopa in mean decrease in number of hot flashes prior to crossover.	Improved hot flashes with methyldopa and placebo in the first phase but only for methyldopa (p<0.02) during the second phase.	Fair
Nesheim, 1981[201]	40	Not reported	Methyldopa 250 mg twice daily; increased if needed to maximum of 500 mg twice daily	Placebo crossover	30 days each phase	Improved hot flash frequency in methyldopa vs. placebo group in the second phase (p=0.01) but not the first (p=0.06); improved Visual Analogue Score in methyldopa vs. placebo group (p=0.002).	Significant reduction in hot flashes with methyldopa (p<0.05).	Fair

Table 12. Trials of phytoestrogens and isoflavones

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Soy isoflavones—dietary								
Albertazzi, 1998[203], 1999[204]	104	53 (48-61)	Soy powder 60 grams (76 mg isoflavones)	60 grams casein powder	12 weeks	Improved hot flash frequency with soy vs. casein at 12 weeks (p<0.01); no differences between groups on Kupperman Index.	Improved hot flash frequency in both groups (44% reduction with soy, 31% with placebo); no changes in Kupperman Index.	Fair
Balk, 2002[205]	27	57 soy; 58 placebo	Soy and corn flour cereal (100 mg/day isoflavones)	Wheat cereal (Grapenuts)	6 months	No differences between groups in hot flushes, night sweats, palpitations, headache, depression, vaginal dryness, or decreased libido over 6 months (Menopause Symptoms Questionnaire); soy group had greater insomnia than placebo (p=0.017).	Improved hot flashes, night sweats, and vaginal dryness with placebo (p<0.05).	Poor
Burke, 2003[206]	241	51 (45-55)	1. Soy drink with 42 mg/day isoflavones 2. Soy drink with 58 mg/day isoflavones	Soy drink with isoflavones removed	24 months	No differences between groups in frequency and severity of hot flashes and night sweats (self-reported symptom diary).	Improved hot flash frequency and severity in all groups (p<0.0001).	Fair
Dalais, 1998[208]	52	54 soy; 55 linseed; 54 wheat; (45-65)	1. Soy diet (high in isoflavones) 2. Linseed diet (high in isoflavones)	Wheat diet (low in isoflavones) cross over	12 weeks each phase	Not reported	Improved rate of hot flushes (diary) with linseed diet (41% decrease) or wheat diet (51% decrease), but not soy.	Poor
Han, 2002[207]	82	48 isoflavone; 49 placebo; (45-55)	Soy isoflavone (50 mg soy protein and 33 mg isoflavones)	Placebo	5 months	Not reported	Improved hot flashes, insomnia, mood, and Kupperman Index scores in soy group.	Fair

Table 12. Trials of phytoestrogens and isoflavones (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results		Quality
						Between group differences	Within group differences	
Soy isoflavones—dietary (continued)								
Knight, 2001[212]	24	52 soy; 54 placebo; (40-65)	Soy isoflavone powder beverage 60 g/day (134.4 mg/day isoflavones)	Casein powder	12 weeks	No differences between groups in flushing frequency or Greene Menopause Symptom Scores.	Improved flushing frequency in both groups.	Fair
Murkies, 1995[209]	58	54 soy; 56 wheat	Soy flour 45 grams/day	Wheat flour 45 grams/day	14 weeks	No differences between groups for hot flashes and general symptom scores.	Improved hot flashes and general symptom scores in both groups at 12 weeks ($p<0.05$).	Fair
Penotti, 2003[210]	62	53 (45-60)	Soy tablet (36 mg/day isoflavone and 48 mg/day soy saponine)	Placebo	6 months	No difference between groups in hot flashes (hot flush daily dairy)	40% reduction in hot flashes overall in both groups.	Fair
St. Germain, 2001[211]	69	42-62	1. Soy protein (80 mg/day isoflavone) 2. Soy protein (4.4 mg/day isoflavone)	Placebo (whey protein)	24 weeks	No differences between groups in hot flush frequency or severity, mood, vaginal dryness, urinary or sexual symptoms (Menopausal Index).	Improved hot flashes in all groups ($p=0.03$).	Fair
Washburn, 1999[213]	51	51 (45-55)	1. Soy protein 20 grams (34 mg/day phytoestrogen) 2. Soy protein 20 grams (34 mg/day phytoestrogens) in 2 doses	Placebo	6 weeks	Improved severity of hot flashes (diary) with soy vs. placebo ($p<0.001$); hypoestrogenic symptom score was improved with soy vs. placebo ($p<0.05$); no differences in number of hot flushes, night sweats, sleep disturbance, or general health score.		Poor

Table 12. Trials of phytoestrogens and isoflavones (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Soy isoflavones—extract								
Duffy, 2003[215]	36	59 soy; 57 placebo; (50-65)	Soy isoflavone supplement (60 mg/day)	Placebo	12 weeks	No differences between groups on the Greene Climacteric Score or mood. Improved memory with soy vs. placebo (delayed recall of pictures, p<0.03; immediate story recall, p<0.06; reversal of the simple discrimination rule, p=0.05;improved time to learn complex tasks, p<0.05).	No changes in menopausal symptoms.	Fair
Faure, 2002[216]	75	53 soy; 54 placebo	Soy isoflavone extract (70 mg genistin/daidzin/ day)	Placebo	16 weeks	Improved hot flush frequency (diary) with soy vs. placebo (p=0.01);no effect on other symptoms (not described).	Improved hot flushes in soy (61% reduction) and placebo groups (21% reduction).	Fair
Kritz-Silverstein, 2003[214]	56	61 (55-74)	Soy extracted supplement (isoflavone 100 mg/day)	Placebo	6 months	Improved cognitive test (category fluency) for soy vs. placebo (p=0.05); no differences between groups for 2 tests of verbal memory and Trails B test.	Improved cognitive tests for both groups.	Fair
Scambia, 2000[217]	39	54 soy; 53 placebo; (29-63)	Soy extract (400 mg/day with 50 mg/day isoflavone) followed by CEE 0.625 mg/day for 4 weeks	Placebo followed by CEE 0.625 mg/day for 4 weeks	12 weeks	Improved mean number of hot flushes/week (score card) and Greene Climacteric Scale score with soy vs. placebo at 6 weeks (p<0.01).	Improved hot flushes with CEE in both groups.	Poor
Upmalis, 2000[218]	177	55 soy; 54 placebo	Soy isoflavone extract tablet 50 mg/day	Placebo	12 weeks	Improved average hot flush severity (diary) with soy vs. placebo (p=0.01); no difference in frequency of night sweats.	Improved hot flushes and night sweats in both groups.	Fair

Table 12. Trials of phytoestrogens and isoflavones (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results		Quality
						Between group differences	Within group differences	
Phytoestrogens								
Brzezinski, 1997[219]	145	54 phyto-estrogen; 51 placebo; (43-65)	Phytoestrogen rich diet (tofu, soy drink, miso, flax seed, approx 182 mg daidzein, 255 mg genistein, 4 mg lignans)	Regular Israeli diet	12 weeks	Improved hot flush severity (p=0.004) and vaginal dryness severity (p=0.005) with phytoestrogen vs. control; no difference in Menopause Symptom Questionnaire score.	Both groups improved on the Menopause Symptom Questionnaire score.	Poor
Carranza-Lira, 2001[220]	30	52 phyto-estrogen, 51 placebo	Phytoestrogen cream (4 mg/day)	Placebo (identical cold cream)	1 month	No differences in Kupperman Index score between groups.	Improved Kupperman Index score in both groups (p<0.001).	Poor
Crisafulli, 2004[221]	90	52 genistein; 52 estrogen proges-terone treatment; 51 placebo; (47-57)	Genistein (54 mg/day)	1. Placebo 2. Estradiol (1 mg/day) combined with noresthisterone	1 year	Genistein group, hot flush score decreased by 22% vs. placebo at 3 months (p<0.01), 29% at 6 months (p<0.001), and 24% at 12 months (p<0.01). Estrogen group, hot flush score decreased by 53% vs. placebo at 3 months (p<0.001) and maintained at 6 and 12 months. Improvement with estrogen greater than genistein at all measurements (p<0.05).		Fair
Komesaroff, 2001[222]	50	54 (45-60)	Wild yam cream preparation (Biogest, one teaspoonful twice daily to arms, legs or abdomen)	Placebo cross over	3 months	No differences between groups (diary) including flushing frequency, severity, mood, breast tenderness, libido, and energy level.	Improved flushing, symptom score, and energy in both groups; improved mood with yam cream.	Poor

Table 12. Trials of phytoestrogens and isoflavones (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Phytoestrogens (continued)								
Sammartino, 2003*,[223]	70	51	Genistein 36 mg/day	Placebo	12 months	Improved Kupperman Index score with genistein vs. placebo ($p<0.05$).	Improved Kupperman Index score with genistein ($p<0.05$).	Fair
Combinations								
Russo, 2003[224]	50	53 (48-54)	Soy based isoflavones (80 mg/day) with *C. racemosa* (black cohosh) (30 mg/day)	Placebo	3 months	Improved hot flush symptoms (questionnaire) in treatment vs. placebo group ($p<0.05$).		Poor

Abbreviations
CEE=Conjugated equine estrogen

*Not double blinded (open).

Table 13. Trials of complementary and alternative therapies

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Acupuncture								
Cohen, 2003[234]	18	47 (43-53)	6 acupuncture treatments specific to menopausal symptoms	6 general tonic acupuncture treatments (shen mein)	9 weeks	Not reported	Improved mean monthly hot flush severity (diary) at 2, 3, and 4 months in treatment; month 4 in control. Improved sleep disturbance in both groups. Improved mood change in treatment, not control.	Poor
Sandberg, 2002[235]	30	54 (48-60)	14 electro-acupuncture treatments specific to menopausal symptoms	Superficial needle insertion (sham)	12 weeks	Treatment group mood (MOOD Scale) improved vs. control at 8 (p=0.05) and 12 weeks (p=0.01). No differences in climacteric or well-being between groups.	Improved mood (MOOD Scale) in treatment group; climacteric symptoms (Visual Analog Scale) and well-being (SCL-50) improved in both groups.	Poor
Wyon, 1995[236]	24	54 (47-62)	10 electro-acupuncture (2 Hz) treatments specific to menopausal symptoms over 8 weeks	Superficial needle insertion (sham)	8 weeks	No differences between groups on any measure.	Number of flushes/day (logbook) decreased in both groups; climacteric symptoms (Visual Analogue Scale) decreased in treatment group, not control; Kupperman Index improved for both groups; no change in well-being for either group.	Poor
Wyon, 2004[264]	45	51-55 (43-59)	14 electro-acupuncture treatments specific to menopausal symptoms	Superficial needle insertion (sham) vs. conjugated estrogen 0.625 mg/day	12 weeks	For flushes, more pronounced effect in estrogen group vs. electro-acupuncture (p<0.001).	All three groups had significant improvement in Kupperman Index, Visual Analogue Scale and self-reported daily symptom diary.	Fair

Table 13. Trials of complementary and alternative therapies (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Chinese herbs								
Chen, 2002[235]	62	50-52 (45-65)	Chinese herbs (JWSYS=a collection of thirteen herbs)	CEE 0.625 mg/day and MPA 2.5 mg/day	16 weeks	No differences between groups in total symptom score, anxiety, depression, somatic symptoms, and vasomotor symptoms (Greene Climacteric Score). Improved sexual symptoms with CEE/MPA vs. JWSYS (p<0.05).	Improved psychological and somatic measures in both groups (Greene Climacteric Score).	Poor
Davis, 2001[238]	78	54-56 (45-70)	Chinese medicinal 12 herb formula	Placebo	12 weeks	No differences between groups in vasomotor symptoms (daily diary) or Menopause Specific Quality of Life Questionnaire scores. Those having previously not used natural therapies for menopausal symptoms showed improved physical, vasomotor, and sexual domains compared to placebo (p<0.05).	Improved vasomotor symptoms (daily diary) and Menopause Specific Quality of Life Questionnaire scores in both groups.	Poor
Hartley, 2003[239]	34	58-59 (53-65)	Ginseng; ginkgo tablet 120 mg/day containing 25% ginkgo flavonoids and 6% terpenoids	Placebo	1 week	No difference between groups on menopausal symptoms, mood, or sleepiness (Greene Climacteric Scale). No difference on 7 of 8 memory tests. Improved non-verbal memory and sustained attention in treatment group.	Improved symptoms (Greene Climacteric Scale) in both groups (p<0.001).	Poor
Hirata, 1997[240]	71	52 (44-69)	4.5 grams/day of dong quai from root material	Placebo	24 weeks	No differences in symptoms between groups (Kupperman Index).	Improved symptoms (Kupperman Index) in both groups (p<0.0001).	Fair

Table 13. Trials of complementary and alternative therapies (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Chinese herbs (continued)								
Wiklund, 1999[241]	384	53-54 (45-65)	Standardized ginseng extract (Ginsana, containing 100 mg of the standardized ginseng extract G115; 2 capsules/day)	Placebo	16 weeks	Improved depression, well-being, and health scores with ginseng vs. placebo ($p<0.05$) (Psychological General Well Being index). No differences between groups on Women's Health Questionnaire, Visual Analog Scale, or hot flushes.	Improved vasomotor symptoms and sleep in both groups.	Fair
Woo, 2003[242]	136	56-57 (50-65)	Pueraria lobata (PL) (a traditional Chinese herbal remedy) and isoflavone 100 mg/day	1. Placebo 2. CEE 0.625 mg/day and MPA 5 mg/day during second 14 days of the month	3 months	No differences between groups in menopausal symptoms or well being measures. No differences in word finding or rate of learning. CEE or PL vs. placebo: Cognitive tests and digital symbol improvement for both treatments ($p<0.05$). PL vs. placebo: Flexible thinking improved for PL group ($p<0.05$). CEE vs. placebo: Motor skills worsened in the CEE group.	No differences of well being.	Fair
Red clover								
Atkinson, 2004[243]	205	55 (49-65)	Red clover isoflavone tablet (Promensil) 40 mg/day	Placebo	12 months	No differences between groups in number of hot flushes or menopausal symptoms score (diary).	Improved number of hot flashes and symptoms score in both groups.	Fair
Baber, 1999[244]	51	45-65	Red clover isoflavone tablet (Promensil) 40 mg/day	Placebo	7 months cross-over	No differences in symptoms between groups (Greene Climacteric Score, hot flush frequency).	Improved symptoms in both groups (Greene Climacteric Score, hot flush frequency).	Fair

Table 13. Trials of complementary and alternative therapies (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Red clover (continued)								
Jeri, 2002[245]	30	51-52	Red clover isoflavone tablet (Promensil) 40 mg/day	Placebo	16 weeks	Not reported	Improved frequency and severity of hot flushes in treatment group (p<0.001).	Fair
Knight, 1999[246]	37	54.5 (40-65)	1. Red clover isoflavone tablet (Promensil) 40 mg/day 2. Red clover isoflavone tablet (Promensil) 160 mg/day	Placebo	12 weeks	No differences between groups in flushing frequency or Greene Climacteric Scale.	Flushing frequency decreased in all groups.	Poor
Tice, 2003[247]	252	52 (45-60)	1. Red clover isoflavone tablet (Promensil) 82 mg isoflavones/day 2. Red clover isoflavone tablet (Rimostil) 57 mg isoflavones/day	Placebo	12 weeks	No differences between groups in Greene Climacteric Scale or number of hot flushes (p<0.001). Reduction in hot flashes was faster for Promensil compared to placebo (p=.03).	Improved Greene Climacteric Scale and number of hot flushes in all groups.	Good
van de Weijer, 2002[248]	30	53-54 (49-65)	Red clover isoflavone tablet (Promensil) 80 mg/day	Placebo	12 weeks	Improved hot flushes with isoflavone vs. placebo (p=0.0154); no difference in Greene Climacteric Scale score.	Improved hot flushes in isoflavone group; no change in Greene Climacteric Scale score.	Fair
Black cohosh								
Wuttke, 2003[249]	62	40-60	*C. racemosa* preparation (CR BNO 1055;Klimadynon/Menofem) 40 mg herbal drug/day	1. Placebo 2. Conjugated estrogen 0.6 mg/day	12 weeks	Improved hot flushes (menopause rating scale) with estrogen vs. placebo (p=0.046).	Improved symptoms for all groups (menopausal rating scale).	Fair

Table 13. Trials of complementary and alternative therapies (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Combinations								
Hudson, 1998[250]	13	Not reported	Botanical formula 500 mg 2 capsules three times per day (combined dry herb including burdock root [2 parts], licorice root [2 parts], motherwort [1 part], Dong Quai root [2 parts] and Mexican wild yam root [1 part])	Placebo	3 months	No differences between groups in number and severity of hot flashes (diary).	Improved number and severity of hot flashes for both groups (diary).	Poor
Other supplements								
Bellipanni, 2001[251]	79	42-62	Melatonin 3 mg/day	Placebo	6 months	Improved mood and morning depression (questionnaire) in melatonin vs. placebo group ($p<0.05$);no differences between groups for other symptoms.		Poor
Blatt, 1953[252]	748	Not reported	1. Vitamin E 50-100 mg 3 times daily 2. Ethinyl estradiol 0.05 mg/day 3. CEE 1.25 mg/day 4. Phenobarbital 15 mg 3 times daily	Placebo	3 years	Not reported	Improved hot flash symptoms with CEE and ethinyl estradiol (67% of women), phenobarbital (24%), Vitamin E (13%), and placebo (16%).	Poor
Bygdeman, 1996*, [256]	39	58 (43-76)	Vaginal moisturizer (Replens) 3 times per week	Dienoestrol vaginal cream 0.5 mg/day for 2 weeks, then 3 times per week	3 months	Improved vaginal dryness index with dienoestrol vs. moisturizer ($p=0.0001$).	Improved vaginal dryness index in both groups.	Poor

Table 13. Trials of complementary and alternative therapies (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Other supplements (continued)								
Cagnacci, 2003[253]	80	50-52 (47-53)	1. Kava kava 100 mg/day + calcium 1g/day 2. Kava kava 200 mg/day + calcium 1g/day	Calcium 1g/day	3 months	Improved anxiety with treatment vs. placebo; no differences between groups in Greene Climacteric Score or depression score.	Improved Greene Climacteric Score, anxiety, and depression score in both treatment groups.	Fair
Chenoy, 1994[254]	56	54 (45-67)	Evening primrose oil (gamolenic acid) 2,000 mg/day with natural vitamin E 10 mg/day	Placebo	6 months	Improved maximum number of daytime hot flushes (diary) with placebo vs. treatment ($p<0.05$).		Poor
Makkonen, 1993[255]	30	52-54 (44-60)	Guar gum 5 grams three times daily	Placebo	6 months	No differences between groups in Kupperman Index scores.	Improved Kupperman Index scores in both groups ($p<0.001$).	Poor
Nachtigall, 1994*, [257]	30	Not reported	Vaginal moisturizer (Replens) 3 times/week	CEE vaginal cream 2 grams/day	12 weeks	Not reported	Improved vaginal elasticity, pH, fluid volume, and moisture in both groups.	Poor
Rachev, 2001[258]	64	50-52 (41-59)	Phospholipid liposomes (Liposom Forte) 28 mg/2ml intramuscular injection every other day	Placebo injection every other day	60 days	Improved climacteric index ($p=0.0013$) and anxiety (Hamilton Anxiety Scale) ($p<0.001$) with treatment vs. placebo.	Improved climacteric index and anxiety for both groups ($p<0.001$ for both).	Fair
Salmaggi, 1993[259]	80	51 (45-59)	S-adenosyl-L-methionine (SAMe) 1600 mg/day	Placebo	30 days	Improved depression in treatment vs. placebo group (Hamilton Depression Rating Scale; Rome Depression Inventory; Clinical Global Impression Improvement Scale; Psychoasthenia Scale of the MMPI).		Poor

Table 13. Trials of complementary and alternative therapies (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Manual therapies								
Cleary, 1994[260]	30	50-60	Low force osteopathic manipulation of pelvis, spine, and cranium	Sham low force touch in similar areas	10 weeks treatment	Improved hot flushes and night sweats (questionnaire), urinary frequency, depression, and insomnia in treatment vs. control group.		Fair
Energy therapies								
Williamson, 2002[261]	80	50.8 (45-60)	Reflexology with 9 sessions over 19 weeks	Standard foot massage	9 sessions of treatment over 19 weeks	No differences between groups in severity of hot flushes and night sweats (Women's Health Questionnaire, Visual Analogue Scale, and a self-completed measure of quality of life).		Poor

Abbreviations

MPA=Medroxyprogesterone acetate
CEE=Conjugated equine estrogen
MMPI = Minnesota Multiphasic Personality Inventory

*Not double blind study (open).

Table 14. Trials of behavioral interventions

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Aiello, 2004[265]	173	61	Aerobic exercise 225 minutes/ week	Stretching 45 minutes/week	12 months	No differences between groups in hot flash frequency, sleep, depressive mood, or cognitive function. A subset of women with recent menopause showed improved memory in aerobic vs. stretching group.	Not reported	Fair
Freedman, 1995[268]	24	53	Paced respiration training in 8 1-hour biweekly treatment sessions	Alpha-EEG biofeedback in 8 1-hour biweekly treatment sessions	4 weeks	Not reported	Decreased hot flash frequency for the paced-respiration group ($p<0.001$) but not for the alpha wave feedback group.	Poor
Germaine, 1984[270]	14	50 (44-61)	Progressive muscle relaxation in 6 1-hour weekly trainings	Alpha-EEG biofeedback in 6 1-hour weekly trainings	6 months	Improved time for onset of hot flush ($p<0.01$) (physiological laboratory testing) in progressive muscle relaxation vs. biofeedback group.	Reduced hot flash frequency in relaxation group at 6 month follow-up ($p<0.01$).	Poor
Hunter, 1999[272]	86	Over 50	Health/ menopause and stress relief education	Usual care	5 year follow-up	Control group more likely to contribute aches and pains to menopause than intervention group ($p<0.01$). No differences between groups on mood, health, vaginal dryness or sexual relationships. Knowledge of menopause increased in the intervention group.	Improved maintenance of knowledge, less concern with menopause, more exercise, and less estrogen use in intervention group. More women in the control group lost interest in sex.	Fair

Table 14. Trials of behavioral interventions (continued)

Study, year	N	Mean age (range)	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Irvin, 1996[269]	45	49-53 (44-66)	Relaxation (diaphrag-matic breathing 20 minutes/day) and charting hot flashes	1. Reading and charting hot flashes 2. Charting hot flashes only	10 weeks	Not reported	Significant improvement in hot flash intensity, tension/anxiety, and depression for the relaxation group ($p<0.05$). Reduction in trait anxiety and confusion in reading group ($p<0.05$). No differences in hot flash frequency in any groups. No changes in control group.	Poor
Lindh-Astrand, 2004[266]	30	51-54 (48-63)	Exercise 3 sessions/ week	1. Estradiol 2 mg/day for 12 weeks minimum 2. Wait listed controls	38 weeks	Not reported	Improved hot flushes, Kupperman Index, symptom list, Visual Analogue Score, and Mood Scale with estrogen; improved Kupperman Index, symptom list, and Visual Analogue Score with exercise.	Poor
Rankin, 1989[271]	40	49 (40-58)	Low frequency sound wave audiotape; 20 minutes 3 times/week for 2 weeks	Usual care	2 weeks	No differences between groups in menopausal, somatic, and psychological symptoms.	Improved frequency of menopausal (Neugarten-Kraines Menopausal Index Scale), somatic, and psychological symptoms with sound waves in menopausal group.	Poor
Teoman, 2004[267]	81	51 (45-65)	Aerobic exercise 3 times/week	Usual care (taking hormone therapy)	6 weeks	Improved quality of life measures (Nottingham Health Profile) in exercise vs. control group.	Exercise group showed changes in quality of life; no changes for control group.	Fair

Table 15. Summary of benefits of therapies

	Total number of trials					Number of trials reporting benefit/total number of trials					
			Quality rating			Hot flashes			Other symptoms		
Therapy	Included in report	Reported compari-sons	Good	Fair	Poor	Improved vs. placebo	Improved or same vs. other therapy	Other therapy	Improved vs. placebo	Improved or same vs. other therapy	Other therapy
Estrogen											
Vasomotor symptoms*											
Estradiol (oral)	10	10	10			9/10					
Estradiol (transdermal)	11	11	11			11/11					
Conjugated equine estrogen	8	8	8			8/8					
Urogenital symptoms*	9	9	9						3/4	5/5	E
Sexual function*	11	11	11						3/6	5/5	E
Sleep*	3	3	3						2/3		
Mood and depression	13	10	3	3	4				4/8	1/3	R, C
Quality of life*	9	9	9						7/8	1/1	E
Progestin											
Progesterone	3	3	1	1	1	1/2			0/3		
Medroxyprogesterone acetate	2	2			2	2/2			1/2		
Androgen											
Testosterone with estrogen	10	6	1	4	1		2/2	E	1/1	5/5	E +/- P
Dehydroepiandrosterone	2	1		1		0/1			0/1		
Tibolone	20	19	3	4	12	5/5	8/10	E +/- P	6/7	11/11	E +/- P
Antidepressants											
Paroxetine	1	1	1			1/1			0/1		
Moclobemide	1	0									
Venlafaxine	1	1		1		0/1			1/1		
Veralipride	5	4		1	3	2/2	1/2	E +/- P	1/2	0/1	E +/- P
Other Drugs											
Clonidine	10	10		1	9	3/8	1/2	E + P		0/1	E + P
Methyldopa	3	3		2	1	1/3					
Gabapentin	1	1	1			1/1			0/1		
Bellergal	1	1			1	0/1			1/1		

Table 15. Summary of benefits of therapies (continued)

Therapy	Total number of trials					Number of trials reporting benefit/total number of trials					
			Quality rating			Hot flashes			Other symptoms		
	Included in report	Reported comparisons	Good	Fair	Poor	Improved vs. placebo	Improved or same vs. other therapy	Other therapy	Improved vs. placebo	Improved or same vs. other therapy	Other therapy
Phytoestrogens											
Soy isoflavones—dietary	10	8		6	2	2/8			1/5		
Soy isoflavones—extracts	5	5		4	1	3/3			2/2		
Phytoestrogen	5	5		2	3	4/5	0/1	E + P	1/2		
Combinations	1	1			1	1/1					
Complementary and Alternative Medicine											
Acupuncture	4	3		1	2	0/3	0/1	E	1/3		
Chinese herbs	6	6		3	3	0/5	2/2	E + P	3/4	2/2	E + P
Red clover	6	5	1	3	1	1/5			0/5		
Black cohosh	1	1		1		0/1	0/1	E			
Combinations	1	1			1	0/1			1/1		
Other supplements	9	7		2	5	2/4			3/3	0/1	E
Manual therapies	1	1		1		1/1			1/1		
Energy therapies	1	1			1	0/1			0/1		
Behavioral Interventions	8	5		3	2	0/5	1/3		1/4		

Abbreviations

E=Estrogen
P=Progestin
R=Raloxifene
C=Clonidine

*Trials from published systematic reviews[15, 17]

Table 16. Trials in women with breast cancer

						Main results		
Study, year	N	Population	Therapy	Comparison	Duration	Between group differences	Within group differences	Quality
Barton, 1998[275]	125	18 and older with previous breast cancer; 54% taking tamoxifen	Vitamin E succinate 800 IU daily	Placebo crossover	4 weeks each phase	Prior to cross-over and in summary: No differences between groups in hot flash frequency or severity (diary questionnaire).	Improvements within groups were not significant.	Fair
Carpenter, 2002[289]	15	18 and older with previous breast cancer	6 magnetic devices attached to participants' skin over acupuncture/acupressure sites used to balance energy and treat hot flashes	Placebo crossover; placebo was identical but blinding not effective because of magnet properties	72 hours + 2 days follow-up each phase	Summary statistics: Improved hot flash frequency with placebo (10.5 to 6.6) vs. magnet (9.6 to 8.3) (p=0.02); improved "bothersome" hot flashes with placebo (4.4 to 3.2) vs. magnets (4.2 to 4.1) (p=0.02). No differences between groups for hot flash severity, interference scale, or overall quality of life.		Poor
Ganz, 2000[287]	76	Mean age 54.5; all have breast cancer; 56% taking tamoxifen	Counseling by nurse practitioner, tailored therapy, and support. Therapy includes any of the following: hot flashes—bellergal, clonidine patch, megestrol; behavioral symptoms—slow abdominal breathing; vaginal dryness—moisturizer or lubricant; urinary symptoms—Kegel's, Replens, phenylpropanolamine; psychosocial—referral for counseling or group support.	Usual care	4 months	Improved adjusted mean change in menopause symptoms (p=0.0004) and adjusted mean change in sexual functioning with intervention vs. usual care (p=0.04); no differences between groups for vitality score.		Fair

Table 16. Trials in women with breast cancer (continued)

Study, year	N	Population	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Goldberg, 1994[284]	116	54 (30-76); all have breast cancer and taking tamoxifen	Clonidine transdermal 0.1 mg/day	Placebo cross over	4 weeks each phase	Prior to cross-over: Improved median hot flash frequency (p<0.04), severity (p<0.03), and score (p<0.04) for clonidine vs. placebo. Summary statistics: No difference between clonidine and placebo for hot flash frequency, severity or score. Patients preferred clonidine vs. placebo (p=0.02).		Fair
Hernandez Munoz, 2003[286]	136	>35 years; all have estrogen receptor positive breast cancer and taking tamoxifen	Black cohosh 20 mg one tablet twice daily	Usual care	60 day	Improved hot flashes with treatment (47% free of hot flashes) vs. usual care (0% free of hot flashes) (p<0.01).		Poor
Jacobson, 2001[276]	85	18 and older; all have breast cancer; 69% taking tamoxifen	Black cohosh 1 tablet twice daily	Placebo	60 days	Improved sweating in black cohosh vs. placebo group (p=0.04). No differences between groups in mean number of hot flashes, hot flash severity, sleep, irritability, nervousness, depression, headaches, and palpitations.	Improved sleep, irritability, nervousness, depression, headaches, palpitations, excessive sweating in both groups; global rating of well being did not change in either group.	Fair

Table 16. Trials in women with breast cancer (continued)

Study, year	N	Population	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Loprinzi, 1994[280]	97	Women with history of breast cancer;	Megestrol acetate 20 mg twice daily.	Placebo cross-over	4 weeks each phase	Prior to cross-over: Improved hot flash frequency (26% of baseline for megestrol vs. 73% of baseline for placebo, p<0.001). Improved median hot flash score (17% of baseline for megestrol vs. 73% of baseline for placebo, p<0.001). Reduction of 50% in hot flash frequency: 71% of megestrol group vs. 24% of placebo group, p<0.001. From baseline hot flash frequency of 6.1 hot flashes/day (range 0.9-21.4).		Good
Loprinzi, 1997[281]	52	Women ≥ 18 with history of breast cancer and persistent vaginal dryness and/or itching for > 2 months	Polycarbophil-based vaginal moisturizer	Placebo (water-soluble lubricating)	4 weeks each phase	Not reported	Vaginal dryness scores improved in both groups (decreased by 64% in Replens group and 62% in placebo group after 4 wks, p=0.3). Dyspareunia scores decreased in both groups after 4 wks: 60% in Replens group and 41% in placebo group, p=0.05.	Fair
Loprinzi, 2000[282]	229	Women >18 with have breast cancer or perceived high risk; 69% taking tamoxifen	Venlafaxine 37.5 mg/day, 75 mg/day, 150 mg/day	Placebo	4 weeks each phase	Prior to cross-over: Improved hot flash frequency and score with all doses of venlafaxine vs. placebo (p<0.001); improved quality of life with venlafaxine vs. placebo (p=0.02). No differences between groups in depression score or libido.		Fair

Table 16. Trials in women with breast cancer (continued)

Study, year	N	Population	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Loprinzi, 2002[283]	87	18 and older; have breast cancer or perceived high risk; 54% taking tamoxifen	Fluoxetine 20 mg/day	Placebo crossover	4 weeks each phase	Prior to cross-over: Fewer reports of trouble sleeping sleep with fluoxetine vs. placebo (p=0.03). No significant decrease in hot flash frequency (p=0.54) or score (p=0.35). Summary statistics: Improved hot flash frequency (p=0.01), hot flash score (p=0.02) with combined data at end of both cross over periods; No overall differences between groups for sleep, quality of life, depression, or libido.		Fair
Nikander, 2003[279]	62	Mean age 54 (35-69); all have breast cancer; 5% had used tamoxifen>5 months prior	Phytoestrogen tablet 114 mg; 3 twice daily	Placebo crossover	3 months each phase	Prior to cross-over: No differences between groups in Kupperman Index, or hot flashes.	Improved Kupperman Index in both groups; improved hot flash intensity with placebo; no effect on anxiety, working ability, or self confidence in either group.	Fair
Pandya, 2000[285]	198	Mean age 53-55 (35-77); all have breast cancer and taking tamoxifen	Clonidine 0.1 mg/day	Placebo	8 weeks treatment + 4 weeks follow-up	Improved mean hot flash frequency, hot flash score, and duration with clonidine vs. placebo. Improved quality of life score with clonidine vs. placebo. No differences between groups in hot flash severity. Increased difficulty sleeping with clonidine vs. placebo.		Good

Table 16. Trials in women with breast cancer (continued)

Study, year	N	Population	Therapy	Comparison	Duration	Main results: Between group differences	Main results: Within group differences	Quality
Quella, 2000[277]	182	women >18; previous breast cancer; 78% on tamoxifen	Soy isoflavone 600 mg tablet one three times daily (each contains 50 mg of soy isoflavones: 40-45% genistein, 40-45% diadzein, and 10-20% glycitein)	Placebo crossover	4 weeks each phase	Summary statistics: No differences in hot flash score or frequency between groups. For outcome of reduction by half in hot flash frequency, 36% for placebo vs. 24% for soy (p=0.01).		Fair
Secreto, 2004[288]	262	≥35; women with breast cancer included (<25%); none on tamoxifen	1. Isoflavones 40 mg midday, and isoflavones 40 mg with melatonin 3 mg evening 2. Isoflavones 40 mg midday and evening 3. Placebo midday, and melatonin 3 mg evening	Placebo midday and evening	3 months	No differences between groups in the total score or sub scores of Greene Climacteric Scale.	Improved Greene Climacteric Scale scores in all groups: 38% placebo; 26% melatonin alone; 38% isoflavone alone; 39% isoflavones and melatonin.	Fair
Van Patten, 2002[278]	157	Mean age 55-56; all have breast cancer; 31% taking tamoxifen	Soy beverage totaling 90 mg/day isoflavones	Placebo	12 weeks	No differences between groups in frequency and intensity of hot flashes.	Improved hot flash frequency and intensity in both groups.	Good

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Literature Search Strategies

KQ1 MEDLINE

Searched 1966 through mid-November 2004

Cognitive
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp Neurobehavioral Manifestations/
5 3 and 4
6 cognit$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 3 and 6
8 exp Delirium, Dementia, Amnestic, Cognitive Disorders/
9 3 and 8
10 5 or 7 or 9
11 limit 10 to english language
12 10 not 11
13 limit 12 to abstracts
14 11 or 13

Depression
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 CLIMACTERIC/px [Psychology]
5 MENOPAUSE/px [Psychology]
6 4 or 5
7 DEPRESSION/
8 exp Depressive Disorder/
9 7 or 8
10 6 or 9
11 3 and 10
12 limit 11 to english language
13 11 not 12
14 limit 13 to abstracts
15 12 or 14

Mood
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp Affect/
5 exp Mood Disorders/
6 mood$.mp.
7 4 or 5 or 6
8 3 and 7
9 exp EMOTIONS/
10 3 and 9
11 8 or 10
12 limit 11 to english language
13 11 not 12
14 limit 13 to abstracts
15 12 or 14

Ovarian Aging
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 climacteric/ or menopause/
2 exp OVARY/
3 exp AGING/ or exp CELL AGING/
4 senescen$.mp.
5 3 or 4
6 1 and 2 and 5

Quality of Life
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 "Quality of Life"/
5 3 and 4
6 (qualit$ adj5 (life or living)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 3 and 6
8 5 or 7
9 exp Life Change Events/

10 3 and 9
11 8 or 10
12 limit 11 to english language
13 11 not 12
14 limit 13 to abstracts
15 12 or 14

Sexual Function
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp sex disorders/
5 3 and 4
6 exp "Sexual and Gender Disorders"/
7 3 and 6
8 (sex$ adj3 (disorder$ or dysfunctio$ or function$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9 3 and 8
10 (sex$ adj3 activ$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
11 3 and 10
12 exp Sexual Behavior/
13 3 and 12
14 5 or 7 or 9 or 11 or 13
15 limit 14 to english language
16 14 not 15
17 limit 16 to abstracts
18 15 or 17

Sleep
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp Sleep Disorders/
5 3 and 4
6 exp SLEEP/
7 3 and 6
8 5 or 7
9 (sleep$ or slept).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]

10 3 and 9
11 insomn$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
12 3 and 11
13 5 or 8 or 10 or 12
14 limit 13 to english language
15 13 not 14
16 limit 15 to abstracts
17 14 or 16

Somatic
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp pain/
5 somat$.mp.
6 4 or 5
7 3 and 6
8 limit 7 to english language
9 7 not 8
10 limit 9 to abstracts
11 8 or 10

Urination
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp Urination Disorders/
5 3 and 4
6 incontinen$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 3 and 6
8 5 or 7
9 urinat$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
10 3 and 9
11 8 or 10
12 limit 11 to english language
13 11 not 12
14 limit 13 to abstracts

15 12 or 14

Uterine Bleeding
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 exp Uterine Hemorrhage/
5 3 and 4
6 (((uterine or uterus) adj5 (bleed$ or bled or hemorrhag$)) or menorrhag$).mp.
7 3 and 6
8 5 or 7
9 limit 8 to english language
10 8 not 9
11 limit 10 to abstracts
12 9 or 11

Vaginal Dryness
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 (vagina$ adj5 dry$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 3 and 4
6 exp VAGINA/mi, bs, ph, pp, en, se, ir, me [Microbiology, Blood Supply, Physiology, Physiopathology, Enzymology, Secretion, Innervation, Metabolism]
7 3 and 6
8 5 or 7
9 limit 8 to english language
10 8 not 9
11 limit 10 to abstracts
12 9 or 11

Vasomotor
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 MENOPAUSE/
2 CLIMACTERIC/
3 1 or 2
4 vasomotor.mp. or exp vasomotor system/

5 3 and 4
6 (hot flash$ or hot flush$ or night sweat$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 Body Temperature Regulation/ or SWEATING/
8 6 or 7
9 3 and 8
10 5 or 9
11 limit 10 to english language
12 10 not 11
13 limit 12 to abstracts
14 11 or 13

KQ1 PSYCHINFO

Searched 1974 through May 2004

Cognitive
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 (cognit$ or memor$ or dement$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 1 and 2

Mood
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp emotional states/
3 (mood$ or depress$ or anxi$ or irritab$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 2 or 3
5 1 and 4

Quality of Life
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp "quality of life"/ or exp life satisfaction/ or exp lifestyle/ or exp lifestyle changes/ or exp well being/

3 (qualit$ adj3 life).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 2 or 3
5 1 and 4

Sexual Function
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp Sexuality/ or exp Psychosexual Behavior/
3 (sex$ adj3 (function$ or dysfunction$ or activ$)).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 2 or 3
5 1 and 4

Sleep
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 sleep$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 (insomn$ or hypersomn$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 (awak$ or wak$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
5 2 or 3 or 4
6 1 and 5

Somatic
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 somat$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 exp pain/
4 (pain$ or ache$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
5 2 or 3 or 4
6 1 and 5

Urination
Database: PsycINFO

Search Strategy:

---

1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 (urinat$ or urinar$ or incontin$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 1 and 2

Uterine Bleeding
Database: PsycINFO
Search Strategy:

---

1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 (uterin$ or uterus).mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 (hemorrhag$ or menorrhag$ or bleed$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 2 or 3
5 1 and 4

Vaginal Dryness
Database: PsycINFO
Search Strategy:

---

1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 vagin$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 1 and 2

Vasomotor
Database: PsycINFO
Search Strategy:

---

1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 fl#sh$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 sweat$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 vasomotor$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
5 body temperature.mp. [mp=title, abstract, heading word, table of contents, key concepts]
6 2 or 3 or 4 or 5
7 1 and 6

KQ2 MEDLINE

Searched 1966 through mid-November 2004

Age of Onset

Database: Ovid MEDLINE(R)
Search Strategy:

---

1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 "Age of Onset"/
5 (age adj3 onset).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6 (age adj2 menopause).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 (menopaus$ adj2 transit$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8 4 or 5 or 6 or 7
9 3 and 8
10 exp Age Factors/
11 exp Time Factors/
12 10 or 11
13 9 and 12
14 limit 13 to english language
15 13 not 14
16 limit 15 to abstracts
17 14 or 16
18 from 17 keep 1-458

BMI

Database: Ovid MEDLINE(R)
Search Strategy:

---

1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 (body mass index or bmi).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 3 and 4
6 limit 5 to english language
7 5 not 6
8 limit 7 to abstracts
9 6 or 8

Depression
Database: Ovid MEDLINE(R)
Search Strategy:

---

1 CLIMACTERIC/
2 MENOPAUSE/
3 1 or 2
4 CLIMACTERIC/px [Psychology]
5 MENOPAUSE/px [Psychology]
6 4 or 5
7 DEPRESSION/
8 exp Depressive Disorder/
9 7 or 8
10 Depress$.mp.
11 6 and 10
12 3 and 9
13 11 or 12
14 limit 13 to english language
15 13 not 14
16 limit 15 to abstracts
17 14 or 16

Ethnicity
Database: Ovid MEDLINE(R)
Search Strategy:

---

1 CLIMACTERIC/
2 MENOPAUSE/
3 ((perimenopaus$ or menopaus$) adj3 (sign$ or symptom$)).mp.
4 1 or 2 or 3
5 eh.fs.
6 exp Population Groups/
7 Cross-Cultural Comparison/
8 5 or 6 or 7
9 4 and 8
10 limit 9 to english language
11 9 not 10
12 limit 11 to abstracts
13 10 or 12

Surgical
Database: Ovid MEDLINE(R)
Search Strategy:

---

1 CLIMACTERIC/
2 MENOPAUSE/

3 1 or 2
4 surgical menopause.mp.
5 exp OVARIECTOMY/
6 3 and 5
7 (oophorectom$ or ovariectom$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8 (ovar$ adj3 remov$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9 7 or 8
10 3 and 9
11 4 or 6 or 10
12 limit 11 to human
13 limit 12 to english language
14 12 not 13
15 limit 14 to abstracts
16 13 or 15

KQ2 PSYCHINFO

Searched 1974 through May 2004

Depression
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp emotional states/
3 (mood$ or depress$ or anxi$ or irritab$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 2 or 3
5 1 and 4

KQ3 AMED

Searched 1985 through August 2004

Menopause
Database: AMED (Allied and Complementary Medicine)
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=abstract, heading words, title]

KQ3 COCHRANE

Searched through 2nd Quarter 2004

Alternative

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:

---

1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.
2 exp medicinal plant/ or exp plants, medicinal/ or exp plant medicinal product/ or exp plant extracts/ or (botanical$ or herb or herbal or red clover or black cohosh or primrose or yam or ginseng or dong quai or progesterone cream).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 exp traditional medicine/ or exp alternative medicine/ or exp complementary therapies/ or ((Alternative or complement$) adj5 (medic$ or treat$ or therap$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 (homeopath$ or naturopath$ or Ayurvedic).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 (acupunct$ or reflexol$ or magnet$ or electromagnet$ or tradition$ or folk).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 2 or 3 or 4 or 5
7 1 and 6

Androgens

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:

---

1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.
2 exp androgens/ or androgen$.mp. or testosteron$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 (dhea or dihydroepitestosteron$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 dihydrotestosteron$.mp.
5 2 or 3 or 4
6 1 and 5
7 from 6 keep 1-384

Antidepressants

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:

---

1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.

2 exp antidepressant agents/ or exp antidepressive agents/ or Antidepress$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 fluoxetine.mp.
4 venlafaxine.mp.
5 paroxetine.mp.
6 2 or 3 or 4 or 5
7 1 and 6
8 exp depression/
9 exp depressive disorder/
10 8 or 9
11 1 and 10
12 7 or 11

Exercise
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.
2 exp Exercise Movement Techniques/ or exp kinesiotherapy/ or exp exercise/
3 (aerobic$ or exercis$ or yoga or tai chi or pilates).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 ((exp psychophysiology/ or exp feedback system/ or exp Mind-Body/) and Relaxation Techniques/) or (biofeedback$ or feedback$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 ((pace or paced or pacing) adj3 (breath$ or respirat$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 2 or 3 or 4 or 5
7 1 and 6

Hormones (covers estrogen and progestin)
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 exp pain/ or (Pain or pains or painful or ache or aching or ached or aches or headach$ or migrain$ or somat$).mp.
2 exp urination disorders/ or exp urinary dysfunction/ or ((vagina$ adj5 dry$) or enuresis or polyuria or oliguria or incontinen$ or (urin$ adj3 frequen$) or urinat$ or vaginit$ or vulvovaginit$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 exp Delirium, Dementia, Amnestic, Cognitive Disorders/ or exp memory disorder/ or exp memory disorders/ or exp cognitive defect/ or (Cognit$ or amnes$ or deliri$ or dement$ or memor$ or remember$ or think$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 exp sexuality/ or exp Sexual behavior/ or exp sex disorders/ or exp sexual dysfunction/ or ((sex$ adj3 (disorder$ or dysfunctio$ or function$ or activ$ or desir$)) or

Dyspareuni$ or vaginismus).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 exp sleep/ or exp sleep disorders/ or exp sleep disorder/ or (Sleep$ or slept or insomn$ or awak$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6 exp uterine bleeding/ or exp uterus bleeding/ or (((uterine or uterus) adj5 (bleed$ or bled or hemorrhag$)) or menorrhag$).mp.
7 exp affect/ or exp mood disorders/ or exp mood disorder/ or exp mood/ or exp temperament/ or (mood$ or emotion$ or depression or depressive or irritat$ or anxi$ or Affective).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8 exp quality of life/ or (qualit$ adj5 (life or living)).mp.
9 exp body temperature regulation/ or exp body temperature disorder/ or exp vasomotor disorder/ or exp vasomotor system/ or exp adrenergic system/ or (Vasomotor or fl#sh$ or sweat$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.
12 exp estrogens/ or exp estrogen/ or estrogen$.mp.
13 exp hormone replacement therapy/ or exp hormone substitution/ or (hormone replacement therapy or hormone substitution).mp.
14 exp progesterone/ or exp progestins/ or exp gestagen/ or (progestin$ or progesterone$ or gestegen$ or neta or mpa or megestrol).mp.
15 12 or 13 or 14
16 10 and 11 and 15

Other Drugs
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.
2 gabapentin.mp.
3 clonidine.mp.
4 methyldopa.mp. or exp METHYLDOPA/
5 exp Ergotamine/ or bellergal.mp.
6 2 or 3 or 4 or 5
7 1 and 6

Phytoestrogens
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.

2 exp phytoestrogen/ or exp isoflavones/ or exp isoflavone derivative/ or (phytoestrogen$ or isflavone$ or soy or soya or soybean$ or genistein or flax).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 and 2

Tibolone
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 (exp menopause/ and climacterium/) or exp climacteric/ or (menopaus$ or climacter$ or premenopaus$ or postmenopaus$ or perimenopaus$).mp.
2 tibolone.mp.
3 1 and 2

KQ3 MANTIS
Searched 1880 through July 2004

Menopause
Database: Mantis
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, descriptors]

KQ3 MEDLINE
Searched 1966 through mid-November 2004

Alternative
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 limit 1 to complementary medicine
3 (botanical$ or red clover or black cohosh or primrose or yam or ginseng or dong quai or progesterone cream).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 exp Complementary Therapies/
5 (homeopath$ or naturopath$ or Ayurvedic).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6 3 or 4 or 5
7 1 and 6
8 2 or 7
9 limit 8 to english language
10 8 not 9
11 limit 10 to abstracts

12 9 or 11
13 limit 12 to (guideline or meta analysis or randomized controlled trial)
14 from 13 keep 1-310

Androgens
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 exp androgens/ or androgen$.mp. or testosteron$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 (dhea or dihydroepitestosteron$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 dihydrotestosteron$.mp.
5 2 or 3 or 4
6 1 and 5
7 limit 6 to female
8 limit 7 to english language
9 7 not 8
10 limit 9 to abstracts
11 8 or 10
12 limit 11 to (guideline or meta analysis or randomized controlled trial)

Antidepressives
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 exp Antidepressive Agents/
3 fluoxetine.mp.
4 venlafaxine.mp.
5 paroxetine.mp.
6 exp DEPRESSION/de, dt [Drug Effects, Drug Therapy]
7 exp Depressive Disorder/dt [Drug Therapy]
8 2 or 3 or 4 or 5 or 6 or 7
9 1 and 8
10 limit 9 to (guideline or meta analysis or randomized controlled trial)

Estrogen/Progestin
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 CLIMACTERIC/
2 MENOPAUSE/
3 (climacter$ or menopaus$ or perimenopaus$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]

4 1 or 2 or 3
5 exp Hormone Replacement Therapy/
6 exp ESTROGENS/
7 exp PROGESTINS/
8 5 or 6 or 7
9 4 and 8
10 limit 9 to (guideline or meta analysis or randomized controlled trial)
11 limit 10 to (guideline or meta analysis or randomized controlled trial)
12 limit 11 to english language
13 11 not 12
14 limit 13 to abstracts
15 12 or 14

Exercise
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 exp Exercise Movement Techniques/
3 (aerobic$ or exercis$ or yoga or tai chi or pilates).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 (biofeedback$ or feedback$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 ((pace or paced or pacing) adj3 (breath$ or respirat$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6 2 or 3 or 4 or 5
7 1 and 6
8 limit 7 to english language
9 7 not 8
10 limit 9 to abstracts
11 8 or 10
12 limit 11 to (guideline or meta analysis or randomized controlled trial)

Other Drugs
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 gabapentin.mp.
3 clonidine.mp.
4 methyldopa.mp. or exp METHYLDOPA/
5 exp Ergotamine/ or bellergal.mp.
6 2 or 3 or 4 or 5
7 1 and 6
8 limit 7 to english language
9 7 not 8

10 limit 9 to abstracts
11 8 or 10
12 limit 11 to (guideline or meta analysis or randomized controlled trial)

Phytoestrogen
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 exp Isoflavones/
3 (phytoestrogen$ or isflavone$ or soy or soya or flax).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 2 or 3
5 1 and 4
6 limit 5 to english language
7 5 not 6
8 limit 7 to abstracts
9 6 or 8
10 limit 9 to (guideline or meta analysis or randomized controlled trial)

Tibolone
Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp CLIMACTERIC/ or (climacter$ or menopaus$).mp.
2 tibolone.mp.
3 1 and 2
4 limit 3 to english language
5 3 not 4
6 limit 5 to abstracts
8 limit 7 to (guideline or meta analysis or randomized controlled trial)

KQ3 PSYCHINFO
Searched 1974 through May 2004

Alternative
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp alternative medicine/ or exp dietary supplements/ or exp "medicinal herbs and plants"/
3 (red clover or cohosh or herb or herbal$ or acupunct$ or reflex$).mp. [mp=title, abstract, heading word, table of contents, key concepts]

4 holist$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
5 (complementar$ adj2 (medic$ or therap$)).mp. [mp=title, abstract, heading word, table of contents, key concepts]
6 (alternat$ adj2 (medic$ or therap$)).mp. [mp=title, abstract, heading word, table of contents, key concepts]
7 2 or 3 or 4 or 5 or 6
8 1 and 7

Antidepressants
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp Antidepressant Drugs/
3 (fluoxetine or venlafaxine or paroxetine).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 exp Serotonin Reuptake Inhibitors/
5 ssri.mp. [mp=title, abstract, heading word, table of contents, key concepts]
6 antidepress$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
7 2 or 3 or 4 or 5 or 6
8 1 and 7

Exercise
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp exercise/ or exp movement therapy/
3 (exercis$ or (physical$ adj3 activ$)).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 (pac$ adj2 respir$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
5 biofeed$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
6 (meditat$ or relax$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
7 2 or 3 or 4 or 5 or 6
8 1 and 7

Hormones (covers estrogen, progestin, and androgen)
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 exp sex hormones/
3 (estrogen$ or progestin$ or progesterone$ or estradiol$ or mpa or neta or megestrol or androgen$ or testosteron$ or dhea).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 (hormon$ adj2 therap$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
5 2 or 3 or 4
6 1 and 5

Other Drugs
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 (gabpentin or clonidine or methyldopa or bellergal).mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 1 and 2

Phytoestrogens
Database: PsycINFO
Search Strategy:
---
1 (menopaus$ or climacter$ or perimenopaus$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
2 (phytoestrogen$ or soy or soya or flax or isoflavon$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
3 (phytoestrogen$ or soy or soya or flax or isoflavon$ or genistein$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
4 1 and 3

Tibolone
Database: PsycINFO
Search Strategy:
---
1 tibolone.mp.

KQ4 MEDLINE

Searched 1966 through mid-November 2004

Breast Cancer

Database: Ovid MEDLINE(R)
Search Strategy:

---

1 exp Breast Neoplasms/co [Complications]
2 (menopaus$ or perimenopaus$ or premenopaus$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 1 and 2
4 (breast adj (cancer$ or tumor$ or malignan$) adj3 survivor$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 2 and 4
6 3 or 5
7 limit 6 to english language
8 6 not 7
9 limit 8 to abstracts
10 7 or 9

SERMS

Database: Ovid MEDLINE(R)
Search Strategy:

---

1 MENOPAUSE/
2 CLIMACTERIC/
3 1 or 2
4 exp Selective Estrogen Receptor Modulators/ad, ae, ct, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Therapeutic Use, Toxicity]
5 3 and 4
6 limit 5 to english language
7 5 not 6
8 limit 7 to abstracts
9 6 or 8

All KQ's DARE

Searched through 2nd Quarter 2004

Menopause

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:

---

1 menopaus$.mp. [mp=title, full text, keywords] (73)
2 perimenopaus$.mp. [mp=title, full text, keywords] (4)
3 climacter$.mp. [mp=title, full text, keywords] (6)

4 postmenopaus$.mp. [mp=title, full text, keywords] (63)
5 1 or 2 or 3 or 4 (106)
6 from 5 keep 1-10 (10)
7 from 6 keep 1-10 (10)
8 from 6 keep 1-10 (10)

Inclusion and Exclusion Criteria

Criteria for Reviewing Abstracts

Key Question 1 (Symptoms)

Include	Relevant to question Cohort, cross-sectional, review, meta-analysis, or unclear study design Community or population based U.S. applicable Appropriate sample size Mid-aged females Undergoing menopause
Exclude	Not relevant to question Wrong design No data Wrong population Paper only available in non-English language Comment or opinion

Key Question 2 (Symptom characteristics and influencing factors)

Include	Relevant to question Cohort, cross-sectional, review, meta-analysis, or unclear study design Community or population based U.S. applicable Appropriate sample size Mid-aged females Undergoing menopause
Exclude	Not relevant to question Wrong design No data Wrong population Paper only available in non-English language Comment or opinion

Key Question 3 (Benefits and adverse effects of treatments)

Include	Relevant to question RCT, review, or meta-analysis One or more listed interventions One or more menopause-related outcomes Perimenopausal or menopausal women
Exclude	Not relevant to question Wrong study design No data Wrong population: premenopausal or postmenopausal women or men Available in non-English language Nonhuman/animal Methodological fatal flaw Comment or opinion

Key Question 4 (Specific characteristics and treatments)

Include	Relevant to question RCT, review, or meta-analysis One or more listed interventions One or more menopause-related outcomes Perimenopausal or menopausal women
Exclude	Not relevant to question Wrong study design No data Wrong population: premenopausal or postmenopausal women or men Available in non-English language Nonhuman/animal Methodological fatal flaw Comment or opinion

Criteria for Reviewing Full-Text Papers

Key Question 1 (Symptoms)

Include	Cohort, cross-sectional, review, or meta-analysis Peri, currently menopausal women, or early postmenopausal women with symptoms Describes one of the symptoms in key question 1 Population based Data specific to women Appropriate outcomes measures N $\geq$ 100
Exclude	Major concurrent disease

Key Question 2 (Symptom characteristics and influencing factors)

Include	Cohort, cross-sectional, review, or meta-analysis Peri, currently menopausal women, or early postmenopausal women with symptoms Describes one of the symptoms in key question 1 and/or one of the factors in key question 2 Population based Data specific to women Appropriate outcomes measures N $\geq$ 100
Exclude	Major concurrent disease

Key Question 3 (Benefits and adverse effects of treatments)

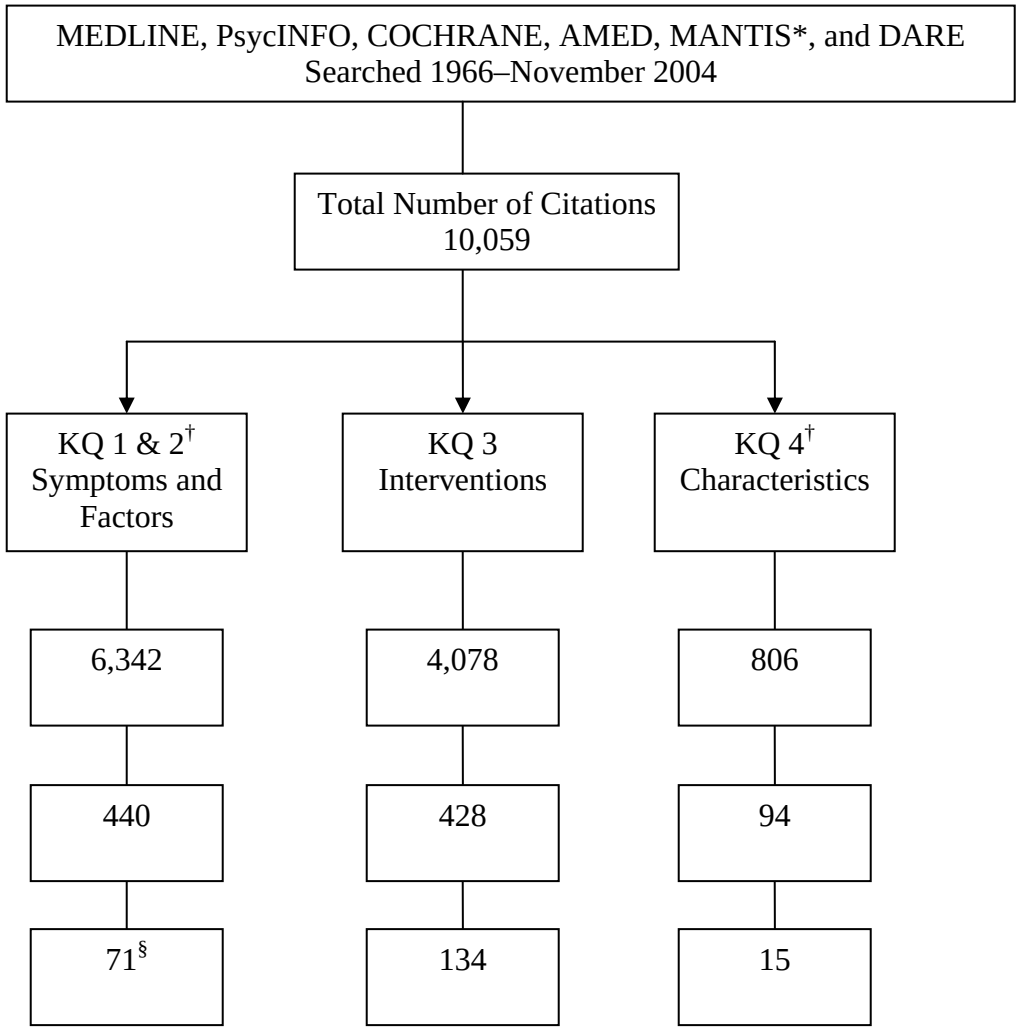
Include	RCT, review, or meta-analysis Peri, currently menopausal women, or early postmenopausal women with symptoms Describes one of the treatments in key question 3 Appropriate agent (currently available, non-injectable, etc.) Dose explicitly stated Appropriate length of treatment (e.g. $\geq$ 12 weeks for estrogen use) Data specific to women Appropriate outcome measures Appropriate power (N)
Exclude	No major concurrent disease

Key Question 4 (Specific characteristics and treatments)

Include	RCT, review, or meta-analysis Peri, currently menopausal women, or early postmenopausal women with symptoms Describes one of the specific characteristics in key question 4 Appropriate agent (currently available, non-injectable, etc.) Dose explicitly stated Appropriate length of treatment (e.g. $\geq$ 12 weeks for estrogen use) Data specific to women Appropriate outcome measures Appropriate power (N)
Exclude	No major concurrent disease

Appendix E. Literature Search Tree

Literature Search Tree



* MANTIS was searched starting in 1880, and only for KQ 3g, h, i

† COCHRANE database was not searched for KQ's 1, 2, & 4

‡ Citations may overlap among key questions

§ Only cohort and cross-sectional from cohort studies could be quality rated

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Avis, 1994	Massachu-sett's Women's Health Study	2565	Cohort	Internal	5 years	Random sample of 8,050 women ages 45-55 in Massachusetts, from which 2,565 were identified as having menstruated in the past 3 months, having a uterus and ≥ one ovary	Population based recruitment of premenopausal women	_
Avis, 1997	Massachu-sett's Women's Health Study	454 (131 for some analyses)	Cross-sectional analyses from cohort	Internal	4.5 years	Sample was part of larger cohort of 8,050 women randomly selected; 2,565 were pre- or early menopausal	Community-based, Massachusetts	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Avis, 1994	_	_	_	_	_
Avis, 1997	45-55 in 1982 (baseline)	For this analysis, women who were premenopausal at baseline and naturally post-menopausal at the last study f/u (4 yrs later, 6th clinic visit).	Telephone and mailed questionnaires	94-95% retention over 6 contacts for cohort of 2,565 pre- and early menopausal women	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Avis, 1994	CES-D for depression Seven measures of health care utilization Self-assessed health, physical symptoms, restricted activity and chronic conditions. Surgical menopause included either hysterectomy or BSO.	–	–	–	–	–
Avis, 1997	hot flashes and night sweats (frequency and bothersomeness) consult with MD regarding menopause	All women in this analysis progressed from pre to post menopausal (natural) over the course of the f/u period	Excluded	Excluded	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Avis, 1994	–	–	–	–	–	–
Avis, 1997	Current smoking at baseline 41%	Excluded	NR	23% were <u>not</u> bothered by HF/NS at any of the six interviews. HF and NS bothersomeness were highly correlated. Length of perimenopause was not correlated with number or bothersomeness of symptoms. Women with more negative attitude toward menopause report HF/NS more frequently.		

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Avis, 1994	_	_	_	_	_
Avis, 1997					

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Avis, 1994	–	–	–
Avis, 1997			

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Avis, 1994	_	Used CES-D score of <16 vs. ≥16 as dichotomous outcome variable. Logistic regression model adjusted for HRT, menopausal symptoms at T2, T1-T2 menopausal transition and T1 CES-D score.	_
Avis, 1997	Smoking (;<0.05), physical symptoms (p<0.01), psychological symptoms (p<0.001), having had a surgery for a benign breast cyst, greaster alcohol consumption and agreeing with the statement "many women think they are no longer "real" women after the menopause" were related to FH/NS bothersomeness.	Stepwise logistic regression.	"Smoking (;<0.05), physical symptoms (p<0.01), psychological symptoms (p<0.001), having had a surgery for a benign breast cyst, greaster alcohol consumption and agreeing with the statement ""many women think they are no longer ""real"" women after the menopause"" were related to FH/NS bothersomeness. Primary variables predicting frequncy of HF/NS reporting were premenopausal symptoms and attitudes toward menopause. Age at inception of peri-menopause was associated with length of perimenopause (r=-0.16, p=0.0005).

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Avis, 1994	_	Depression at baseline was most predictive of subsequent depression (OR 9.12, p<0.0001). A menopausal symptoms variable was also significant contributor (OR=3.55, <0.0001). The menopausal transition was significant as a single variable but the individual variables were not. (OR 0.59 to 1.28, all CI crossing 1). Comparing the prevalence of depression among groups, the peak prevalence of depression for those not depressed at baseline, was for those who were peri-peri. For those who were depressed at baseline, the peak prevalence of depression occurred in the pre/peri-post group (see figure in paper, no numbers given in text).
Avis, 1997	OR for HF/NS frequency from stepwise logistic regression: smoking 1.44 (CI 1.02, 2.05) tubal ligation 0.47 (CI 0.29, 0.78) any college 0.59 (0.42, 0.84) physical symptoms 1.47 (1.18, 1.83) psychological symptoms 2.14 (1.38, 3.35) length of perimenopause 1.24 (1.07, 1.44).	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Avis, 2000	Massachu-sett's Women's Health Study	2000	Cross-sectional analyses from cohort	Intenral	5 years (1986-91)	Random pop-based sample of 8,050 women in Mass. 2,569 women ages 45-55 selected for f/u. Of these 427 (78.6% of 543) were eligible for this study. 200 included in this analysis.	Community-based, Massachusetts	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Avis, 2000	51-61, mean age 54	Inclusion criteria: 1. Intact uterus and 1 ovary 2. No HRT in past 2 yrs 3. Current sexual partner 4. Living within 1 hr of Boston 5. <12 months consecutive ammenorrhea 6. No major cancer in last 5 years.	Questionnaires	RR 77% from initial recruitement.	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Avis, 2000	Sexual activity questionnaire adapted for Amssachusetts male Agin Study Satisfaction with current sexual relationship Frequency of sexual intercourse Sexual desire Belief that interest in sex declines with age Level of arousal Difficulty reaching organsm Pelvic area pain		Exlcuded	Excluded	Excluded if within 5 years	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Avis, 2000	Current smoking 22%	Excuded (n=51)	BMI range 17-49, mean±SE=27.9±5.5			

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Avis, 2000	Overall: 12.6% had CES-D score ≥16. 39.8% had psychological symptoms				

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Avis, 2000	Fewer perimenopausal women reported never having difficulty reaching orgasm (NS). Level of sexual desire was lower among post-menopausal women compared with premenopausal women ($p<0.05$). Frequency of sexual intercourse and pain during intercourse did not vary by menopausal status.	Satisfaction with life did not vary by menopausal status.	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Avis, 2000	The following variables were unrelated to any aspect of sexual functioning: employment status, vasomotor symptoms, parter stress, alcohol , exercise and BMI	Multiple regression	Sexual Function: Recent vaginal dryness was related to pain during or after intercourse (OR 3.86) and difficulty reaching orgasm (OR 2.51). Menoapausal status was not related to either pain during intercourse or difficulty reaching orgasm. Age was negatively related to difficulty reaching orgasm.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Avis, 2000		

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Avis, 2001	SWAN	14,906	Cross-sectional	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Avis, 2001	47.1 (40-55)	Exclusion: 450 missing race/ethnicity data 341 uncertain menopausal status 55 pregnant or breastfeeding 313 incomplete data on symptoms or covariates	_	87.70%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Avis, 2001	_	Surgical 20.8% Postmenopausal 14.6% Perimenopausal 27.2% Premenopausal 29.7% Hormone user 7.7%	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Avis, 2001	_	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Avis, 2001	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Avis, 2001	_	_	Factor 1 - psychosomatic symptoms Factor 2 - vasomotor symptoms Symptoms had to load $\geq$ 0.40 on a factor for all ethnic groups.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Avis, 2001	Age, education, self-assessed health, economic strain, geographic site interaction terms for race/ethnicity and menopausal status	Multiple linear regression model for Factors 1 and multiple logistic regression for Factor 2.	<u>Factor 1: Psychosomatic symptoms</u> Significant predictors (p<0.0001) Age Education (reference postgraduate degree) - high school degree/equivalent Self-assessed health (reference excellent) - very good, good, fair/poor Difficult to pay for basics (reference not at all hard) - somewhat hard or very hard Racial/ethnic group (reference Caucasian) - AA, H, Chinese, Japanese, Hispanic Menopausal status (reference premenopausal) - peri and surgical menopause, HRT users Geographic site (reference Detroit) - Boston, Newark <u>Factor 2: Vasomotor symptoms (1 vs. 0)</u> Education (ref postgraduate degree) - college graduate or less education Self-assessed health (ref excellent) - very good, good, fair/poor Difficult to pay for basics (ref not at all hard) - somewhat hard or very hard Racial ethnic group (ref Caucasian) - AA: Chicago; AA: Detroit; Chinese; Japanese Menopausal status (ref premenopausal) - peri, post, surgical, and HRT users <u>Factor 2: Vasomotor symptoms (2 vs. 0)</u> Age; Education (ref postgraduate degree) - college graduate or less education; Self-assessed health (ref excellent) - very good, good, fair/poor; Difficult Racial ethnic group (ref Caucasian) AA (all sites); Chinese, Japanese, Hispanic Menopausal status (ref premenopausal) - peri, post, surgical, and HRT u Geographic site (ref Detroit) - Pittsburgh, L.A.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Avis, 2001		Psychosomatic symptom reporting differs by both race/ethnicity and by menopausal status. All other racial/ethnic groups report significantly fewer symptoms than Caucasian women. Peri-menopausal women, HRT users and women with surgical menopause report more symptoms than premenopausal women. Vasomotor symptom reporting also varies by race/ethnicity and menopausal status. Effects are greater when looking 2 symptoms vs. none. AA were more likely and Hispanic, Japanese, Chinese were less likely than Caucasian women to report vasomotor symptoms. All menopausal groups reported significantly more symptoms than premenopausal women.
	1.22-1.29; 1.38-2.58; 1.15-1.30	
	1.41; 1.59; 0.60; 0.65; 1.69-1.96	
	1.05; 1.53-1.79; 1.69-3.72; 1.18-1.55	
	1.28-1.82; 0.25-0.77; 3.35-3.81; 0.74-0.75	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Avis, 2003	SWAN	3,193	Cross-sectional	_	_	_	_	AA 28.15% Chinese 7.68% H 8.44% J 8.63% W 47.1%
Bromberger, 2001	SWAN	10,374	Cross-sectional	N/A	N/A	_	_	AA 25.8% Chinese 5 H 13.5 J 6.3 W 49.2

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Avis, 2003	46.2 (42-52)	Data on menopausal status and SF-36 outcomes missing for 109 of 3302	_	96.70%	_
Bromberger, 2001	40-55 mean 45.9 with distress mean 46.4 without distress	5213 of 16065 were excluded for 1) exogenous hormone use preceding 3 months, 2) pregnancy, 3) hysterectomy, 4) no menses past 12 months due to pregnancy, breast-feeding, severe weight loss, or illness	_	64.57%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Avis, 2003	5 subscales of SF-36 as measures of health related quality of life (HRQL): bodily pain, role limitations due to physical health, role limitations due to emotional problems, social functioning and vitality menopausal status, sociodemographic and lifestyle variables, health variables psychosocial variables including the Center for Epidemiological Studies (CES-D) scale, Perceived Stress Scale, Medical Outcomes Study Social Support Survey	Premenopause 53.82 % Early perimenopause 46.18% Late perimenopause 0% Post-menopause 0%	–	–	–	–
Bromberger, 2001	12-item questionnaire of physical and psychological symptoms Psychological distress = presence of all 3 symptoms feeling tense or nervous, feeling blue or depressed, feeling irritable or grouchy (categorical - present or absent)	Premenopause 43.2 % Early perimenopause 34 Late perimenopause 5.8 Post-menopause 16.8 Proportion with psychological distress: Premenopause 20.9 % Early perimenopause 28.9 Late perimenopause 25 Post-menopause 22	Ineligible	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Avis, 2003	_	_	_	_	_	_
Bromberger, 2001	Smoking: current 22.5% past 23 never 53.6	_	_	Yes 32.5% No 67 Those with vasomotor flushes (36.6%) were more likely than those without (18.0%) to have psychological distress (p<0.001).	NR	Difficulty sleeping: Yes 36.1% No 62.7 Those with difficulty sleeping (39.7%) were more likely than those without (15.4%) to have psychological distress (p<0.001).

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Avis, 2003	_	_	_	_	_
Bromberger, 2001	Psychological distress: Yes 24.1% No 75.9	NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Avis, 2003	–	–	–
Bromberger, 2001	NR	NR	The following variable were significantly associated with psychological distress ($p<0.001$): menopause status, race/ethnicity, education, marital status, smoking, availability of perceived social support, number close friends/relatives, paying for basics, perceived health.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Avis, 2003	SES, sociodemographic, health, lifestyle and social circumstance variables	Adjusted models for impaired function (women at or below the 25th percentile) on the SF-36 scales	In unadjusted models, early perimenopause and ethnic group were significantly associated with Impaired Function. In models adjusted for health conditions, impaired function did not differ by menopausal status. In adjusted models, Hispanic women were more likely than whites to report bodily pain and impaired social functioning. Blacks were more likely than Whites to report impaired social functioning.
Bromberger, 2001	**Significant:** menopause status, race/ethnicity, education, smoking, availability of perceived social support, close friends/relatives, paying for basics, perceived health, health limitations, difficulty sleeping, vasomotor symptoms, age **Not significant:** employment status, marital status, site, physical activity, number of reported medical conditions.	Multivariate association of psychological distress with menopausal status	Early perimenopause as compared to premenopause was associated with increased odds of psychological distress (OR 1.2). AA, H, J, Chinese race as compared to W race was associated with decreased odds of psychological distress (OR 0.73, 0.65, 0.61, 0.43). The presence of vasomotor symptoms was associated with increased odds of psychological distress (OR1.96).

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Avis, 2003	_	"Symptoms are important mediators between physiological conditions and HRQL."
Bromberger, 2001	_	Early perimenopause and vasomotor symptoms were associated with increased odds of psychological distress. Late perimenopause and post-menopause were not associated with increased odds of psychological distress.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Bromberger, 2003	SWAN	3,161	Cross-sectional	N/A	N/A	_	_	AA 28.3 % Chinese 7.7 H 8.2 J 8.7 W 47.2

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Bromberger, 2003	42-52 mean 46.2	White or site-predetermined ethnicity, menses within the previous 3 month, have uterus and at least one ovary, not pregnant, no use of reproductive hormones or birth control pills within the previous 3 months. 141 excluded because of missing data for dysphoric mood and menopausal status	_	95.73%	N/A

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Bromberger, 2003	Symptom checklists, SF-36 Role Emotional scale, Medical Outcomes Study Social Support Survey, modification of Psychiatric Epidemiology Research Interview, adapted Baecke questionnaire Dysphoric mood = summary scale 0-16 (dichotomized 0-6 v 7-16) of the 4 mood measures feeling blue, feeling irritable, feeling nervous, or experiencing mood changes on $\geq$ 6 days in preceding 2 weeks.	Premenopausal 53.4 % Early perimenopausal 46.6 %	Ineligible	Ineligible	NR	Ineligible

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Bromberger, 2003	Nonsmokers 82.9 %	N/A	NR	None 89%	NR	Disturbed 31%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Bromberger, 2003	Use of medication for nervous condition 10% possible PMS 15.3%	NR	Pain: severe/very severe 7.1% moderate 22% very mild/mild 54.2%	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Bromberger, 2003	NR	NR	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Bromberger, 2003	Study site, menopausal status, ethnicity, age, difficulty of paying for basic necessities, use of medication for nervous conditions, pain, disturbed sleep, vasomotor symptoms, possible premenstrual syndrome, social support, number of upsetting events, relationship presence/quality, recreational/sport activity, study site	Logistic regression models for each of four mood symptoms: Feeling blue, irritable, nervous, or experiencing mood changes on >= 6 days in preceding 2 weeks. Logistic regression model of dysphoric mood. Menopausal status, study site, age, race/ethnicity forced into all adjusted models.	In comparison to premenopause, early perimenopause was associated with increased odds of : feeling irritable (OR 1.33) feeling nervous (OR 1.54) experiencing mood changes (OR 1.52). dysphoric mood score >= 7 (OR 1.8) dysphoric mood in previous 2 weeks (OR 1.62). In comparison to W women, AA had decreased odds of: feeling blue (OR 0.62) feeling irritable (OR 0.61) feeling nervous (OR 0.46) Chinese women had decreased odds of: feeling blue (OR 0.35) feeling irritable (OR 0.30); J women had decreased odds of: feeling blue (OR 0.44) feeling nervous (OR 0.51). Vasomotor symptoms were associated with all of the mood symptoms ($p<0.001$). Lower education level was associated with increased odds of dysphoric mood: some college (OR 2.04) high school or less (OR 2.35)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Bromberger, 2003	_	Early perimenopause was associated with increased odds of mood symptoms and dysphoric mood particularly among women with lower educational attainment.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Brown, 2002 Australia	Australian Longitudinal Study on Women's Health	8,236	Cohort	Internal	2 years	41,500 women selected from all over Australia using national Medicare health insurance database with over-representation of women living in rural and remote areas. The mid-age cohort (age 45-50 years) was targeted for survey 2 in 1998.	_	NR
Busch, 1994	National Health Examination Follow-up Study	395 naturally menopausal women + 178 surgically menopausal women. Drawn from a sample of 3,049 women age40-60 in NHANES	Cohort (also has cross-sectional data)	Internal	10 years	NHANES (stratified probability sample of U.S.)	U.S.	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Brown, 2002 Australia	Mean age 49.7 (sd 1.5) yreas at survey 2	_	_	14,065 mid-age women responded to the mailed survey; 54% of them agreed. For survey 2, 92% of 12,328 women responded (12,328 represents women who consented to further contact and had not died).	6.5% did not return the survey, 1.5% declined participation in survey 2
Busch, 1994	40-60	Women who had participated in NHANES at baseline and the 10 year follow-up study. Included those who were not menopausal at the baseline assessment. Exclusions: 1. Insufficient data to determine menopausal status 2. Cessation of menstruation for reasons other than natural or surgical menopause 3. Reporting surgical menopause but still having a uterus and ovaries 4. Reporting continued menstruation after age 58.	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Brown, 2002 Australia	Menopausal status: self-reported bleeding history or HRT (4 categories); 6 change categories.	_	_	_	_	_
Busch, 1994	Women were selected at random to receive the CES-D and the GWB (Global Well-Being) questionnaires. Sleep disturbance measures by three NHEFS items summed to form a scale: "How often do you have trouble falling asleep?"; "How often to you have trouble with waking up during the night?"; "How often do you have trouble with waking up too early and not being able to fall sleep again?"	_	178/573 had "surgical menopause"	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Brown, 2002 Australia	–	–	–	Relative to pre-pre: Pre-peri: OR 1.3 (1.1, 1.5) Peri-peri: 1.3 (1.1, 1.5) Pre/peri-Post: 1.0 (0.8, 1.2) Not significant Post-post: 0.9 (0.7, 1.2) not significant HRT: 1.5 (1.3, 1.8)	–	Difficulty sleeping: Pre-peri: 1.3 (1.1, 1.5) Per-peri: 1.4 (1.2, 1.7) Pre/peri-Post: 1.5 (1.2, 1.8) Post-post: 1.2 (0.9, 1.6) not significant HRT : 1.5 (1.3, 1.7)
Busch, 1994	NR	NR	NR	NR	NR	No significant differences between women in different menopausal change groups, or between those of surgical vs. natural menopause

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Brown, 2002 Australia	_	_	Stiff or painful joints (compared to pre-pre): Pre-peri: 1.3 (1.1, 1.5) Peri-peri: 1.6 (1.4, 1.9) Pre/peri-Post: 1.1 (0.9, 1.4) Post-post: 1.3 (1.0, 1.7) HRT: 1.4 (1.2, 1.7) Back pain (compared to pre-pre): Pre-peri: 1.2 (1.0, 1.4) Peri-peri: 1.3 (1.1, 1.5) Pre/peri-Post: 1.0 (0.8, 1.2) Post-post: 1.1 (0.9, 1.4) HRT: 1.2 (1.0, 1.4)	Leaking urine (compared to pr-pre): Pre-peri: 1.0 (0.8, 1.2) not significant Peri-peri: 1.3 (1.1, 1.6) Pre/peri-Post: 1.0 (0.8, 1.3) not significant Post-post: 0.8 (0.6, 1.1) not significant HRT: 1.0 (0.8, 1.2) not significant	_
Busch, 1994	No significant differences between women in different menopausal change groups, or between those of surgical vs. natural menopause (Mean CES-D score (s.d.) time 1 vs. time 2) : Pre-pre: 8.9 (9.1) vs. 7.8 (9.0), n=172 Pre-Peri: 10.3 (9.4 vs. 7.8 (6.5), n=58. Pre-Natural Menopause: 8.4 (8.1vs 7.8 (7.5), n=114. Pre-Surgical Menopause: 9.6 (7.5)vs 9.4 (11.1) n=50	NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Brown, 2002 Australia	–	–	–
Busch, 1994	NR	No significant differences between women in different menopausal change groups, or between those of surgical vs. natural menopause (mean (s.d.) at time 1 vs. time 2): pre-pre:48.0 (10.9)vs 49.3(11.1), n=352. Pre-peri: 47.1 (12.6)vs. 47.7 (11.1), n=125. pre-Natural Menopause: 49.2(10.7) vs. 49.5 (10.1), n=281. pre-Surgical Menopause: 45.8 (12.3) vs. 47.0 (13.1).	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Brown, 2002 Australia	_	Adjusted for symptom score at survey 1, physical activity , weight, weight change, life events, smoking status, occupation, country of birth, marital status, and area of residence and age.	_
Busch, 1994	None	No MV modeling	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Brown, 2002 Australia	_	Using pre-pre as the reference group, 1. Headache: OR were not significantly different between groups (all CI crossed 1) 2. Eyesight problems: OR were not significantly different between groups (all CI crossed or included 1), 3. Severe tiredness: OR were highest for HRT (OR 1.5, CI 1.3-1.8), then per-peri (OR 1.3, CI 1.1-1.5) and peri-peri (OR 1.3, CI 1.1-1.5) and lowest for pre/peri-post (OR 0.9, 0.7-1.1) and post-post (OR 1.0, CI 0.7-1.3). 4. Stiff or painful joints 5. Back pain 6. Leaking urine 7. Constipation 8. Difficulty sleeping 9. Hot flashes 10. Night sweats
Busch, 1994	NA	Assume that the categories used to report symptoms are those ascertained at 10 year assessment, because everyone was pre-menopausal at baseline in order to be included.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Dennerstein, 1993 Australia	Melbourne Women's	1,897	Cross-sectional	_	_	_	_	_
Dennerstein, 1994 Australia	Melbourne Women's	1,879	Cross-sectional	_	_	_	_	_
Dennerstein, 1997	Melbourne Women's	405	Longitudinal	_	4 years	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Dennerstein, 1993 Australia	_	_	_	1897/2001 (94.8%) were available for analysis	_
Dennerstein, 1994 Australia	_	Current oc users excluded.	_	_	_
Dennerstein, 1997	45-55	Inclusion: Women who were still experiencing menstrual cycles, or who had no more than 3 months of amenorrhea, who were not taking hormone therapy, or oral contraceptives, had an intact uterus, and at least one ovary Exclusions: HRT use, surgical removal of uterus and/or ovaries, women who refused blood draws	Face to face interview	Subset of cohort of 2001 women	92% retention rate after the 4th round of interviews

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Dennerstein, 1993 Australia	–	–	–	–	–	–
Dennerstein, 1994 Australia	Sexual interest, frequency, dyspareunia sociodemographic and lifestyle variables health status, menopausal status	–	–	–	–	–
Dennerstein, 1997	Affectometer 2 (modified) E_2 FSH Total Testosterone (T) SHBG Free Androgen Index (FAI)	Pre 37% Early Peri 34% Late Peri 17% 1-2 years post 9% > 2 years post 3% Mean age increased across the menopausal categories from 49.4 (pre) to 54.4 (> 2 years post), p<0.001.	Excluded	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Dennerstein, 1993 Australia	_	_	_	By menstrual status: Post 39.4% Peri 31.5% Pre 9.8%	_	Trouble sleeping by menstrual status: Post 41.5% Peri 35.2% Pre 24%
Dennerstein, 1994 Australia	_	_	_	_	_	_
Dennerstein, 1997	_	NR	_	(% in the last 2 weeks) 12.6 18.4 (p<0.05) 54.3 (p<0.001) 57.0 (p<0.001) 48.8 (0.001) p values as compared to pre-menopausal group	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Dennerstein, 1993 Australia	Feeling sad or downhearted by menstrual status: Post 48.7% Peri 33% Pre 24.7%	Difficulty in concentrating by menstrual status: Post 18.3% Peri 27.5% Pre 20.3%	_	Problems with urine control by menstrual status: Post 14% Peri 16% Pre 9.2%	_
Dennerstein, 1994 Australia	_	_	_	_	_
Dennerstein, 1997	Positive affect increased with age ($p<0.05$) and negative affect decreased with age ($p<0.05$) only in the postmenopausal categories. In the pre- and peri-menopausal categories, there were no significant age effects.	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Dennerstein, 1993 Australia	–	–	–
Dennerstein, 1994 Australia	–	–	–
Dennerstein, 1997	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Dennerstein, 1993 Australia	–	–	–
Dennerstein, 1994 Australia	Age, menopausal status, well-being, employment status, years of education, vasomotor symptoms, cardiopulmonary symptoms, skeletal symptoms	Logistic regression model of decrease in sexual interest over the preceding year	Natural menopause On HRT well-being part-time employment no employment 11-12 years of education vasomotor symptoms cardiopulmonary symptoms skeletal symptoms
Dennerstein, 1997	–	Data from years 1-4 was pooled an analyzed as a whole. Generalized linear regression, forward stepwise approach.	Significant coefficients after adjustment for age and hot flashes. None were significant for positive affect in any of the menopausal groups compared with premenopausal group. The mean negarive affect score was higher in early peri (Beta 0.079, $p<0.01$) and 1-2 year post menopause (Beta 0.120, $p<0.05$) groups compared to premenopausal group. Overall, well being tended to decrease with increasing menopausal status, with the lowest in the 1-2 years postmenopausal group ($p<0.01$), followed by an increase in levels of well being in the > 2 years postmenopause group.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Dennerstein, 1993 Australia	–	
Dennerstein, 1994 Australia	1.93 (1.22-3.06) 2.27 (1.42-3.63) 0.76 (0.67-0.87) 1.81 (1.34-2.45) 1.56 (1.16-2.10) 0.65 (0.50-0.87) 1.25 (1.05-1.48) 0.72 (0.61-0.84) 1.32 (1.11-1.50)	Decline in sexual interest was associated with natural menopause, decreased well-being, decreasing employment, vasomotor symptoms, skeletal symptoms, and cardiopulmonary symptoms. It was not associated with age.
Dennerstein, 1997	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Dennerstein, 1999 Australia	Melbourne Women's	354	Longitudinal	_	6 years	_	_	_
Dennerstein, 2000 Australia	Melbourne Women's	172	Longitudinal	_	7 year follow-up	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Dennerstein, 1999 Australia	48.1 at baseline	Exclusions: dropouts (49), surgical menopause (29), oral contraceptive use at any year (6).	Questionnaires, physical exam, blood samples, telephone interview	Retention rate for longitudinal arm 90% at 6 years. Percentage of original cohort eligible for this analysis 80.8%.	_
Dennerstein, 2000 Australia	50.3	172 women of the 438 in the longitudinal cohort were included. They were premenopausal at baseline and either perimenopausal or postmenopausal at follow-up. For women who had hysterectomy, bilateral oophorectomy, endometrial ablation (n=10) or took HRT (n=53), only information prior to the intervention was used.	Questionnaires, physical exam, blood samples, telephone interview	89% for longitudinal cohort at 7year follow-up. Percentage of original cohort eligible for this study 39%.	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Dennerstein, 1999 Australia	Affectometer-2 sociodemographic variables, menopausal status, 22 symptom checklist, self-rated health, lifestyle factors, blood samples FSH, E2, Inhibin, Factor 1 of Personal Experiences Questionnaire	–	–	–	–	–
Dennerstein, 2000 Australia	North American symptom checklist, sociodemographic, health and well-being, menstrual calendars, blood samples E2, FSH	By post-menopause, the average total number of symptoms reported increased by 17% from 4.2 to 4.9 (p<.001)	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Dennerstein, 1999 Australia	–	–	–	–	–	–
Dennerstein, 2000 Australia	–	–	33.6% BMI>25	Night sweats (p<0.01) and hot flushes (p<0.001) increased in the late peri and post-menopause . Magnitude of change between early and late perimenopause +27% for hot flushes, +17% for night sweats.	Vaginal dryness increased in late perimenopause and post-menopause (P<0.001). Magnitude of change between early and late perimenopause +17%.	Trouble sleeping severity score increased in late peri and post-menopause (p<0.05). Magnitude of change +6% between early and late perimenopause (gradual increase across menopausal categories).

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Dennerstein, 1999 Australia	Significant decrease in negative mood with time (p=.005)	–	–	–	–
Dennerstein, 2000 Australia	–	–	Somatic symptoms (other than breast soreness) did not change significantly with transition to late-peri or post-menopause.	Urinary symptoms did not change significantly with transition to late-peri or post-menopause.	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Dennerstein, 1999 Australia	–	–	–
Dennerstein, 2000 Australia	–		Breast soreness severity scores were reduced in late peri and post-menopause compared to pre and early perimenopause ($p<0.001$), Magnitude of change -21%. E2 decreased sharply and FSH increased sharply between early and late perimenopause.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Dennerstein, 1999 Australia	_	_	Significant predictors of Magnitude of Negative Mood (p = 0.002 - 0.02): premenstrual complaints, negative attitudes to aging and menopause, parity of one child, number of symptoms, poor self-rated health, negative feelings for the partner, lack of a partner, current smoking, exercising < once a week, ≥3 daily hassles, moderate or high interpersonal stress Significant predictors of Change in Negative Mood (mood changes if factor changes) (p < 0.001 to p=0.05): symptoms, self-rated health, feelings for partner, marital status, interpersonal stress
Dennerstein, 2000 Australia	FSH, E2, all predictors used in the model are not listed	Logistic regression to determine predictors of symptoms in late perimenopause	**Hot flash model:** number of symptoms > 4 occupation professional occupation sales/white collar smoking pack years at early perimenopause >10 estradiol at late perimenopause 30-100 estradiol at late perimenopause <30 **Night sweats model:** change in E2 from early to late perimenopause **Vaginal dryness model:** education >12 y **Trouble sleeping model:** well-being at early perimenopause 1.7-2.3 well-being at early perimenopause >2.3 Agree to statement of beliefs about menopause Hot flushes at late perimenopause - yes

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Dennerstein, 1999 Australia	_	No direct link between the menopausal transition and negative mood level. However, menopausal transition interacts (amplifies negative effects of these variables on mood) with paid work, self-rated health, daily hassles.
Dennerstein, 2000 Australia	6.2 0.1 0.2 7.0 20.5 5.0 1.1 0.3 0.3 0.1 5.5 5.0	E2 is the best predictor for vasomotor symptoms.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Dennerstein, 2001a Australia	Melbourne Women's	283	Longitudinal	Internal	8 years	_	_	_
Dennerstein, 2001b Australia	Melbourne Women's	267	Longitudinal	_	8 years	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Dennerstein, 2001a Australia	48.5 at baseline	Included: Group M = 197 women who transitioned through menopause Group A = 44 stayed pre-or early perimenopausal Group B = 42 stayed postmenopausal between years 3 and 8 Excluded: dropouts, surgical menopause, oral contraceptive use at any year, had not passed through enough menopausal categories.	Questionnaires, blood samples, telephone interview	88% retention at 8 years, percentage eligible for this study 64.6%.	_
Dennerstein, 2001b Australia	48.8 years at baseline	Excluded: dropouts (57), surgical menopause (36), oral contraceptive use at any year (5), lack of baseline data on some measures (5), failure to reach late perimenopause during 8 years of study (26), HRT use before reaching late perimenopause (42).	Questionnaires, physical exam, blood samples, telephone interview	88% retention at 8 years, percentage eligible for this study 61%.	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Dennerstein, 2001a Australia	Personal Experiences Questionnaire (SPEQ, based on the McCoy Female Sexuality Questionnaire). PEQ factors include: feelings for partner, sexual responsivity, frequency of sexual activities, libido, partner problems, vaginal dryness/dyspareunia FSH, E2, menopausal status/menstrual diaries	–	–	–	–	–
Dennerstein, 2001b Australia	Affectometer-2, menstrual status, sociodemographic variables, lifestyle variables	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Dennerstein, 2001a Australia	–	–	–	–	–	–
Dennerstein, 2001b Australia	–	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Dennerstein, 2001a Australia	–	–	–	–	–
Dennerstein, 2001b Australia	Mean positive mood scores by study year did not show any linear trend with time. No significant change in positive mood over the menopausal transition. Premenopausal positive mood scores correlated significantly with late perimenopausal (r=0.61) and postmenopausal (r=0.66) positive mood scores. Late perimenopause positive mood scores correlated with post-menopause positive mood scores (r=0.68)	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Dennerstein, 2001a Australia	Total SPEQ scores fell **from early to late perimenopause** (p<0.001). Sexual responsivity (SPEQ2) decreased signifi-cantly (p<0.0001). Sexual frequency, libido, and vaginal dyspareunia did not change significantly. Partner's problems with sexual performance in-creased significantly (p<0.001) and women's positive feelings for partner declined significantly (p<0.05). From late peri to postmenopause total SPEQ score declined further (p<0.01) as did scores for sexual responsivity (p<0.01), libido (p<0.01), and frequency of sexual activities (p<0.05). Significant increase in vaginal dyspareunia (p<0.01) and partner's problems with sexual performance (p<0.05).	_	In control group A (pre- or early perimenopausal), the only parameter to show change with time (1st to 7th year) was sexual responsivity (mean change -0.67, p=0.0005). FSH levels increased (+19.3, p<0.0001) between years 1-7, E2 levels decreased (-212, p<0.01) between years 3-8. In control group B (post-menopausal), the only parameter to show change was sexual responsivity (mean change -0.42, p=0.036). No significant
Dennerstein, 2001b Australia	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Dennerstein, 2001a Australia	–	–	–
Dennerstein, 2001b Australia	–	General linear model of factors affecting positive moods during midlife. Final model: Predictors of Positive Mood Late in the Menopausal Transition	Premenopausal positive mood scores were significantly influenced by baseline interpersonal stress (B=-0.113, p=0.009) and baseline attitudes to aging (B=0.054, p=0.026). Postmenopausal positive mood scores were significantly influenced by premenopausal positive mood scores (B=0.717, p=0.000), dysphoric symptom change (B=-0.085, p=0.000), change in marital status (B=0.342, p=0.007), major life events (B=-0.124, p=0.042), daily hassles (B=-0.016, p = 0.014), work satisfaction (B=0.493, p=0.000). Premenopausal positive mood scores (B=0.730, p=0.000) dysphoric symptom change (B=-0.108, p=0.000) change in marital status (B=0.353, p=0.004) major life events (B=-0.136, p=0.019) daily hassles (B=-0.015, p = 0.011) work satisfaction (B=0.456, p=0.000).

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Dennerstein, 2001a Australia	_	Sexual responsivity (SPEQ2) decreases with time across all groups. The other five domains of sexual functioning were not affected by time but changed with the menopausal transition.
Dennerstein, 2001b Australia	_	The most important predictor of positive mood in late peri- and post-menopause is positive mood in pre- and early perimenopause. BMI was not a significant predictor of positive mood. Smoking was not a significant predictor of positive mood.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Dennerstein, 2002a Australia	Melbourne Women's	226	Longitudinal	_	8 years	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Dennerstein, 2002a Australia		Participants included in this analysis could provide at least one measure of well-being during early menopausal transition, late transition and post-menopause. Yearly measures associated with HRT were excluded. The original longitudinal cohort of 438 had 57 drop out, 36 had surgical menopause, 5 used oral contraceptives. 226 of 340 eligible participants were included.	Questionnaires, physical exam, blood samples, telephone interview	Retention rate for longitudinal arm 88% at 8 years. Percentage of original cohort (438) used in this study 51.6%. Percentage of those eligible for this analysis 66.5%.	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Dennerstein, 2002a Australia	Well-being using Affectometer-2 symptoms demographics lifestyle factors BMI menopausal status FSH, E2, Testosterone	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Dennerstein, 2002a Australia	–	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Dennerstein, 2002a Australia	No significant change in positive mood scores with menopausal transition. Significant decrease in negative mood and significant improvement in well-being scores between early and late perimenopause and early and post-menopause.	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Dennerstein, 2002a Australia	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Dennerstein, 2002a Australia	14 predictors including baseline measures of physical and mood symptoms, lifestyle measures, and well-being	Multifactor model of well-being change during midlife - late menopausal transition model. Influence of vasomotor symptoms and vaginal dryness on well-being. Influence of hormone levels on well-being. Final model of well-being in the late menopausal transition using findings from the previous models. (Results were the same for post-menopause.) Regression analysis on change in well-being from early to late menopausal transition.	Well-being in the early menopause was the only baseline variable that influenced well-being in the late menopause. Well-being before late menopause (B 0.72, p 0.00) dysphoric symptoms (B -0.20, p 0.00) changing marital status (becoming married or taking a partner (B 0.46, p 0.02) change in satisfaction with work (B 0.63, p 0.00) experiencing a severe life event (B -0.2, p 0.03) increase of hassles (B -0.02, p 0.04). No significant effect of vasomotor symptoms, vaginal dryness, or hormones on well-being. Well-being before late menopause (B 0.63, p 0.00) changing marital status (becoming married or taking a partner (B 0.54, p 0.01) change in satisfaction with work (B 0.71, p 0.00) experiencing a severe life event (B -0.17, p 0.06) increase of hassles (B -0.03, p 0.00) Changing marital status (becoming married or taking a partner (B 0.71, p 0.00) change in satisfaction with work (B 0.80, p 0.00) experiencing a severe life event (B -0.23, p 0.03)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Dennerstein, 2002a Australia	_	As women transition from early to late perimenopause and post-menopause there is an improvement in measures of well-being. Well-being appears to be influenced by psychosocial factors.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Dennerstein, 2002b Australia	Melbourne Women's	226	Longitudinal	_	8 years	_	_	_
Freeman, 2004	Penn Ovarian Aging Study	332	Longitudinal	_	4 years	Random digit dialing to all households in Philadelphia County	African American and White women	AA 50% W 50%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Dennerstein, 2002b Australia	Year 1 - mean age of women in early menopausal transition was 49.1 years. Year 8 - mean age of postmenopausal women was 57.1 years.	Women were excluded from analysis if they dropped out, had surgical menopause, took oral contraceptives or hormones, or did not complete the sexuality measure or blood sampling. 226 of original 438 were available for analysis.	Questionnaires, physical exam, blood samples, telephone interview	88% retention at 8 years, percentage eligible for this study 51.6%.	_
Freeman, 2004	35-47	75% of eligible participants were enrolled in the full cohort (218 AA, 218 W), 353 of these provided data for this study, 332 did not have usable blood samples and were thus excluded	Questionnaire and interview	75%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Dennerstein, 2002b Australia	Personal Experiences Questionnaire (SPEQ, based on the McCoy Female Sexuality Questionnaire), Affectometer 2, FSH, E2, T (testosterone), DHEAS, SHBG (sex hormone-binding globulin, menopausal status/menstrual diaries	_	Excluded	_	_	_
Freeman, 2004	CES-D, DSM-IV criteria for MDD	Women were initially all premenopausal (n=332), by year Breakdown: Pre 227/312 Early transition 64/312 Late transition 10/312 Post 11/312	Excluded	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Dennerstein, 2002b Australia	–	–	–	–	–	–
Freeman, 2004	–	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Dennerstein, 2002b Australia	Positive and negative mood did not correlate with any of the hormone measures. Positive mood increased with age (B 0.01, p 0.042) and negative mood decreased with age (B -0.009, p 0.012).	–	–	–	–
Freeman, 2004	CES-D scores of 16 or higher incrased during the transition to menopause and were lower after menopause (p=0.047) MDD present in 10-13% of premenopausal and ≤ 4% in transition phases	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Dennerstein, 2002b Australia	42% of women in early menopausal transition at year 1 had SPEQ scores in-dicating sexual dysfunction com-pared with 88% of postmenopausal women at year 8 of follow-up.	–	–
Freeman, 2004	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Dennerstein, 2002b Australia	_	"Repeated-measures linear regression was used to model total and domain scores on SPEQ and mood scores as a function of age, log of free testosterone index, and log of free estradiol index."	**Total SPEQ score**: age (B -0.2, p 0.0) log estradiol (B 0.13, p 0.01) log free estradiol index (B 0.12, p 0.014) **Sexual responsivity**: age (B -0.07, p 0.0) log estradiol (B 0.04, p 0.052) **Frequency of sexual activities**: age (B -0.05, p 0.0) **Libido**: age (B -0.45, p 0.0) log estradiol (B 0.087, p 0.001) log free estradiol index (B 0.08, p 0.001) **No aspect of sexual functioning was correlated with any of the androgen measures.**
Freeman, 2004	Race, age, history of depression, menopausal status, severe PMS, poor sleep, not employed, hot flashes, FSH, antidepressant medications	Multivariate models of CES-D scores and MDD	**CES-D** Menopausal status (pre is reference group) Early transition OR 1.55 (CI 1.04-2.32) Late transition OR 2.89 (CI 1.29-6.45) Postmenopausal OR 0.78 (CI 0.1-6.17) Race (White is reference) AA OR 1.89 (CI 1.35-2.63) History of depression OR 2.45 (CI 1.61-3.72) **MDD** Race (White is reference) AA OR 1.52 (1.03-2.24) Menopausal status NS History of depression OR 4.75 (CI 3.17-7.13)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Dennerstein, 2002b Australia	_	"Female sexual functioning declines with the natural menopause transition." No association of androgen levels with sexual functioning. However, there was an association of decreasing estrogen levels with decline in sexual functioning.
Freeman, 2004	See Significant Predictors column	Only relevant significant predictiors listed for these models. There were other significant predictors in the models.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Glazer, 2002	Ohio	208	Cohort	Internal	27 months	Community recruitment	NR	57% White 43% African American
Gold, 2000	SWAN	12,425	Cross-sectional (baseline survey 1995-7)	N/A	N/A	_	_	AA 29.5% C 46.5 J 5.7 Chinese 4.4 H 13.8

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Glazer, 2002	40-60 (mean 48)	Reported	Kupperman Index	208 recruited 175 to 1st follow-up 165 completed	_
Gold, 2000	40-55 range %: 40-43 28.3% 44-47 31.0% 48-51 24.0% 52-55 16.7%	3640 of 16065 were excluded because 1) menses had stopped because of medication, radiotherapy, pregnancy/lactation, or extreme weight change, 2) reported use of exogenous female hormones in the past 3 months, 3) reported race/ethnicity as mixed/other.	_	77.34%	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Glazer, 2002	Coping Scale Kaufert and Syrotvik Index Hobfoll Core Evaluation Bowles Menopause Attitude Scale Depression Scale Health Promoting Activities	Pre: 38% Peri: 17% Post: 14% SMP: 33%	NR	NR	NR	NR
Gold, 2000	Yes/No questions regarding presence of vasomotor, psychological, and physical symptoms during the previous 2 weeks	Surgical 16% Postmenopausal 14.2 Late perimenopausal 4.9 Early perimenopausal 28.6 premenopausal 36.3	1988/12425 (16%)	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Glazer, 2002	Evaluated	NR	_	_	_	_
Gold, 2000	Smoking: current 23.4% past 23.3 never 53.3	_	BMI: <19 6.4% 19-26.9 42.7% 27-31.9 21.5% >=32 19.4% Compared to BMI 19-26.9, OR for hot flashes (p<0.05): 27-31.9 OR 1.15 ≥ 32 OR 1.18	By menstrual status: surgical 46.9% post 48.8% late peri 56.8% early peri 36.9% pre 19.4% Compared to premeno-pausal status (p<0.05): surgical OR 2.4 post OR 2.81 late peri OR 4.32 early peri OR 2.06	By menstrual status: surgical 19.4% post 21.2% late peri 18.2% early peri 12.9% pre 7.1% Compared to premeno-pausal status (p<0.05): surgical OR 2.39 post OR 2.57 late peri OR 2.30 early peri OR 1.77	Difficulty sleeping by menstrual status: surgical 43.5% post 40.4% late peri 43.9% early peri 40.6% pre 30.9% Compared to premeno-pausal status (p<0.05): surgical OR 1.52 post OR 1.37 late peri OR 1.48 early peri OR 1.25

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Glazer, 2002	_	_	_	NR	NR
Gold, 2000	_	Forgetfulness by menstrual status: surgical 43.8% post 42% late peri 44.8% early peri 44% pre 31.2% Compared to premeno-pausal status (p<0.05): surgical OR 1.27 post OR 1.28 late peri OR 1.43 early peri OR 1.44	Stiff/sore by menstrual status: surgical 59.4% post 54.8% late peri 58.4% early peri 57.9% pre 45.8% Compared to premeno-pausal status (p<0.05): surgical OR 1.50 post OR 1.31 late peri OR 1.48 early peri OR 1.48	Urine leakage by menstrual status: surgical 22.1% post 17.7% late peri 19.6% early peri 20.6% pre 12.3% Compared to premeno-pausal status (p<0.05): surgical OR 1.64 post OR 1.24 late peri OR 1.42 early peri OR 1.67	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Glazer, 2002	NR	NR	Menstrual irregularity and hysterectomy associated with significant level of increased anxiety in univariate analysis, but not multivariate analysis
Gold, 2000	NR	NR	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Glazer, 2002	Menopausal status included in models Education coping effectiveness of resources Attitude toward menopause Coping use Age Race Job Income Marital status Religion	Multivariate with 3 outcomes	Predictors of anxiety: Loss of resources Education level Coping effectiveness Predictors of depression: Loss of resources Education Predictors of health promoting activities: Coping effectiveness Attitude towards menopause
Gold, 2000	Age, education, employment status, difficulty paying for basics, race/ethnicity, marital status, parity, menstrual status, BMI, smoking, physical activity, study site, parity	Several multiple logistic regression models for the following symptoms: hot flashes/night sweats, urine leakage, vaginal dryness, stiff/sore, heart pounding, forgetful, difficulty sleeping.	See Table 3 p.468 (Key points) -All symptoms were more frequent in women who were not premenopausal ($p<0.05$). -Hot flashes/night sweat prevalence was associated with BMI >=27 ($p<0.05$). -Vaginal dryness was not associated with BMI. -Hot flashes were not associated with an increased BMI in late perimenopausal and postmenopausal women (data not shown). -Compared to W women, J and Chinese had decreased odds of hot flashes (OR 0.63, 0.65), AA women had increased odds (OR 1.56). H had increased odds of vaginal dryness (OR 1.85)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Glazer, 2002	_	
Gold, 2000	_	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Gracia, 2004	Penn Ovarian Aging Study	326	Cross-sectional analyses from cohort	Internal	4 years	Women in Philadephia County indentified through random digit dialing	Community-based, Philadephia	AA 48-51%
Guthrie, 1996 Australia	Melbourne Women's	453	Cross-sectional	_	3rd year of follow-up	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Gracia, 2004	35-47	Excluded: Serious illness with potential to effect hormone levels Any hormone use in past 3 months Preganancy, lactation, or use of psychotropic drugs Use of alcohol/illicit drugs in past 1 yr	Serum blood samples Questionnaires	Of 578 eligible, 75% agreed to participate. Of those participating, 326 were eligible for this analysis.	3 for medical problems, 6 for family conflicts, 5 moved, 2 deceased, 8 too busy, 26 lost to f/u, 27 had insufficient hormone measures, 3 withdrew consent, 30 gave no reason.
Guthrie, 1996 Australia	By menstrual group	Longitudinal cohort, excluded if they had undergone hysterectomy by the time of follow-up	_	_	_
	No change 50.2 Change in flow 50.1				

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Gracia, 2004	CES-D Total testosterone, DHEAS FSH, LH, E2 Libido assessed with one question "Have you experience a decrease in libido?"	Premenopausal 147 (45%) Early menopausal (variable cycle lengths) 140 (42%) Late menopausal (3-11 mo of ammenorrhea) Post-menopausal 14 (4.3%)	Excluded	Excluded	NR	Excluded
Guthrie, 1996 Australia	–	–	–	–	–	–

12%

19%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Gracia, 2004	NR	Excluded if HRT or any hormone within past 3 months	Mean BMI 28			
Guthrie, 1996 Australia	No significant difference in smoking status between women who did and did not have hot flashes for the whole cohort and by menstrual group.	_	BMI in kg/m2 did not differ across menstrual groups (p=.239) 26.6 27.4	≥ 1 in last 2 weeks by menstrual status (p<.001): post 62% peri 37% pre 13% HRT users 15% As the frequency of hot flash reporting increased the FSH levels increased and E2 levels decreased.	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Gracia, 2004					
Guthrie, 1996 Australia	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Gracia, 2004	At 4 years (6th assessment): 27% (87 of 326 women) reported a decreased in libido or sexual interest vs 73% (239) reported no change. Women with decreased libido were more likely to report vaginal dryness (38% vs 13%) and depressive symptoms (52% vs 28%)		
Guthrie, 1996 Australia	–	–	FSH, E2, and inhibin (INH) levels by menstrual group. Compared to no change group ($p<0.05$): FSH levels were higher in all groups but change in flow and change in frequency. E2 and INH were lower in both amenorrhea groups, INH was lower in HRT group. FSH 13 E2 249.3 Inhibin 187.4 FSH 13.8 E2 243.7 Inhibin 189.6

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Gracia, 2004	Variables in the model: age, BMD, race, marital status, depression (CES-D), presence of child <18 yr old at home, vaginal dryness, mean testosterone level.	multivariate models	In MV analysis, vaginal dryness was strongly associated with decreased libido (OR 3.5, CI 1.8, 6.6), as was depression (OR 3.4, CI 1.9, 6.1) Depression remained a significant predictor of decreased libido eeven after excluding women on anti-depressants Fluctuation in testosterone was associated with decreased libido Overal levels of testostertone and DHEAS were no different between those with decrease in libido and those with no change. Fluctuation of other hormones was not relatex to libido. Age, BMI and Causasian race were not associated with decreased libido.
Guthrie, 1996 Australia	Hormonal, physical, and lifestyle variables	Effect of variables on presence of vasomotor symptoms multiple linear logistic regression conducted in peri- and post-menopausal women.	Peri: premenstrual complaints 1.42 (1.04-1.93) FSH 1.71 (1.15-2.55) Estradiol NS Post: premenstrual complaints NS FSH NS Estradiol NS

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Gracia, 2004	Significant predictors of decreased libido were: Having children < age 18 at home OR 1.4 (CI 1.1, 1.7), p=0.014 Depression OR 3.4 (1.9, 6.1), p<0.0001 Vaginal dryness OR 3.5 (1.8, 6.6), p<0.0001 Degreee of testosterone fluctuation was divided into quartiles. All quartiles	No results for hormone levels or libido by menoapusal status. No adjustment for menopausal status in the MV analysis.
Guthrie, 1996 Australia	–	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Guthrie, 1996 Australia (continued)								

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Guthrie, 1996 Australia (continued)	Change in frequency 59.8 Change in flow and frequency 51.2 Amenorrhea >3<12 months 52.4 Amenorrhea >12 months 53.7 Hormone therapy 52.7				

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Guthrie, 1996 Australia (continued)		6%				
		20%				
		15%				
		15%				
		24%				

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Guthrie, 1996 Australia (continued)			25.6			
			25.9			
			26.7			
			26.2			
			25.3			

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Guthrie, 1996 Australia (continued)					

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Guthrie, 1996 Australia (continued)			FSH 19.7 E2 196.8 Inhibin 170.2 FSH 19.5 E2 256.9 Inhibin 165.2 FSH 69.2 E2 81.4 Inhibin 98.9 FSH 93.9 E2 37.9 Inhibin 76.2 FSH 26 E2 357.4 Inhibin 89.5

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Guthrie, 1996 Australia (continued)			

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Guthrie, 1996 Australia (continued)		

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Hallstrom, 1985 Sweden	Gothenburg	899	Cohort	Internal	6 years	Systematic sampling of Gothenburg Sweden population using Taxation Office Register. Sampling methods described elsewhere. Unclear in this paper how the "psychiatric population" was selected from the larger sample	_	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Hallstrom, 1985 Sweden	38-60	_	_	899 participated in the first wave, of these 800 were examined. Of those 800 677 (84.6%) were examined in the second wave	12 died, 30 moved or could not be reached, 81 refused.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Hallstrom, 1985 Sweden	<age 38 considered pre-climacteric age>44 and regularly menstruating= premenopausal irregular menstruations=perimenopausal amenorrhea for 12-35 months=early menopause amenorrhea for 36 months=post-menopause. Global assessment of functioning, disability grade, diagnostic interview for diagnoses of major depression, anxiety states, neurastenic state, phobic disorder, obsessive compulsive disorder, psychoses, alcoholism.	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Hallstrom, 1985 Sweden	–	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Hallstrom, 1985 Sweden	Cross-sectional data at baseline: Major depression N=55 (6.9%) anxiety N=18 (2.3%) Neurasthenic state N=14 (1.8%) Phobic disorder N=10 (1.3%) Obsessive compulsive disorder N=2 (0.3%) Pyschosis N=4 (0.5%) Alcoholism N=2 (0.3%) 1 year onset rate of any psychiatric symptoms: Pre climacteric: N=78 (15.5%) age <38 Pre menopause: N=190 (37.8%) Peri: N=126 (25.1%) Early Post menopasue: N=54 (10.8%) (12-35 months after menopause) Late postmenopause: N=54 (10.8%) (menopause > 3 years ago)	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Hallstrom, 1985 Sweden	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Hallstrom, 1985 Sweden	_	No MV modeling	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Hallstrom, 1985 Sweden	_	Proportion of women developing a mental disorder within one year after the menopause compared with the proportion of women developing a mental disorder without life events one year before: 9 (15.8%) after menopause vs. 15 (12.8%) prior to menopause and without a life event (NS by Fisher's exact). Lumped all mental disorders together.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Hardy, 2002 Britain	Medical Research Council (MRC) National Survey for Health and Development	1572	Cohort	Internal	52 years	Socially stratified sample of all births in March 1943 in Britain	Socially stratified birth cohort in Britain, those interviewed in 1993 (age 43) were representative of the native population of that age.	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Hardy, 2002 Britain	52	_	_	2548 women enrolled at birth (March1946). 1778 still in contact as of 1993. 1572 women returned at least one questionnaire (84-90% RR) over the next 4 years for this study.	232 living abroad; 296 refused to participate; 88 could not be located; 154 had died as of 1993.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Hardy, 2002 Britain	Checklist of 20 health problems (1-4 for each symptom)	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Hardy, 2002 Britain	_	_	_	Vasomotor symptom score: Peri-peri: 12.31 (10.44, 14.18) Post-post: 0.29 (-1.55, 2.12) Hysterectomy-hysterectomy: 3.46 (1.72, 5.19) HRT-HRT: -2.93 (-4.6, -1.26) Pre-peri: 8.44 (6.11, 10.79) Vasomotor change in % score: Pre-post: 17.3 (6.33, 29.13) Pre-HRT: 19.25 (12.96, 25.52) Pre-hysterectomy: 9.87 (-0.37, 20.10) Pre-Peri: 8.44 (6.11, 10.76) Post-Post: 0.29 (-1.55, 2.12)	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Hardy, 2002 Britain	Psychological change score: Pre-post: 4.74 (-1.74, 11.23) Pre-HRT: 6.4 (2.12, 10.69) Peri-HRT: 4.38 (1.54, 7.21) Pot-post: -0.12 (-1.40, 1.15) Peri-Hysterectomy: -1.12 (-8.36, 6.15) Peri-Post: 1.58 (-0.65, 3.81) Peri-peri: 0.98 (-0.30, 2.26) Hysterectomy-hysterectomy: 0.41 (-0.75, 1.57) Pre-peri: 1.57 (-0.15, 3.29) Pre-hysterectomy: 2.43 (-4.78, 9.63)	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Hardy, 2002 Britain	–	–	Found the largest change in percentage vasomotor symptom score between women who were premenopausal and became postmenopausal (17.73) and those who were premenopausal and started HRT (19.25). Change scores were high among those who were peri-menopausal and remained peri-menopausal after 6 years (12.31). Those who were post-menopausal and remained post-menopausal had the lowest change score (0.29). Change in percentage psychological symptom score was highest among those women who were premenopausal and became post-menopausal (4.74); those who were pre-menopausal and went on HRT (6.4), and those who were peri-menopausal and went on HRT (4.38). Lowest psychological change scores were found in those who were post- and remained post (-0.12) and those who

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Hardy, 2002 Britain	_	MV models adjusted for prior psychological status and personality (neuroticism score at age 16, present state examination (PSE) for anxiety and depression at age 36), health related behaviors, socio-economic status (highest education, job held at age 43), attitude to menopause, smoking, BMI at age 36, age and baseline score.	Change in menopausal status. Change in work stress. Change in family stress. (true for both HR and psychological outcomes)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Hardy, 2002 Britain	_	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Hunter, 1989 London	None	682	Cross-sectional	_	_	Newspaper ads, radio program, volunteers for ovarian cancer screening	Women aged 45-65 years predominantly from London and South-East England	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Hunter, 1989 London	52.3 (45-65)	Excluded: Women receiving estrogen therapy, women who had undergone hysterectomy	Questionnaires	78% (850/1090) to initial postal survey, 62.6% after exclusions	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Hunter, 1989 London	"Women's Health Questionnaire" developed by the authors Pilowsky Hypochondriasis Questionnaire General Health Questionnaire	Premenopausal 18% Perimenopausal 26% Postmenopausal 56%	Excluded	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Hunter, 1989 London	_	_	_	Vasomotor symptoms increased with menopausal status. 55% of peri- and postmenopausal vs. 15% premenopausal women (p<0.000).	Vaginal dryness increased with menopausal status. 25% of pre- and perimenopausal vs. 45% postmenopausal women (p NR).	Sleep problems increased with menopausal status (p <0.005) even when controlling for age.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Hunter, 1989 London	Depressed Mood category of symptoms increased with transition to peri- and post-menopause (p<0.002) but there were only two items in this group that increased significantly "lack of enjoyment" and "no feelings of well-being, reported by 5% of premenopausal and 15% of peri- and postmenopausal women.	No significant difference by menopausal status.	No significant difference by menopausal status.	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Hunter, 1989 London	Sexual problems increased with menopausal status ($p<0.04$). Sexual interest decreased significantly in peri- and post-menopausal women even when controlling for age. Sexual satisfaction did not change with menopausal status.	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Hunter, 1989 London	Menopausal status, age, reported current illness, marital status, social class, employment status (only 45-54 year olds included).	Multiple regression for each factor score (symptom group)	Symptoms groups with menopausal status as a significant predictor ($p<0.05$). **Depressed Mood**: menopausal status **Somatic symptoms**: menopausal status **Vasomotor symptoms**: menopausal status **Sexual problems**: menopausal status **Sleep problems**: menopausal status Menopausal status was not a significant predictor for cognitive difficulties and anxiety/fears.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Hunter, 1989 London		Factor analysis done prior to use of scores for ANCOVA and regression analysis.
	B 0.17	
	B 0.17	
	B 0.29	
	B 0.16	
	B 0.11	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Kaufert, 1992	Manitoba	469	Cross-sectional and longitudional	_	3 years	Mail survey of women from general population of Manitoba, Canada Age 40-59 years	Manitoba, Canada	NR
Koch, 1995	University of Minnesota and Tremin Trust Longitudinal Study	391	Cross-sectional from cohort	Internal	Preva-lence	College class	852 eligible participants from college class of 1963 and the Tremin Trust Longitudinal Study 505 surveys returned 391 eligible	99% White

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Kaufert, 1992	45-55 (mean 48.4)	Inclusion: menstruated in the last 3 months, or had previously had a hysterectomy, age 45 or older	Mail and telephone surveys	68% to mail survey 87% of those eligible for longitudional follow up agreed to participate	_
Koch, 1995	Mean 46	Specified	Survey		_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Kaufert, 1992	CES-D Modified Worsley's 'Role Problem Checklist' Questions regarding recent life events, menses, 4 health conditions (arthritis, allergies, high blood pressure, thyroid problems), and present state of health (good, fair, or poor)	_	136 (no differentiation by oophorectomy status)	NR	NR	NR
Koch, 1995	Survey	Excluded	NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Kaufert, 1992	_	_	_	_	_	_
Koch, 1995	NR	NR	24% reported Significantly related to age and menopausal status	36% in perimenopausal group	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Kaufert, 1992	Depression 26% of all women were depressed at one interview or another. Across all 5 interviews, the percentage of women with CES-D $\geq$ 16 was 9-11%. All depression data was collapsed across the 5 interviews to look at the association between depression and transition from one menopausal status to another. A woman's menopausal status does not significantly alter the likelihood of her becoming depressed (hysterectomized women excluded). Hysterectomized women who were not depressed at baseline were more likely than women in any other menopausal category to become depressed (OR 1.7, CI 1.15, 2.6).	–	–	–	–
Koch, 1995	NR	NR	NR	NR	46% noted change in prior year

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Kaufert, 1992	_	_	_
Koch, 1995	NR	NR	Age Marital status Menopausal status Vaginal dryness Hot flashes

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Kaufert, 1992	_	_	_
Koch, 1995	Change in desire, marital status, vaginal dryness, enjoyment with partner, age. Menopausal status not related to reduced desire, reduced orgasm, or less	Logistic regression	Only Betas and x^2 reported for each predictor variable

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Kaufert, 1992	_	_
Koch, 1995	_	Premenopausal: 21% Perimenopausal: 79%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Koster, 1993a	Copenhagen	621	Cross-sectional from cohort	Internal	4 years	NR	Danish women born in 1936, from 4 municipalities in Copenhagen	100% Danish
Koster, 1993b	Copenhagen	621	Cross-sectional from cohort	Internal	11 years	NR	Danish women born in 1936, from 4 municipalities in Copenhagen	100% Danish

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Koster, 1993a	51 year olds	Inclusion: In 1976, all 40 year old women born in 1936, resident in 4 municipalitites in Copenhagen, in good general health	Questionnaire	526 (88%)	By 1987, 22 died, 2 emigrated (n=597) from original cohort 526 usable questionnaires returned
Koster, 1993b	40-51 year olds	Inclusion: In 1976, all 40 year old women born in 1936, resident in 4 municipalitites in Copenhagen, in good general health	Questionnaire and interview	NR	474 (76%) of original cohort in this study

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Koster, 1993a	Postal questionniare and telephone contact	**In 1987** Pre 47 (9%) Peri 91 (7%) Post 129 (25%) HRT 175 (33%) SM 84 (16%) **In 1986** Pre 66 (13%) Peri 121 (23%) Post 93 (18%) HRT 163 (31%) SM 83 (16%) **In 1985** Pre 135 (26%) Peri 95 (18%) Post 129 (25%) HRT 144 (27%) SM 81 (15%) **In 1984** Pre 205 (39%) Peri 67 (13%) Post 51 (10%) HRT 125 (24%) SM 78 (15%)	Examined	_	_	_
Koster, 1993b	Questionnaire, interview, clinical assessment from a trained psychiatrist using diagnostic criteria developed by Bollerup for The Glostrup Population Studies (psychological health status), criteria from The Danish National Institute of Scoial Research (social status)	See Koster 1993	Examined	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Koster, 1993a	_	Excluded	_	Increased prevalence within groups Pre to peri: beta 0.81 (p<0.0001) OR 2.24 (1.90-2.64) Peri to post: beta 0.41 (p<0.0001) OR 1.51 (1.25-1.81)	_	_
Koster, 1993b	_	Excluded	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Koster, 1993a	Increased prevalence of moodiness within groups Pre to peri: beta 0.17 (p<0.017) OR 1.19 (1.03-1.37)	_	Increased prevalence of fatigue within groups Pre to peri: beta 0.24 (0.004) OR 1.27 (1.08-1.49) Peri-post: beta 0.21 (p<0.041) OR 1.23 (1.01-1.50)	_	_
Koster, 1993b	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Koster, 1993a	_	_	_
Koster, 1993b	Anticipation of decreased sexuality at 40 years was only significant predictor of decreased sexual desire ($p<0.01$) at 51 years.	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Koster, 1993a	Not significant: Headache, depression, moodiness from peri - post menopausal status	Logistic regression models	_
Koster, 1993b	Not significant: Social background (education, marital, and social status), life-style (smoking, alcohol-intake, physical fitness)	Multiple logistic regression models	Age Marital status Emplyment status Social status

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Koster, 1993a	OR (see symtom columns)	Prevalence data reported.
Koster, 1993b		

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Koster, 2002 Denmark	Copenhagen	621 invited 548 initially enrolled	Cross-sectional	Internal	20 years	NR	Women in Denmark Age 40 in 1976	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Koster, 2002 Denmark	40 at baseline	NR	Survey Telephone questionnaires or personal interview	65-88%	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Koster, 2002 Denmark	Survey evaluating sociodemographic, attitudes, symptoms, general health, sexualty, body image, medication, life events, aging.		Assessed by numbers NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Koster, 2002 Denmark	Assessed (see measures used column)	NR	NR	Prevalence by age (%): 40: NR 45: NR 51: 56 60: 29 Prevalence by menopausal status (%): Pre: 31 Peri: 46 Post: 68 HRT: 56 Surgical menopause: 61	NR	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Koster, 2002 Denmark	Depression by age (%): 40: NR 45: NR 51: 18 60: 20 Depression by menopausal status (%): Pre: 12 Peri: 21 Post: 16 HRT: 28 Surgical menopause: 38 Moodiness by age (%): 51: 28 60: 31 Moodiness by menopausal status (%): Pre: 33 Peri: 34 Post: 32 HRT: 49 Surgical menopause: 60	_	Headache by age (%): 40: 56 51: 49 60: 38 Headache by menopausal status (%): Pre: 44 Peri: 49 Post: 38 HRT: 56 Surgical menopause: 61 Fatigue by age (%): 41: 41 51: 34 60: 29 Fatigue by menopausal status (%): Pre: 21 Peri: 30 Post: 26 HRT: 35 Surgical menopause: 56	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Koster, 2002 Denmark	Decreased sexuality by age (%): 51: 37 60: 67	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Koster, 2002 Denmark	Strongest predictor of woman's menopause experience was prior health. Sexuality depended on prior sexual experiences. No association between menopausal/peri-menopausal and depression/moodiness, but hot flashes and fatigue correlated with transition. Also, hot flashes with fatigue associated with various psychosocial factors, which explained much variation in symptoms.	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Koster, 2002 Denmark	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Kravitz, 2003	SWAN	12,603	Cross-sectional	Internal	N/A	Random digit dialing	Random selection of women from multiple sites (Los Angeles, Pittsburgh, Newark, Boston, Chicago, Detroit, and Oakland)	W=6,304 AA=3,464 Chinese=573 Japanese=606 Hispanic=1,656

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Kravitz, 2003	40-44 (N=4,233) 45-49 (N=4,600) 50-55 (N=3,770)	_	Self report questionnaires and interviews	81%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Kravitz, 2003	12-item symptom questionnaire	Pre=4,425 Early peri=3,521 Late peri=607 Natural post=1,739 Surgical post=701 Post on HRT=1,610	701/12,603	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Kravitz, 2003	NR	NR	NR	_	_	Overall prevalance of sleep difficulty=38% Most prevalent in surgical post=48% Least prevalent in pre=31% Caucasian (40%) and Hispanic (38%) women reported highest rates of sleep difficulty.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Kravitz, 2003	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Kravitz, 2003	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Kravitz, 2003	Ethnicity and age	Bivariate associations bewtween each covariate and sleep difficulty were examined using X^2 tests. Multivariate associations ere examined using a multiple logistic regression.	Ethnicity Age

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Kravitz, 2003	Surgical post = 1.55 (1.25-1.92) Late peri = 1.33 (1.07-1.65) Natural post = 1.21 (1.03-1.43) Post on HRT = 1.12 (0.95-1.31) Early peri = 1.11 (0.99-1.24) Pre = 1.00	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Kuh, 1997 Britain	Medical Research Council (MRC)	1498 (84% of those who were sent the question-naire)	Cross-sectional	Internal	N/A	National prospective birth cohort in England, Scotland and Wales	Socially stratified birth cohort in Britain, those interviewed in 1993 (age 43) were representative of the native population of that age.	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Kuh, 1997 Britain	NR	_	Mailed questionnaire	84%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Kuh, 1997 Britain	Symptom checklist	All women in study (all age 47)	215 (14.3%) salpingo hysterectomy, analyzed separately	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Kuh, 1997 Britain	NR	172 (11.4%) on HRT, analyzed separately	NR	Hot flashes (n=1465): bothered a lot: 7% bothered a little: 24.4% none or not bothered: 68.7% Cold/night sweats (n=1454): bothered a lot: 6.2% bothered a little: 20.0% none/not bothered:73.8%	Vaginal Dryness (n=1399): bothered a lot: 4.2% bothered a little 15.7% none or not bothered 80.1%	Trouble sleeping: bothered a lot: 13.7% bothered a little 35.7% none/not bothered 50.5%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Kuh, 1997 Britain	Anxiety or depression (n=1427): bothered a lot:16.8% bothered a little: 36.0% none/not bothered:50.5% irritability (n=1419): bothered a lot:14.6% bothered a little: 40.2% none/not bothered: 45.2% tearfulness (n=1414) bothered a lot:11.7% bothered a little:30.1% none/not botherred:58.1% feelings of panic (1392): bothered a lot: 7.2% bothered a little: 17.2% none/not bothered: 75.6%	Forgetfulness: bothered a lot: 13.1% bothered a little: 31.2% none/not bothered: 55.7%	Aches and pains (n=1422): bothered a lot:17.1% bothered a little: 42.5% none/not bothered: 39.7% severe headaches (n=1413): bothered a lot: 10.9% bothered a little: 20.9% none/not bothered: 68.2% breast tenderness (n=1422): bothered a lot: 10.1% bothered a little:33.4% none/not bothered: 56.5% palpitations (1406): bothered a lot: 6.3% bothered a little:22.4% none/not bothered: 71.3% pins and needles (n=1399): bothered a lot: 5.4% bothered a little:20.2%	Urinary frequency (n=1410): bothered a lot:7.9% bothered a little:18.6% none/not bothered: 73.5%	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Kuh, 1997 Britain	Difficulties with intercourse (n=1381): bothered a lot: 3.9% bothered a little: 9.1% none/not bothered: 87.0%	NR	Skin crawling sensations (n=1383): bothered a lot: 3.3% bothered a little: 11.1% none/not botherred:85.5% skin wrinkling (n=1389) bothered a lot: 3.3% bothered a little:15.5% none/not bothered: 81.6% hair loss (1383): bothered a lot: 2.1% bothered a little:5.9% none/not botherred:92.0%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Kuh, 1997 Britain	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Kuh, 1997 Britain	_	Women were all aged 47 years; anxiety and depression (assessed by PSE), and health status was assessed at age 36.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Kuh, 1997 Britain (continued)	_	_	_	_	_	_	_	_
Kuh, 1997 Britain (continued)	_	_	_	_	_	_	_	_
Kuh, 1997 Britain (continued)	_	_	_	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Kuh, 1997 Britain (continued)	–	–	–	–	–
Kuh, 1997 Britain (continued)	–	–	–	–	–
Kuh, 1997 Britain (continued)	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Kuh, 1997 Britain (continued)	_	Premenopausal women	_	_	_	_
Kuh, 1997 Britain (continued)	_	_	_	_	_	_
Kuh, 1997 Britain (continued)	_	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Kuh, 1997 Britain (continued)	_	_	_	Bothered by hot flashes (p≤0.001): pre: 17% peri: 40% post: 60% HRT: 40%** hysterectomy:42%** bothered by cold/night sweats (p<0.001) pre: 16% peri: 32% post: 45% HRT: 34%** hysterectomy: 36%**	_	_
Kuh, 1997 Britain (continued)	_	_	_	_	Bothered by vaginal dryness (p<0.01) pre: 11% peri:25% post:35% HRT:25% hysterectomy: 28%	_
Kuh, 1997 Britain (continued)	_	_	_	_	_	Difficulty sleeping (p<0.001) pre: 40% peri:50% post:63% HRT:61% hysterectomy:64%

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Kuh, 1997 Britain (continued)	–	–	–	–	–
Kuh, 1997 Britain (continued)	–	–	–	–	–
Kuh, 1997 Britain (continued)	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Kuh, 1997 Britain (continued)	–	–	–
Kuh, 1997 Britain (continued)	Difficulties with intercourse (bothered a little or a lot, p<0.001) pre: 8% peri: 13% post: 24% HRT:19% hysterectomy: 19%	–	–
Kuh, 1997 Britain (continued)	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Kuh, 1997 Britain (continued)	_	Logistic regression models to predict bothered a little/lot adjusting for menopausal status, life stress at age 36, physical and emotional health at age 36, smoking behavior in earlier adult life, educational background.	For vasomotor symptoms: significant predictors included menopausal status, educational qualifications, work stress worse in past 12 months, smoking at any time in past, 3+health problems at age 36. Stress in family life was not a significant predictor.
Kuh, 1997 Britain (continued)	_	_	Significant predictors include: menopausal status, work stress and previous history of 2+health problems at age 36. Not significant were: education, smoking, anxiety/depression in past, family life stress.
Kuh, 1997 Britain (continued)	_	_	Significant predictors: menopausal status, current stress at home and at work, poorer physical and emotional health at age 36.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Kuh, 1997 Britain (continued)	Adjust OR for vasomotor symptoms (post compared to pre)=4.7 (95%CI 2.6, 8.5). Other groups: peri 2.5**, hysterectomy 2.5**, HRT 3.4** compared to pre.	** data approximated from histogram or OR figure, referred to generally in text.
Kuh, 1997 Britain (continued)	Adjusted OR for sexual dysfunction (combines vaginal dryness and difficulties with intercourse=~4**; Also increased were OR for peri (2.2)**, hysterectomy (3.2)**, and HRT (2.4)**	** data approximated from figure showing Ors for groups. Referred to in text as "almost fourfold increase post vs. pre.
Kuh, 1997 Britain (continued)	Adjusted OR for trouble sleeping: post=3.4 (95% CI 1.9, 6.2); peri =1.5 (95% CI 1.1-02.0); hysterectomy 2.6 (95% CI 1.8, 3.7); and hysterectomy 2.3 (95% CI 1.5, 3.4) compared to pre.	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Kuh, 1999 Britain	MRC	1378	Cross-sectional from cohort	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Kuh, 1999 Britain	48 years	All women with whom the investigators were still in contact from the original cohort of 2548 women	Postal questionnaire sent to 1486 women when they were 48 years old	93% to questionnaire	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Kuh, 1999 Britain	Questionnaire regarding incontinence (incont) symptoms (no statement of questionnaire validation)	Stress incont symptoms by menopausal status: Pre 49.8% Peri 52.7% Post 36.3 % Hyst 53.7% HRT 47.9% Urge incont symptoms by menopausal status Pre 18.1% Peri 23.8% Post 18.6% Hyst 28.8% HRT 21.0% Severe incont symptoms by menopausal status Pre 7.3% Peri 6.0% Post 9.8% Hyst 9.8% HRT 5.0%	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Kuh, 1999 Britain	–	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Kuh, 1999 Britain	–	–	–	55% in the cohort reported incontinence, see menopausal status for breakdown by group, odds of stress symptoms were lower in the postmenopausal versus not menopausal group (OR 0.57, CI 0.33-0.95), no association of urge symptoms or severe incontinence with menopausal status	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Kuh, 1999 Britain	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Kuh, 1999 Britain	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Kuh, 1999 Britain	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Kuh, 2002 Britain	Medical Research Council (MRC) National Survey of Health & Development	2547 women in initial cohort. 1023 were available and completed all six questionnaires between 1993-1998	Cohort with Cross-sectional data	Internal	_	All births to non-manual and agricultural workers and one in four births to manual workers in the 2nd week of march 1946.	Britain, Scotland, Wales	_
Maartens, 2001 Netherlands	Eindhoven	2450	Cohort	Internal	_	Invitation, method NR	All women living in Eindhoven responding to screening recruitment age 46-53 at baseline (n=8503; 6648 agreed to participate)	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Kuh, 2002 Britain	52	_	Mailed questionnaires	_	_
Maartens, 2001 Netherlands	46-53	Inclusion: 1. Dutch, Caucasian women 2. Natural menopause 3. No HRT Exclusion: 1. Women with hysterectomy or bilateral oophorectomy 2. HRT without surgical menopause 3. Non-compliance with questionnaire	Questionnaires	2450 responded and eligible	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Kuh, 2002 Britain	_	Pre 272 Peri 309 Post 208 Hysterectomy 240 HRT 255	240/1284	NR	NR	NR
Maartens, 2001 Netherlands	Population Survey	_	Excluded	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Kuh, 2002 Britain	_	HRT users 255/1284	NR	_	_	_
Maartens, 2001 Netherlands	NR	NR	NR	Prevalence HF OR 5.9 comparing pre to peri menopausal status and OR 1.9 comparing peri to post menopausal status and OR 13.4 comparing pre to post menopausal status	Prevalence peri vs. post OR 1.6	Prevalence peri vs. post OR 1.3 (insomnia)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Kuh, 2002 Britain	–	–	–	–	–
Maartens, 2001 Netherlands	Multivariate adjusted OR for change (increase) in depression score Transition: Pre to peri: not significant Pre to post: 0.57 (statistically significant)	No statistical difference	No statistical difference	No urinary symptoms by stage	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Kuh, 2002 Britain	–	–	–
Maartens, 2001 Netherlands	Pain with intercourse: Pre-peri: not significant Peri-post: 1.86 (statistically significant) Pre-post: 2.13	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Kuh, 2002 Britain	_	_	Menopausal status was not a significant predictor of psychological stress in multivariate modeling, adjusting for child and adult behavioral and psychological factors.
Maartens, 2001 Netherlands	Physical symptoms Demographic Cognitive/Mental Symptoms	Chi square Logistic regression	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Kuh, 2002 Britain	Age adjusted OR for psychological symptom score: "Women reporting higher levels of psychological symptoms in midlife were much more likely than their less symptomatic peers to have had health problems previously during their adult life. There was no variation in psychological symptoms according to menopausal stage but HRT users had a higher level of (psychological) symptoms." OR shown on Table 3, all cross 1 except OR for HRT users (Regression Coefficient=0.44 (0.20, 0.69)	Tables report regression coefficients rather than OR.
Maartens, 2001 Netherlands	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Maartens, 2002 Netherlands	Eindhoven	6648	Prevalence and prospective cohort	Internal	5 years	Invitation to all women in Eindhoven of which 6648 (78%) participated	All women living in Eindhoven responding to screening recruitment age 46-53 at baseline (n=8503; 6648 agreed to participate)	White
McKinlay, 1987	Massachu-sett's Women's Health Study	2500	Cross-sectional analyses from cohort	Internal	27 months	Random sample of 8,050 women ages 45-55 in Massachusetts; 2,500 identified as premenopausal. 77% RR	Population based recruitment of premenopausal women	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Maartens, 2002 Netherlands	46-53	Inclusion: 1. Dutch, Caucasian women 2. Natural menopause 3. No HRT Exclusion: 1. Women with hysterectomy or bilateral oophorectomy 2. HRT without surgical menopause 3. Non-compliance with questionnaire	Questionnaire	Prevalence: 78% Follow-up of 2748 with natural menopause and no HRT: 76% 2103 (76%) participated	_
McKinlay, 1987	_	_	CES-D given once during 1st 27 months; combined into single cross sectional data set "after determining that depression scores did not depend on the follow-up in which the CES-D scale was administered.	77%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Maartens, 2002 Netherlands	Mailed Edinburgh depression scale Gynecologic history General medical history Demographic data	_	Excluded	NR	NR	NR
McKinlay, 1987	CES-D	_	_	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Maartens, 2002 Netherlands	Evaluated	Evaluated	NR	NR	NR	NR
McKinlay, 1987	_	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Maartens, 2002 Netherlands	Prevalence depression at baseline Mean Score: pre - 5.6 per - 6.5 post - 7.8 Prevalence depresssion at follow-up pre - 6.8 per - 7.0 post - 7.8	NR	NR	NR	NR
McKinlay, 1987	Percentage of women with CES-D score≥16 (estimated from figure 1): pre: 7.5% (n=527) peri: 10.5% (n=1632) natural menopause: 8% (n=262) surgical menopause 18% (n=78)	_	Women reporting ≥ 2 physical symptoms are about 4 times as likely to be depressed as women reporting ≤ 1 symptom (15.7% vs. 4.3%).	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Maartens, 2002 Netherlands	NR	NR	_
McKinlay, 1987	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Maartens, 2002 Netherlands	Demographic Major life events Prior episodes depression Time between baseline and follow-up exam	T tests for change	Multivariate adjusted OR for depression: Transition peri-post 1.8 (1.3-2.6) Transition pre-peri 1.8 (1.10-3.3) Prior depression 2.2 (1.6-3.0) Unemployment 2.4 (1.2-4.6) Death of partner 2.4 (1.1-5.6) Financial problems 3.4 (1.5-7.8)
McKinlay, 1987	1. sociodemographic variables: marital status, education, age, employment status, total number of persons in household 2. health status: self-assesssed health, physical symptoms, restricted activity and chronic conditions. 3. utilization behavior: formal and informal health resources, lay consultations, medication use	Logistic regression with CES-D $\geq$16 as outcome	Education and marital status were significantly associated with a CES-D score of $\geq$16; personal stress caused by others (person-induced worry); number of health problems; use of tranquilizer medications

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Maartens, 2002 Netherlands	_	Not adjusted for sleep disturbance
McKinlay, 1987	Not given. RR presented for each of the significant variables in predictor model.	"menstrual change associated with the menopause appears to have no significant effect on depression … those with a recent surgical menopause were the most depressed group."

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
McKinlay, 1989	Massachu-sett's Women's Health Study	2,466	Cross-sectional and prospective cohort	Internal	4.5 years	Random sample	8051 women in the Commonwealth of Massachusetts born 1926-1936.	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
McKinlay, 1989	45-55 in 1982	A cohort of premenopausal women was chosen from the entire sample of women (8050)	Questionnaires	77% to initial survey, 85% overall in follow-up	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
McKinlay, 1989 CES-D		Change in menstrual status over 3 years of follow-up (T0-T3, n=2466): menses in 3 months prior to T3 42.9% menses changed to irregular 16.9% amenorrhea < 12 months 15.5% amenorrhea ≥ 12 months 20.4% Surgical menopause 4.4%	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
McKinlay, 1989	_	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
McKinlay, 1989	CES-D score related cross-sectionally to menstrual status reveals women who have undergone surgical menopause in previous 3 months were twice as likely as the rest of the cohort to have CES-D scores ≥16 (19% v 10%).	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
McKinlay, 1989	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
McKinlay, 1989	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
McKinlay, 1989	_	"Change in menstrual status associated with the menopause appears to have no significant effect on depression, as defined by a CES-D score of 16 or greater." (Minimal data available for this finding.) Some data reported in this study is the same as that reported in McKinlay, 1992

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
McKinlay, 1992	Massachu-sett's Women's Health Study	2,570	Longitudinal and cross-sectional analysis of cohort data	Internal	5 years	Random sample of 8,050 women ages 45-55 in Massachusetts, derived from census lists. Of these, 2,570 were identified as having menstruated in the past 3 months, having a uterus and > one ovary	8050 women in the Commonwealth of Massachusetts born 1926-1936.	NR
Milsom, 1993	Goteberg, Sweden	7,459	Cross-sectional	_	_	Random sampling of population register	Birth cohorts of 1900, 1905, 1910, 1915, 1920, 1930, 1940 from Sweden	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
McKinlay, 1992	45-55 in 1982	Premenopausal women selected from initial sample of 8,050	Questionnaires or telephone interviews if questionnaires not received.	77% of 8,050 responded. Had 94-99% retention of the 2,570 premenopausal cohort	_
Milsom, 1993	46-86	_	Questionnaire regarding urinary incontinence	74.60%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
McKinlay, 1992	Symptoms checklist (any in past 2 weeks): hot flashes, cold sweats, vertigo, feeling blue or depressed, headaches, insomnia, palpitations, lack of energy, diarrhea and/or constipation, persistent cough, backaches, upset stomach, aches/stiffness in joints, shortness of breath, sore throat, loss of appetite, menstrual problems, fluid retention, difficulty in concentrating, nervous tension, urinary tract/bladder infections and "pins and needles" in hand or feet.	_	Excluded	Excluded	NR	NR
Milsom, 1993	_	_	Hysterectomy was associated with increased risk of incontinence in the whole cohort, but not within the individual age	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
McKinlay, 1992	33.5% of premenopausal cohort (n=1178) were current smokers	1% of premenopausal cohort (n=1178) were using HRT	NR	13.4% of premenopausal cohort had HF (n=1178) at baseline. For women 27 mo prior to perimenopause: 10% had HFs; Following the cessation of menses 50% have HF; 4yrs post-menopause 20% have HF.	NR	NR except in aggregate with all symptoms
Milsom, 1993	_	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
McKinlay, 1992	NR	NR	NR	NR	NR
Milsom, 1993	–	–	–	Menopausal status was not associated with incontinence (postmenopausal versus premenopausal)	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
McKinlay, 1992	NR	NR	Lumped HF, sweats and insomnia into "menopausal symptoms," and all other symptoms into non-menopausal symptoms: found that at Time 6, the following proportions of women report both types of symptoms: pre - 27% peri - 46.3% post - 37.7% "Women who were perimenopausal for only one contact were consistently less likely to report hot flashes before, during and after the menopause than were women with a longer perimenopause. Women with short or no perimenopause: 39% had HF vs. remainder of women 51% of whom had HF
Milsom, 1993	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
McKinlay, 1992	_	_	_
Milsom, 1993	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
McKinlay, 1992	_	
Milsom, 1993	_	Prevalence data is by birth cohort, not by menopausal status.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Mishra, 2003 Australia	Australian Longitudinal Study on Women's Health	8,623	Cohort	Internal	2 years	Mailed questionnaires	Random selection of Australian women aged 45-50 in 1996 who completed questionnaires in 1996 and 1998	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Mishra, 2003 Australia	Mean age at baseline 47.7	Exclusions: 1. Women salpingo hysterectomy or oophorectomy (n=3014)	Survey 1996 and 1998, mail (long version, n=11,637) and phone (shorter for those who couldn't/didn't complete the mailed version, n=691)	90.4% response rate for those who were alive at the time of the second survey.	6.9% did not return the survey, 1.5% declined participation at follow-up, 1.1% withdrew from the study.

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Mishra, 2003 Australia	SF-36 scores	Defined on the basis of self-reported bleeding history. Pre: bleeding in last 12 months and with same frequency as in the previous year (55.1% at BL). Peri: bleeding in last 12 months but not in last 3 months (25.4% at BL) Post: no bleeding in past 12 months (7.0% at BL) HRT: on HRT (12.1% at BL; 20.2 at 2 years)	Excluded	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Mishra, 2003 Australia	Current smoking pre: 12.5% peri: 17.9% post: 23.1% HRT: 20.6% (p<0.0001)	NR	Similar body weights among groups. Proportion overweight or obese: pre: 42.4% peri: 45.6% post: 43.6% HRT: 44.7%	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Mishra, 2003 Australia	Adjusted mean score (s.e.) for "general mental health" from the SF-36 at baseline pre: 73.4 (0.5) peri: 70.7 (0.6)* post: 71.0 (0.8)* HRT 68.1 (0.7)* * ;<0.01 in mean adjusted for multiple comparisons when compared to pre-pre group. Adjusted mean change score (s.e.) for "general mental health" from the SF-36 after 2 years. pre-pre: -0.7 pre-peri: -0.4 (0.7) peri-peri: -1.2 (0.7) pre/peri-post: -1.0 (0.8) post-post: 0.0 (0.9) HRT -2.1 (0.6)* * ;<0.01 in mean change adjusted for multiple comparisons when compared to pre-pre group.	NR	Adjusted mean score for bodily pain from the SF-36 at baseline pre: 72.5 (0.7) peri: 68.2 (0.8)* post: 70.3 (1.1)* HRT 65.0 (0.9)* * ;<0.01 in mean adjusted for multiple comparisons when compared to pre-pre group. Adjusted mean change score (s.e.) for "bodily pain" from the SF-36 after 2 years pre-pre: 0.6 (0.7) pre-peri: -0.5 (0.8) peri-peri: -1.8 (0.8)* pre/peri-post: -1.2 (1.0) post-post: -0.6 (1.2) HRT: -2.7 (0.8)* * ;<0.01 in mean change adjusted for multiple comparisons when compared to pre-pre group.	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Mishra, 2003 Australia	NR	Adjusted mean score (s.e.) for "general health perception" at baseline pre: 73.4 (0.6) peri: 68.2 (0.8)* post: 70.3 (1.1) HRT: 65. (0.9)* * ;<0.01 in mean adjusted for multiple comparisons when compared to pre-pre group. Adjusted mean change score (s.e.) for "general health perception" from SF-36 after 2 years. Pre-pre: 0.6 (0.5) pre-peri: -0.2 (0.6) peri-peri: -1.5 (0.6)* pre/peri-post:-0.7 (0.7) post-post:-0.8 (0.8) HRT:-1.8 (0.5)* * ;<0.01 in mean change adjusted for multiple comparisons when compared to pre-pre group.	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Mishra, 2003 Australia	All mean scores calculated after adjusting after adjusting for age, physical activity level, weight, number of life events, smoking status, occupation, country of birth, marital status, and area of residence. All mean changes calculated after adjusting for SF-36 scores at baseline, physical activity levels at baseline and follow-up, weight at baseline, change in weight, change in number of life events, age smoking status, occupation, country of birth, marital status, and area of residence.	MV modeling only reported in terms of adjustments	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Mishra, 2003 Australia	_	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Mitchell, 1996	Seattle	508 entered study 301 year 1 215 year 2 200 year 3	Cohort	N/A	3 years	Women in households within census tracts with mixed ethnicity and income contacted by phone 11,222 - from which 820 eligible	Census tracts in Seattle	W 79% AA 8.3% Asian 8.6% Native Am 3.3%
Mitchell, 2001	Seattle	230	Cross-sectional	Internal	Preva-lence	Women in households within census tracts with mixed ethnicity and income contacted by phone	Census tracts in Seattle	91% White 5% Asian American 3% African American

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Mitchell, 1996	35-55	Exclusion: 1. Amenorrhea > 1 year 2. Pregnant 3. TAH BSO 4. Could not read or speak English 5. Irregular menstrual cycles 6. HRT use	Interview, cycle diary, health update	11,222 phone contacts 820 eligible 508 entered study	NA
Mitchell, 2001	Mean 46.7	Exclusion: 1. Amenorrhea > 1 year 2. Pregnant 3. TAH BSO 4. Could not read or speak English 5. Irregular menstrual cycles 6. HRT use	Interviews	508 initially; this survey conducted among women still participating 96-97 N=230	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Mitchell, 1996	Washington Women's Health Diary	_	Excluded	NR	NR	NR
Mitchell, 2001	Cycle analysis	NR	NR	NR	NR	68% partnered 24% divorced/separated 6% never partnered Mean education 16 years Mean income 42,000

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Mitchell, 1996	NR	NR	NR	NR	NR	NR
Mitchell, 2001	NR	NR	NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Mitchell, 1996	At baseline dysphoric mood explained 23.8% of variance among symptom clusters - highly stable over 3 years.	NR	Somatic symptoms explain 6.5% of variance - highly stable over 3 years.	NR	NR
Mitchell, 2001	142 women reported memory change compared with 88 without memory change. No association with age, education, income between the 2 groups.	_	_	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Mitchell, 1996	NR	NR	_
Mitchell, 2001	NR	NR	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Mitchell, 1996	Factor analysis Important factors identified included dysphoric mood, vasomotor symptoms, insomnia, neuromuscular symptoms, somatic symptoms. Dysphoric mood very stable over 3 years (explained 77% of variance). Neuromuscular symptoms stable (explained 74% of variance). Vasomotor symptoms moderately stable over 3 years.	_	NA
Mitchell, 2001	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Mitchell, 1996	NA	All premenopausal or early perimenopausal. Findings suggest that many symptoms described at baseline are stable over time and MP transition explains none over 3 years.
Mitchell, 2001	This study really only evaluates women's attributions of causes for change in memory (self-reported). Stress, physical health, and aging most frequently cited as attributing to memory change.	Based on cycle analysis Premenopausal: early menopause transition stage (MTS) 53 Mid-menopausal: MTS 54 Late menopausal: MTS 27 Postmenopausal: MTS 12 96 on hormones or hysterectomy or were not classifiable

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Randolph, 2003	SWAN	2,930	Cross-sectional	_	_	_	_	AA 27.6% Chinese 7.4% H 8.8% J 9.0% W 47.1%
Rodstrom, 2002 Sweden	Gothenburg	1462	Cohort	Internal	25+ years	Randomly selected from population	1968-69 1462 women aged 38-60 1302 re-examined 1974-75 (89%) 1154 re-examined 1980-81 plus 47 new women born in 1930 4th exam 1992-93	White

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Randolph, 2003	46.3	253 of 3302 were excluded because of missing data	_	92.30%	
Rodstrom, 2002 Sweden	Initially 38-60	None specified other than those with surgical menopause	Standardized interview	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Randolph, 2003	Height, weight, demographic and lifestyle data. Menopausal status, FSH, DHEAS, SHBG and E2 from venipuncture on day 2-7 of a spontaneous menstrual cycle occurring within 60d of recruitment then annually.	Premenopausal 54.3% early perimenopausal 45.7%	_	_	_	_
Rodstrom, 2002 Sweden	_		Excluded	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Randolph, 2003	Smoking: never 57.6% past 25.4% current <10/d 5.0% current ≥10/d 12.1% Higher mean FSH, testosterone, and SHBG levels for current compared to never smokers in unadjusted analyses (p≤0.0001)	_	Mean 28 kg/m2 For all ethnic groups, SHBG, FSH, E2, and DHEAS levels declined with increasing BMI, and testosterone levels increased with increasing BMI. For SHBG only did BMI and ethnicity interact. BMI distribution varied across ethnicities	_	_	_
Rodstrom, 2002 Sweden	NR	NR	NR	Prevalence of hot flashes increased in linear manner from 11% at age 38, to maximal prevalence of 60% at ages 52-54, to 30% at age 60, 15% at age 66, 9% at age 72. Hot flashes reported significantly less often among women aged 50 in 1980-81 cohort than the age 50 women in the 1968-69 cohort. Cohort differences	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Randolph, 2003	_	_	_	_	_
Rodstrom, 2002 Sweden	NR	NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Randolph, 2003	–	–	Unadjusted mean hormone levels by menopausal status: E2 pg/ml (p NS): pre 74 early peri 77 FSH IU/L (p ≤0.0001): pre 19.7 early peri 29.8 Testosterone ng/ml (p NS): pre 46 early peri 48 DHEAS mcg/dl (p<0.05): pre 135 early peri 128 SHBG nM (p NS): pre 45 early peri 46
Rodstrom, 2002 Sweden	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Randolph, 2003	Ethnicity, menopausal status, study site, day of cycle, BMI, age, smoking, and alcohol	Adjusted models for mean serum hormone concentrations	E2: No affect of menopausal status and ethnicity FSH: Ethnicity ($p<0.05$) Menopausal status ($p\leq0.0001$) T: Ethnicity ($p<0.05$) No affect of menopausal status DHEAS: Ethnicity ($p\leq0.0001$) No affect of menopausal status
Rodstrom, 2002 Sweden	Only age, MP status, and cohort	Chi Square	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Randolph, 2003	_	Adjusted FSH levels were significantly higher in AA and H than W and Asian women. Adjusted FSH levels were significantly higher in early perimenopausal than premenopausal women. Adjusted DHEAS levels were 73% higher in Chinese than AA. Adjusted testosterone levels were slightly lower in in AA and H than W and Asian women.
Rodstrom, 2002 Sweden	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Sherburn, 2001 Australia	Melbourne Women's	1897, 373	Cross-sectional, longitudinal	–	7 year follow-up	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Sherburn, 2001 Australia	_	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Sherburn, 2001 Australia	–	Baseline % noted above. At 7 year follow-up n=373: stayed pre/peri 13.7% became post 54.7% HRT user 22.8% had surgical menopause 8.8%	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Sherburn, 2001 Australia	–	–	–	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Sherburn, 2001 Australia	_	_	_	Urinary incontinence at baseline by menopausal status: pre 10.4% peri 17.3%* post 14% HRT 19%* surgical 17.7%* Total 15.3% *p<0.005 compared to pre. Incidence rate (%) at 7 yr: stayed pre/peri 34% became post 37% HRT user 27% surgical menopause 54% total 35%	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Sherburn, 2001 Australia	–	–	–

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Sherburn, 2001 Australia	_	Logistic regression model of factors associated with urinary incontinence	BMI Other gynecologic surgery participating in lawn bowls urinary tract infection diarrhea or constipation parity arthritis negative mood score (menopausal status was not significant in this model)

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year		RR or OR	Comments
Sherburn, 2001	1.5		"Urinary incontinence in middle-aged women is more closely
Australia	2.17		associated with mechanical factors than with menopausal
	2.26		transition."
	4.75		
	1.95		
	1.47		
	1.55		
	1.64		

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Umbrella	N	Study Design	Type Control Group	Length of Follow-Up	Recruitment (Data source)	Population/ Setting	Race/ Ethnicity
Sowers, 2000 (methods paper for SWAN)	SWAN	16,065 Cross-sectional 3306 longitu-dinal	Cross-sectional and multisite longitudinal study		Ongoing since 1995	Census data, lists, random-digit dialing, "snow-balling"	Community based. Pittsburgh, Boston, Detroit, Chicago, Los Angeles, Oakland, Newark	Each site enrolled non-Hispanic Caucasians and one site-specific minority African-American, Japanese, Chinese, or Hispanic.
Woods, 1997	Seattle	347	Cohort	Internal	2 years	822 eligible 508 participated in interviews 347 completed years 1 and 2 surveys	Seattle Population-based sample chosen to over represent minorities Sampling frame based on phone numbers	80% Whites 8 African Americans 8 Asian Americans

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Age (range)	Inclusion/Exclusion Criteria	Ascertainment of Symptoms	Response Rate	Withdrawals
Sowers, 2000 (methods paper for SWAN)	40-55	*Eligibility criteria for cross-sectional study:* 1) primary residence in designated geographic area, 2) ability to speak English or other designated language, 3) age 40-55 years at time of contact, 4) cognitive ability to provide verbal informed consent, 5) membership in a specific site's targeted ethnic groups *Eligibility criteria for longitudinal study*: 1) aged 42-52 years, 2) no surgical removal of the uterus and/or both ovaries, 3) not currently using exogenous hormone preparations affecting ovarian function, 4) at least one menstrual period in the previous 3 months, 5) self-identification with one of each site's designated race/ethnic group	Interview, written/oral survey, questionnaires, clinic measurements, specimen data, menstrual calendars, abstract medical records for hysterectomy. Materials available in all relevant languages.	46.6% cross-sectional 50.7% longitudinal	
Woods, 1997	35-45 (median 41)	Inclusion criteria: 1) Non-lactating 2) Non-pregnant 3) Menses within last year 4) English reading 5) No hysterectomy 6) Had at least 1 ovary	_	508 of 820 of which 75% completed first year and 90% second year	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Measures Used	Menopausal status	Hyster-ectomy or BSO (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)
Sowers, 2000 (methods paper for SWAN)	Too extensive to list	_	None at enrollment	By definition ineligible for longitudinal study	NR	Ineligible
Woods, 1997	CES-D Scale Menopausal Changes Norbechs LES (Stressful Life Context) Feminine Socialization Socialization for Midlife Health Status Family Resources	_	Excluded	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Hot Flashes	Vaginal Dryness	Sleep
Sowers, 2000 (methods paper for SWAN)	–	–	–	–	–	–
Woods, 1997	NR	NR	NR	NR	NR	NR

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Sowers, 2000 (methods paper for SWAN)	_	NR	NR	NR	NR
Woods, 1997	Patterns (chronic, resolved, emerging) of depressed mood related to stressful life context, past/present health status, and social learning about midlife. Menopausal status did not differentiate woen with depression from non-depressed.	_	_	_	_

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes
Sowers, 2000 (methods paper for SWAN)	–	–	–
Woods, 1997	–	–	

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	Predictors studied (significant/not significant)	Statistical Models	Significant predictors in multivariate (adjusted models)
Sowers, 2000 (methods paper for SWAN)	_	_	_
Woods, 1997	_	Factors prediction	Social learning about midlife Stress life context Past/present health status

Appendix F: Evidence table 6-1. Key Question 1 and 2 cohort studies

Study/Year	RR or OR	Comments
Sowers, 2000 (methods paper for SWAN)	–	
Woods, 1997	NA	Baseline: all premenopausal At year 2 follow up: 22% perimenopausal, 31% hot flashes

Appendix F. Evidence table 6-1. Key Question 1 and 2 cohort studies

Key/Abbreviations

AA = African American
BL = Baseline
BMI = Body mass index
BSO = Bilateral Salpingo Oopherectomy
CES-D = Center for Epidemiologic Studies Depression Scale
DHEAS = Dehydroepiandrosterones
E2 = Estradiol
GWB = Global well-being
H = Hispanic
HF = Hot flash
HRQL = Health related quality of life
HRT = Hormone replacement therapy
INH = Inhibin
ISRO = Index of Sex Role Orientation
J = Japanese
LES = Life event stress
MRC = Medical Research Council
MTS = Menopausal transition stage
MV = Multivariate
NA = Not applicable
NHANES = National Health and Nutrition Examination Survey
NHEFS = National Health Examination Follow-up Study
NR = Not reported
NS = Not significant
oc =Oral contraceptives
OR = Odds ratio
PEQ = Personal Experiences Questionnaire
peri = Perimenopausal
PHS = Perceived health status
PMS = Premenstrual syndrome
post = Postmenopausal
pre = Premenopausal
PSE = Present state examination
RR = Relative risk
sd = Standard deviation
SES = Socioeconomic status
SPEQ = Sexuality questionnaire of Personal Experiences Questionnaire
SWAN = Study of Women's Health Across the Nation
T = Testosterone
T0 = Time zero
T1 - Time one
T2 = Time two
T3 = Time three
TAH = Total abdominal hysterectomy
W = White

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Ditkoff, 1991	36	RCT	P	3 months	Asymptomatic American-born Latina women, aged 45-60, Salpingo hysterectomy, living in East LA. Recruitment info NR.	Inclusion: 1. Age 45-60 2. Previous hysterectomy 3. American born Latina 4. Estradiol <20 5. No subjective HF 6. No HRT for 2 months 7. No medical illnesses 8. No hypnotics or mood altering drugs
Furuhjelm, 1984	48	Cross-over	P	4 2-month periods	Postmenopausal women with climacteric complaints attending outpatient clinic in Sweden Group 1: N=28 with high depression/mental distress scores Group 2: N=9 with mild depression/mental distress scores Group 3: N=11 with no depression/mental distress	Inclusion: 1. No clinical or laboratory signs of endocrine, biliary, GI or renal malfunction 2. No HRT for at least 2 months 3. Complaints of various climacteric disturbances 4. > 1-year post-menopausal

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Ditkoff, 1991	1. Minnesota Multiphasic Personality Inventory-168 2. Profile of Adaptation to Life 3. Beck Depression Inventory 4. Wechsler Adult Intelligence Scales of digit span and digit symbol	36/36	NR	NR	0	NR	NR	0	NR
Furuhjelm, 1984	1. Sabbatsberg General Symptom Scale (for somatic and mental disturbances) 2. Sabbatsberg Distress Self-Rating Scale (for depression) 3. Eysenck Personality Inventory 4. Sabbatsberg Sexual Self-Rating Scale 5. Hormone levels, chemistry, physical exam, pap	NR	NR	NR	NR	NR	NR	0	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Ditkoff, 1991	CEE, 0.625mg or 1.25mg, PO qd for days 1-25 each month	Placebo	None in either group	NR	NR
Furuhjelm, 1984	Period A: 2mg estradiol-17B and 1mg estriol for 12 days, then 2mg estrodiol 17B, 1mg estriol, and 1mg noretristone acetate for 10 days, then 1mg estradiol-17B and 0.5mg estriol; Period B: 4mg estradiol-17B and 2mg estriol for 12 days, then 4mg estrodiol 17B, 2mg estriol, and 1mg noretristone acetate for 10 days, then 1mg estradiol-17B and 0.5mg estriol; Period C: 2mg estrodiol-17B and 1mg estriol for 28 days	Period D: placebo	All groups improved in pre-post comparison during hormone treatment; placebo did not change; no comparison to placebo given. All regimens grouped together.	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Ditkoff, 1991	1. No change in Minnesota Multiphasic Personality Inventory; 2. Significant decrease in Beck Depression Inventory for both doses of CEE pre-post; scores increased with placebo, but change not significant; no comparison between CEE and placebo given. 3. Significant improvement in income management scale pre-post in both CEE groups; no change with placebo; no comparison between CEE and placebo.	No change	NR	NR	NR
Furuhjelm, 1984	All groups improved in pre-post comparison of mental distress during hormone treatment ($p<0.01$). Only depressed group had improvement in depression scores during hormone treatment ($p<0.001$); non-depressed groups and placebo did not change; no direct comparison to placebo given. All regimens grouped together.	NR	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Ditkoff, 1991	NR	NR	NR	NR	0	None	
Furuhjelm, 1984	NR	NR	NR	10/58	3/58	3 with heavy bleeding	Odd analysis of crossover-style study; can't separate out first treatment.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Hall, 1998	60	RCT	P & HH	1 year	Postmenopausal women aged 44-75 with CAD in Sweden. Recruitment info NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hall, 1998	Nottingham health profile and "others evaluated by Wiklund et. al."	NR	NR	NR	NR	NR	NR	NR	"all were overweight" ; mean BMI 25.9.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Hall, 1998	CEE 0.625mg, alone for 18 days, in combo with medroxyprogesterone 5mg for 10 days	Patch TTS E2 50 mcg alone for 18 days, in combo with medroxyprogesterone 5mg for 10 days	NR	NR	No change.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Hall, 1998	Significant improvement in depressed moods (p=0.054) in CEE group; no change in E2 or placebo; no comparison given between groups. Overall improvement in mood reported in all groups with no difference between groups.	Improved in all 3 groups; no difference between groups.	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Hall, 1998	NR	NR	NR	14/60	7/60	Heavy bleeding, edema, allergic skin reaction, palpitations, headache. (Numbers only given for those that withdrew, not total sample.)	

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Hlatky, 2002	2,763	RCT	P	36 months	Postmenopausal women with CAD in HERS study from 20 US clinical centers	Inclusion: 1. < 80 2. Postmenopausal: a) age ≥55 and no menses for 5 years b) no menses for 1 year and FSH >40 c) documented bilateral oophorectomy d) reported oophorectomy and FSH > 40 and E2 < 25 3. CAD: a) prior MI b) angiography showing >50% narrowing of major vessel c) prior coronary revascularization procedure Exclusion: 1. MI or revascularization procedure within 6 months 2. Prior hysterectomy 3. Contraindication to HRT 4. HRT within 3 months 5. Other life-threatening illnesses 6. Unable to return for follow-up visits.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hlatky, 2002	1. Duke Activity Status; 2. RAND 4-item scale on energy/fatigue; 3. RAND mental health inventory; 4. 8-item depression scale developed for National Study of Medical Outcomes;	0	NR	NR	NR	NR	NR	0	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Hlatky, 2002	CEE, 0.625mg and medroxyprogesterone acetate 2.5mg PO qd	Placebo	Reported elsewhere	Reported elsewhere	Reported elsewhere

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Hlatky, 2002	RAND mental health inventory had small decline in all patients over time (p=0.05); no significant interaction between treatment group and time (p=0.10). Depressive symptoms decreased more over time among patients on HRT (p=0.005). In women with flushing at entry, HRT group had improved mental health (+2.6 vs. -0.5, p=0.04) and depressive symptoms (-0.5 vs. +0/007, p=0.01) compared to placebo. No significant change in women without flushing.	NR	NR	Reported elsewhere	Reported elsewhere

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Hlatky, 2002	NR	More rapid decline over time in physical function scores in women on HRT (p=0.03). In women without flushing, HRT had greater decline in physical function (-4.2 vs. -3.3, p=0.04) and worsening of energy/fatigue (-4.6 vs. -3.1, p=0.03) compared to placebo. No significant difference in women with flushing.	Energy/fatigue scores declined overall (P<0.001); faster declines in energy/fatigue in women on HRT (p=0.05).	1/2763 missing all data; 169/1383 on P and 180/1380 on HRT missing some data.	NR	Reported elsewhere	Secondary analysis of HERS trial

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Strickler, 2000	398 (373 in analysis)	RCT	P and HH	1 year	Asymptomatic postmenopausal women aged 47-60; 2-8 years after last menses; 32 study sites; recruitment info NR;	Inclusion: 1. Age 47-60 2. 2-8 years with no menses 3. E2 < 20 4. BMD within 2.5 SD of premenopausal normal women. Exclusion: 1. Intolerable menstrual symptoms requiring treatment 2. Uterine bleeding of unknown cause 3. BMI < 18 or >31 4. History of DVT 5. Use of corticosteroids, estrogen or progestin < 6 months 6. Chronic illness.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Strickler, 2000	Women's Health Questionnaire	NR	NR	NR	NR	NR	NR	0	0

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Strickler, 2000	CEE 0.625	Raloxifene 60mg or 150mg qd or placebo	HRT improved vasomotor symptoms compared to Raloxifene ($p<0.001$) and placebo ($p<0.001$).	NR	No significant difference

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Strickler, 2000	No significant difference in depressed mood. Anxiety improved in Raloxifene 60mg (0.165) compared with placebo (0.028, p=0.03) and estrogen (-0.017, p=0.003). No difference with Raloxifene 150mg (0.076).	No difference in memory/ concentration	No difference in somatic symptoms	NR	Menstrual symptoms: estrogen (-0.169) worse than placebo (0.01, p=0.003). Comparisons with Raloxifene 60mg (-0.73) and 150mg (-0.063) not statistically significant.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Strickler, 2000	No difference in sexual behavior	NR	NR	25/398	NR	NR	Asymptomatic postmenopausal population. Possible error due to multiple comparisons.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Thomson, 1977	42	RCT	P	8 weeks	45-55 yo women referred by local general practitioners.	Inclusion: 1. 45-55 years old 2. Amenorrhea $\geq$ 3 months 3. Symptoms of insomnia, depression, anxiety, and hot flashes Exclusion: 1. Other medications, contraindications to estrogen therapy

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Thomson, 1977	Daily visual analogue scales for mood and anxiety and number of hot flashes. Hamilton anxiety and depression scales.	NR	NR	NR	NR	0	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Thomson, 1977	Piperazin oestrone sulphate 1.5mg BID	Placebo	No significant difference	NR	Improved sleep (intervening wakefulness, frequency of awakenings, and stage of sleep) compared to placebo ($p<0.05$)

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Thomson, 1977	No difference between groups; both groups improved (p<0.001)	NR	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Thomson, 1977	NR	NR	No difference in anxiety between groups; both groups improved (p<0.001).	8 of 42	NR	NR	

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Vestergaard, 2002	1,006	RCT (Open label)	No HRT	5 years	45-58 year old women; recruited by mailing to random sample.	Inclusion: 1. Women aged 45-58 a) 3-24 months past last period or b) experiencing perimenopausal symptoms (irregular menses) with elevated FSH or 2. Women aged 45-52 Salpingo hysterectomy with elevated FSH. Exclusion: 1. Metabolic bone disease / osteoporosis 2. HRT within 3 months 3. Current or past treatment with glucocorticoids > 6 months 4. Malignancy 5. Newly diagnosed or uncontrolled chronic disease 6. Alcohol or drug addiction.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Vestergaard, 2002	Modified Greene scale (visual analogue scale from 0-4 for severity of symptoms.)	192/1006	NR	NR	0	NR	NR	0	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Vestergaard, 2002	First line: E2 2mg days 1-12; E2 mg and norethisterone 1mg days 13-22; E2 1mg days 23-28 for women with uterus. E2 2mg po qd for women without uterus. Women allowed to use other regimens if they requested change.	None	HRT reduced severity of HF compared to placebo (p<0.01).	HRT less vaginal dryness (p<0.01)	Less sleeping difficulties related to HF on HRT (p<0.01). No difference in sleeping difficulties unrelated to HF (p=0.17).

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Vestergaard, 2002	No significant difference in mood swings.	NR	No significant difference in headaches.	No significant difference in voiding frequency or incontinence.	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Vestergaard, 2002	Trend toward less reduction in libido with HRT (p=0.08)	NR	Blood pressure decreased overall; no difference with HRT.	54/502 on HRT; 55/504 not on HRT	NR; 40% changed HRT regimen or terminated HRT due to AEs	39 headaches; 14 edema/fluid retention; 21 mood swings/ depression	Open label study; high rate of contamination; outcome measures single items, less well-validated. Part of Danish Osteoporosis Prevention Study.

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Voss, 2002	1,008	RCT	HH	6 month	Healthy postmenopausal women in 129 gynecological practices in Europe, South Africa and Israel.	Inclusion: 1. Healthy ambulatory women age ≥65 2. Natural menopause ≥ 2 years earlier 3. Elevated FSH in women age < 57 Exclusion: 1. Hysterectomy, ovariectomy, breast cancer, estrogen-dependant cancer 2. Any other cancer within 5 years 3. DVT, liver disease, thyroid disease 4. Did not qualify for therapy according to prescribing information for E2 or NETA 5. Endometrial pathology 6. Severe postmenopausal symptoms requiring HRT 7. Treatment with estrogens within 6 months 8. Treatment with hypolipidemic drugs within 3 months Note: intravaginal estrogens and oral estriol up to
Wheatley, 1977	58	RCT	P	4 weeks	Depressed women	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Voss, 2002	Women's Health Questionnaire	0	0	NR	0	0	NR	0	NR
Wheatley, 1977	Global rating; Hamilton Depression Scale; Hopkins Symptom Checklist	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Voss, 2002	Oestradiol 2mg and norethisterone acetate 1mg	Raloxifene 60mg qd	HRT: -0.21 R: -0.03 p<0.001 favoring HRT	NR	HRT: -0.08 R: -0.04 p=0.086
Wheatley, 1977	Piperazin oestrone sulphate 1.5mg BID (with amitryptline)	Placebo (with amitryptiline)	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

	Main Outcomes (continued)				
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Voss, 2002	Depressed mood: HRT +0.03, R:-0.02, p=0.004 favoring Raloxifene. Anxiety/fears: HRT 0.00; R: -0.01; p=0.6.	Memory/concentration: HRT: -0.04; R: +0.02; p=0.02 favoring HRT	HRT: -0.02; R: -0.01; p=0.3.	NR	Menstrual symptoms: HRT +0.10; R: +0.02; p<0.001 favoring Raloxifene
Wheatley, 1977	No difference between groups; both groups improved.	NR	NR	NR	NR

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Voss, 2002	HRT: -0.11 R:-0.02; p=0.007 favoring HRT	NR	Greater treatment satisfaction (p=0.004) and compliance (p<0.01) with R than HRT	54/495 on R; 116/513 on HRT	24/495 on R; 65/513 on HRT	Vaginal bleeding (R 6.8%, HRT 55%, p<0.01)	
Wheatley, 1977	NR	NR	NR	NR	NR	NR	

Appendix F: Evidence table 6-2. Key Question 3A Estrogens for depression

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Voss, 2002	HRT: -0.11 R:-0.02; p=0.007 favoring HRT	NR	Greater treatment satisfaction (p=0.004) and compliance (p<0.01) with R than HRT	54/495 on R; 116/513 on HRT	24/495 on R; 65/513 on HRT	Vaginal bleeding (R 6.8%, HRT 55%, p<0.01)	
Wheatley, 1977	NR	NR	NR	NR	NR	NR	

Appendix F. Evidence table 6-2. Key Question 3A Estrogens for depression

Abbreviations
AE = Adverse Effect
CEE = Conjugated Equine Estrogens
E2 = Estrodial
HH = Head to head
HRT = Hormone Replacement Therapy
NETA=norethidrone acetate
NR = Not reported
P = Placebo
RCT = Randomized Controlled Trial
HF = Hot flash
GI = Gastrointestinal
SD = Standard deviation
MI = Myocardial infarction
CAD = Coronary artery disease
DVT = Deep vein thrombosis
R = Raloxifene
HERS = Heart and Estrogen/Progestin Replacement Study
RAND = RAND Mental Health Inventory
BMI = Body mass index
SERMs = Selective Estrogen Receptor Modifiers
BMD = Bone mineral density

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Barrett-Connor, 1999	311 in 4 groups	DB RCT	HH	2 years	Surgically menopausal White women. Mean age approx 45 (21-65)	Inclusion: 1. White women 2. 21-65 years old 3. Surgically menopausal: Undergone bilateral oophorectomy and hysterectomy > 3 months before but < 5 years prior to screening 4. Within 75-125% of ideal body weight 5. In stable relationship for > 6 months Exclusion: 1. Receiving estrogens or HRT in previous 6 weeks 2. Receiving psychotropic drugs in the previous 4 weeks 3. History of pelvic or breast malignancy 4. Dependence on alcohol, tobacco, or illicit drugs
Braunstein, 2003 (abstract only)	447	DB RCT	P	24 weeks	Surgically menopausal women with hypoactive sexual desire	Inclusion: 1. Surgically menopausal women 2. Had Hypoactive Sexual Desire Disorder
Davis, 2003 (abstract only)	77	DB RCT	P	24 weeks	Surgically menopausal women with hypoactive sexual desire	Inclusion: 1. Surgically menopausal women 2. Had Hypoactive Sexual Desire Disorder

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Barrett-Connor, 1999	Modified Kupperman Scale	311	311	NR	0	NR	NR	No HRT in prior 6 weeks	Approxi-mately 25	CEE 0.625 mg/day oral (CEE-L); CEE 1.25 mg/day oral (CEE);
Braunstein, 2003 (abstract only)	SAL PFSF	447/447	NR	NR	NR	NR	NR	0	NR	Testosterone 150, 130, or 450 mcg/day Transdermal patch twice per week
Davis, 2003 (abstract only)	SAL PFSF PGWB PDS	77/77	77/77	NR	NR	NR	NR	0	NR	Testosterone 300 mcg/day Transdermal twice per week

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Cognitive**	**Somatic**
Barrett-Connor, 1999	E2 0.625 mg + MT 1.25 mg/day oral (E+ A-L); E2 1.25 mg + MT 2.5 mg/day oral (E + A)	Improved in all treatment groups (p value not reported)	Improved in all treatment groups (p value not reported)	NR	NR	NR	No significant difference between treatment groups.
Braunstein, 2003 (abstract only)	Oral estrogen	NR	NR	NR	NR	NR	NR
Davis, 2003 (abstract only)	Transdermal estrogen	NR	NR	NR	NR	NR	Statistically significant positive effect on the composite score of PGWB in T group, $p<0.05$

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Barrett-Connor, 1999	NR	NR	Non-significant trend toward greater improvement in well-being and sexual interest in the E + A groups (data on Kupperman scale.)	NR	Significantly increased BMD in the E+A group at lumbar spine and hip in comparison to the CEE group at 24 months. No statistically significant differences in hirsutism scores between treatment groups (Ferriman-Gallwey scale)
Braunstein, 2003 (abstract only)	NR	NR	In the 300 mcg/d group, a 30% increase in satisfying sexual activity observed in T vs. P ($p<0.05$) and 81% increase from baseline ($p<0.05$) on SAL. Sexual desire score also increased ($p<0.05$) on PFSF.	NR	Increased mean concentrations of free and bioavailable T.
Davis, 2003 (abstract only)	NR	NR	Increase in sexual desire score on PFSF in T group compared to P, $p<0.05$	NR	Increased mean concentrations of free and bioavailable T.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Barrett-Connor, 1999	112 (non drug related-24, protocol violation-21, loss to follow-up-22)	45	Nausea (6% E+A-L; 3% E+A; 11% CEE-L and 22% CEE) Acne/hirsutism/chloasma (3 in E+A-L; 4 in E+A;1 CEE)	Participants in study not selected based on presence/severity of menopausal symptoms.
Braunstein, 2003 (abstract only)	NR	NR	NR	
Davis, 2003 (abstract only)	NR	NR	NR	

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Dobs, 2002	40	DB RCT	HH	16 weeks	Menopausal women Mean age 56.9 (41.4-76.3)	Inclusion: 1. Surgically or naturally menopausal women 2. Required to have been on HRT for > 3 months before screening to remove confounding hypoestrogenic symptoms Exclusion: 1. Uncontrolled hypertension or hyperlipidemia 2. Medication known to affect lipids 3. Poorly controlled diabetes mellitus 4. Unstable angina or congestive heart failure 5. Myocardial infarction < 3 months of study 6. Preexisting liver disease 7. Renal impairment 8. Hepatic adenoma 9. History of breast or uterine cancer 10. Gall bladder disease 11. History of thromboembolic events

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Dobs, 2002	BISF -W SRS SIQ QUALMS	NR	21/40	NR	NR	NR	NR	0	NR	E2 1.25 mg/day + MT 2.5 mg/day oral or

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Cognitive**	**Somatic**
Dobs, 2002	E2 1.25 mg/day oral	Improved in E2/MT at week 4 (p=0.024) and week 10 (p=0.003) QUALMS Scale	NR	Improved in E2/MT at week 4 (p=0.024) and week 10 (p=0.003) QUALMS Scale	No significant change	No significant change	Improved in E2/MT group at week 4 (p=0.004) and week 10 (p=0.021) QUALMS Scale

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Dobs, 2002	NR	NR	Frequency/psycho-sexual (p=0.05) and pleasure/orgasm (p=0.041) scores of BISF-W increased. Total SRS score improved in E2/MT (p value not reported). Improved SIQ score in E2/MT at week 10 (p=0.031) and week 16 (p=0.014).	See QUALMS data	Sex hormone levels

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Dobs, 2002	3	3 (E2/MT - 2 E2 - 1)	Bloating/weight gain (E2/MT) Migraine (E2/MT) Hirsutism (E2/MT) Insomnia, breast swelling, headache (E2)	Sexual function and quality of life secondary outcome. Healthier baseline sexual function reported in E2 group compared to E2/MT (specific data not reported)

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Floter, 2002	50 in 2 groups	RCT Cross-over	HH	24 weeks	Surgically menopausal women Mean age 54 (45-60)	Inclusion: 1. 45-60 years old 2. History of hysterectomy and bilateral salpingo ophorectomy for benign disorders 3. Body mass index between 18 and 29 kg/m2 4. Blood pressure > 170 mmHg systolic and/or 105 mmHg diastolic 5. Normal mammogram within past year Exclusion: 1. Previous use of HRT within past 2 months 2. Other medication within past 2 months (other sex hormones, anabolic steroids, corticosteroids, danazol, calcium antagonists, beta-blocking agents, barbiturates, carbamazepines, griseofulvins, hydantion, rifampicin, herbal/homeopathic therapy) 3. History of or present premalignancies/malignancies 4. Liver disease 5. Cardiovascular, cerebrovascular, or thromboembolic disorders 6. Present psychiatric disease 7. Regular use of tranquillizers and/or antihistamines, alcohol abuse, or smoking of > 10 cigarettes/day was allowed

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Floter, 2002	McCoy's Sex Scale PGWB-I	50/50	50/50	NR	0/50	NR	NR	NR	Mean 25.7	Estradiol valerate 2 mg/day

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic
Floter, 2002	Estradiol valerate 2 mg/day + testosterone undecanoate 40 mg/day	NR	NR	NR	Both treatment groups with significant improvement, p< 0.001 PGWB Index	NR	NR

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Floter, 2002	NR	NR	Both treatment groups with significant improvement (p< 0.01) on McCoy Sex Scale.	Both treatment groups with significant improvement on PGWB Index, p< 0.05	Sex hormone levels

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Floter, 2002	6	1	Migraine Acne Hirsutism Body swelling	

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Hickok, 1993	26 in 2 groups	DB RCT	HH	6 months	Postmenopausal White women 40-60 years Mean age: E2=50 E2 + MT= 52	Inclusion: 1. Women from Department of Obstetrics and Gynecology at Oregon Health and Science University 2. Caucasian 3. 40-60 years old Exclusion: 1. Menstrual bleeding in the last 12 months 2. History of steroid ingestion in 4 weeks prior to study 3. Receiving adrenergic agonists or antagonists, peripheral vasodilators, cholesterol-lowering agents, beta-blockers, beta-mimetics, or thyroid hormones 4. Smoking within the past 12 months 5. History of genital tract disease 6. Current or previous estrogen-dependent malignancy 7. History of jaundice or elevated liver enzymes, gallbladder disease, or cardiovascular disease 8. Current hypertriglyceridemia or severe hypertension

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Hickok, 1993	4 point menopausal symptom scale (0-3)	NR	NR	NR	NR	NR	Non-smokers	NR	NR	E2 0.625 mg + MT 1.25 mg/day oral

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic
Hickok, 1993	E2 0.625 mg/day oral	Decrease in symptom severity in both groups, p<.01. No significant difference between groups.	Decrease in symptom severity in both groups, p<.01. No significant difference between groups.	Decrease in symptom severity in both groups, p<.01. No significant difference between groups.	NR	NR	NR

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Hickok, 1993	NR	NR	NR	NR	Decreased symptom severity in other symptoms measured. No significant differences between the 2 groups.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Hickok, 1993	0	0	Acne (E2 + MT - 5) Facial hair (E2 + MT - 2; E2 - 1)	Menopausal symptoms measured on 4 point scale (0=absent to 3=severe): hot flushes, cold sweats, vaginal dryness, cold hands and feet, breast pain or tenderness, numbness and tingling, skin crawls, edema, increased facial or body hair, voice deepening, acne, trouble sleeping, heart pounding, dizzy spells, pressure or tightness in head or body.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Lobo, 2003	218 in 2 groups	DB RCT	HH	4 months	Postmenopausal women with hypoactive sexual desire. Mean age approx 53 (40-65)	Inclusion: 1. Healthy postmenopausal women (natural or surgical > 6 months) 2. 40-65 years old 3. Receiving estrogen (0.625 mg of conjugated equine estrogens for > 3 months or equivalent of 0.9 mg if dose decreased for last cycle before study) 4. Experienced hypoactive sexual desire associated with onset of menopause (not overt mood disorders) scoring higher than 3.0 on Thoughts/Desire Dimension of the BISF-W 5. History of adequate sexual interest before onset of menopause Exclusion: 1. Dyspareunia 2. Unresolved or recent sexual abuse 3. Depressive or anxiety symptoms 4. Physical limitations that interfered with normal sexual functioning 5. Abnormal mammogram 6. Relevant clinical laboratory test abnormalities 7. Recent previous high-dose HRT or other sex hormones 8. Lipid-lowering agents 9. Antidepressants (including SSRI's) 10. Anxiolytics 11. Thyroid replacement medication (unless a stable dose) 12. Antihypertensive drugs

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Lobo, 2003	SIQ BISF-W	NR	Approx-imately 68/218 (30.8 % EE/MT and 31.5% EE)	NR	NR	NR	NR	None	E2 26.7 ± 5.4 and E2/MT 25.5 ± 4.6	E2 0.625 mg/day oral and E2 0.625 mg/day + MT 1.25 mg/day oral

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic
Lobo, 2003	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Lobo, 2003	NR	NR	SIQ scores for mean sexual interest/desire and responsiveness significantly increased, p=.047 and p=.002, respectively.	NR	Mean bioavailable T levels increased in E2/MT group, p< .010, decreased in HDL in EE/MT, p<.010.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Lobo, 2003	E2 16/111 E2/MT 20/107	E2: 5 E2/MT: 9	Headache (E2/MT 9.3% vs. E2 7.2%) Infection (E2/MT 9.3% vs. E2 6.3%) Acne (E2/MT 5.6% vs. E2 2.7%) Hot flushes (E2/MT and E2 7%) Breast pain (E2/MT 3.7% vs. E2 7%) Acne (E2/MT 5.6% vs. E2 3%) Rhinitis (E2/MT 4% vs. E2 6%)	

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Penotti, 2001	40 in 2 groups	Open RCT	HH	8 months	Postmenopausal women. Mean age: HRT + T 57.4 HRT 55.3	Inclusion: 1. Attending the Menopause Clinic of the Second Department of Obstetrics and Gynecology, University of Milan 2. Receiving HRT > 1 year 3. Receiving Transdermal E2 (50 ug/d) for between 1-5 years and cyclic medroxyprogesterone acetate (10 mg/d) for 12 days every 2 months Exclusion: 1. Suffering from any major disease including hypertension, heart disease, diabetes, renal or peripheral vascular diseases 2. Undergone surgical removal of the uterus or ovaries
Raisz, 1996	18 in 2 groups	Open RCT	HH	9 weeks	Postmenopausal women. Mean age: CEE 65.7 E2/MT 59.8	Inclusion: 1. Postmenopausal women (last spontaneous menstrual cycle occurred > 5 years) 2. Within 25% of ideal body weight 3. Non-smoker 4. Negative mammogram and Pap smear within 1 year and normal electrocardiograms Exclusion: 1. Receiving estrogens within last 6 months 2. Prior history of estrogen-dependent cancer, hypercortisolism, hyperthyroidism, or metabolic bone disease 3. Any prior treatment with drugs that might affect bone metabolism, other than calcium supplements and estrogens, or with drugs known to alter hepatic enzymes (including excess vitamin A and D, steroid hormones, cholesterol-lowering agents, heparin, anticonvulsants, high dose nonsteroidal anti-inflammatory drugs, and high dose thyroid hormone replacement

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Penotti, 2001	VAS	0	0	NR	NR	NR	NR	None	HRT + T =24.1 and HRT =24.9	HRT + Testosterone undecanoate 40 mg/day oral
Raisz, 1996	Modified Kupperman with 0-3 scale	0	CEE 3/15	NR	0	NR	Non-smokers only	No estrogen for 6 months prior	CEE =25.1 and E2/MT =26.5	CEE 1.25 mg/day oral or E2 1.25 mg + MT 2.5 mg/day oral

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Cognitive**	**Somatic**
Penotti, 2001	HRT: E2 50 mcg/day Transdermal + MPA 10 mg/day for 12day/month	NR	NR	NR	NR	NR	NR
Raisz, 1996	Oyster shell calcium tablet (Oscal) 500 mg 1 or 2 tablets/day oral	Decreased in both groups, p<.05	Decreased in both groups, p<.05	Improved in E + A group, p<.05	Improved in E2/MT group, p<.05	NR	Significant relief in E2/MT group, p<.05

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Penotti, 2001	NR	NR	No difference observed between the 2 groups of VAS scores at any of the time points (baseline, 4 months, 8 months)	NR	NR
Raisz, 1996	NR	CEE 5 E2/MT 4	NR	NR	Markers of bone formation and resorption, lipids, and SHBG

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Penotti, 2001	HRT 2/20 and HRT + T 5/20	HRT + T: 3	Hyperandrogenism Nausea, nervousness, and Aggressiveness in 2 patients	VAS (visual analogue scale) used to evaluate changes in psychological well-being and sexual desire and satisfaction
Raisz, 1996	NR	NR	Headache (6 CEE; 2 E2/MT) Breast pain (6 CEE; 3 E2/MT) Acne (1 CEE; E2/MT) Bleeding (CEE 5; E2/MT 4)	Results reported by 3 groupings: Somatic symptoms: hot flashes, sweating episodes, vaginal dryness Psychosomatic symptoms: fatigability, insomnia, palpitations Psychological symptoms: irritability, nervousness, depression, anxiety, decreased concentration.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Shifren, 2000	75	DB RCT	P	36 weeks	Surgically menopausal women with impaired sexual function. Mean age 47 (31-56)	Inclusion: 1. Women 31-56 years old at nine clinics in the United States 2. Undergone bilaterial salpingo-oophorectomy and hysterectomy before natural menopause between 1-10 years earlier 3. Had serum testosterone concentrations < 30 ng/deciliter or serum free testosterone concentrations < 3.5 pg/milliliter 4. Received CEE of > 0.625/day orally for > 2 months 5. Been in stable, monogamous, heterosexual relationship for > 1 year 6. Had BMI between 19.5 - 33.5 7. Impaired sexual function determined by questionnaire (score < 33.6 on Brief Index of Sexual Functioning for Women) Exclusion: 1. Received oral, topical, or vaginal androgen therapy in previous 3 months, or injectaable or implantable androgen therapy in previous 6 months 2. Had > 20 moderate or severe hot flashes per week 3. Had severe acne (grade 3 on Palatsi et al scale) 4. Mild or severe hirsutism (score of > 6 on Loprinzi scale) 5. Hyperlipidemia 6. Psychiatric illness 7. Dyspareunia 8. Physical limitations that interferred with normal sexual functioning 9. Receiving glucocorticoids, selective serotonin-reuptake inhibitors, tricyclic antidepressants, antiandrogen agents, ginseng, yohimbine, phytoestrogens, dehydroepiandrosterone, or melatonin

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Shifren, 2000	BISF-W PGWB	75/75	75/75	NR	NR	NR	NR	0	25.8 (19.5-33.5)	Testosterone 150 + 300 mcg/day Transdermal

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic
Shifren, 2000	Oral CEE 0.625 mg/day - 41 CEE 0.9 mg/day - 12 CEE 1.25 mg/day - 20 CEE 1.8 mg/day - 1 CEE 2.5 mg/day - 1	No change from baseline	NR	NR	Significant increase in depressed - mood measure of PGWBI in testosterone 300 mcg/d group only, p=0.03	NR	NR

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Shifren, 2000	NR	NR	Composite score of BISF increased for all treatment groups, p=0.05	Mean composite score of PGWBI increased for all treatment groups, p=0.04	No significant effects on total cholesterol, HDL, LDL, triglycerides, fasting glucose or insulin, blood counts, or LFT's.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Shifren, 2000	18	4	Anxiety - 2 Nipple discharge - 1 Skin reaction - 1	Participants on variable doses of estrogen.

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	N	Study design	Comp-arison	Length of Trial	Population	Inclusion/Exclusion Criteria
Simon, 1999	93 in 5 groups	RCT	P	3 months	Naturally menopausal women with mild to moderate vasomotor symptoms. Mean age 53.7	Inclusion: 1. Naturally menopausal women with both ovaries intact 2. Recruited from Georgetown University (Washington, DC), The Worcester Foundation for Experimental Biology (Worcester, MA), The Middleton Foundation (Olympia, WA) 3. Experienced amenorrhea > 6 months duration (range 6 months - 14 years) prior to study 4. Had follicle-stimulating hormone levels > 55 mIU/mL, normal clinical laboratory test results (biochemistry, hematology, thyroid function, and lipid profile), normal Pap smear, EKG, and mammogram prior to entering study 5. Experienced mild to moderate vasomotor symptoms 6. Non-smoker 7. Within + 25% of ideal body weight (based on Metropolitan Life Insurance tables) 8. In heterosexual relationships of > 1 year duration Exclusion: 1. Receiving estrogens, progestins, androgens, or anabolic steroids within 8 weeks of study enrollment 2. Active breast, uterine, or ovarian cancer or history thereof 3. Recent history of vaginal bleeding
Watts, 1995	66 in 2 groups	DB RCT	HH	2 years	Surgically menopausal women	Inclusion: 1. 21-60 years old 2. Surgically menopausal: Undergone bilateral oophorectomy and hysterectomy at least 4 weeks before study entry Exclusion: 1. Had concomitant illness

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Specific Characteristics of Population								
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen
Simon, 1999	Kupperman	0	0	NR	0	0	100% non-smokers	NR	Mean 27.1	E2 0.625 + MT 1.25 mg/day E2 1.25 + MT 2.5 mg/day
Watts, 1995	Modified Kupperman with 0-7 scale	66/66	66/66	NR	0	NR	NR	NR	E2-24.9 E2/MT-25.8	E2 1.25 mg/day oral

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

		Main Outcomes					
Study/Year	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic
Simon, 1999	E2 0.625 mg/day E2 1.25 mg/day	All active treatment groups shared significant improvement ($p \leq 0.05$)	All active treatment groups shared significant improvement ($p \leq 0.05$)	No treatment effect	No treatment effect	NR	All active treatment groups shared significant improvement ($p \leq 0.05$)
Watts, 1995	E2 1.25 mg/day + MT 2.5 m/day oral	No difference between treatment groups at baseline or after treatment	No difference between treatment groups at baseline or after treatment	No difference between treatment groups at baseline or after treatment	NR due to small numbers of symptomatic patients	NR	NR due to small numbers of symptomatic patients

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Main Outcomes continued

Study/Year	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life	Other Outcomes
Simon, 1999	NR		NR	NR	Sex hormone levels
Watts, 1995	NR	NR	NR	NR	Lipids and Spinal bone mineral density

Appendix F. Evidence table 6-3. Key Question 3C Testosterone

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Simon, 1999	3	1 - high dose estratest	Rash	Only somatic symptoms reported
Watts, 1995	E2 3 E2/MT 7	E2 3 E2+MT 5	Headache (E2 16; E2/MT 9) Hot flashes (E2 7; E2/MT 3) Rdema (E2 10; E2/MT 10) Breast pain (E2 9; E2/MT 13) Hair disorder (E2 1; E2/MT 12) Acne (E2 2; E2/MT 10)	Modified Kupperman scale used to assess menopause symptoms.

Appendix F: Evidence table 6-3. Key Question 3C Testosterone

Key/Abbreviations

A = Androgen
BISF-W = Brief Index of Sexual Function for Women
BMD = Bone mineral density
BMI = Body mass index
CEE= Conjugated equine estrogens
DB = Double blind
E = Estrogen
E2 = Estradiol
EE = Esterified Estrogen
HH = Head to head
HRT = Hormone replacement therapy
MT = Methyltestosterone
NR = Not reported
P = Placebo
PDS = Personal Distress Scale
PFSF = Profile of Female Sexual Function
PGWB = Psychological General Well-Being
PGWB-I = Psychological General Well-Being Index
QUALMS = Quality of Life Menopause Scale
RCT = Randomized controlled trial
SAL = Sexual Activity Log
SERMs = Selective Estrogen Receptor Modifiers
SIQ = Sexual Interest Questionnaire
SRS = Sabbatsberg Revised Sexual Rating Scale
SSRI = Selective Serotonin Reuptake Inhibitor
T = Testosterone
VAS = Visual Analogue Scale

Appendix F. Evidence table 6-4. Key Question 3C DHEA

Study/Year	N	Study design	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Barnhart, 1999	60 in 2 groups	DB RCT	P	3 months	Perimenopausal women with altered mood and well-being. Mean age 48 (45-55)	Inclusion: 1. Perimenopausal women 2. 45-55 years old 3. Symptoms include fatigue, lack of energy, anxiety, tension, irritability, depression, insomnia, forgetfulness, concentration difficulties, decreased libido, or global reports of a decreased sense of well-being Exclusion: 1. Any contraindication to HRT 2. Exposure to injectable or implantable sex steroid within 6 months or systemic steroid within 90 days of treatment 3. Used antidepressants and/or antianxiolitics 4. Current diagnosis of major psychiatric disorder, diabetes mellitus, hypercholesterolemia, or cardiovascular disease 5. Abnormal renal or liver function
Stomati, 1999	22 in 3 groups	RCT	HH	3 months	Postmenopausal women (50-55 years)	Inclusion: 1. Postmenopausal women 2. 50-55 years old 3. Climacteric complaints 4. Normal body mass index 5. Basal plasma DHEA levels < 5 ug/ml Exclusion: 1. Previous or current estrogen-dependent neoplasia, thromboembolic disease, liver, pancreatic or renal disease, and diabetes mellitus

Appendix F. Evidence table 6-4. Key Question 3C DHEA

		Specific Characteristics of Population								Treatment	
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)	Main Drug type; dose; regimen	Other Drugs type; dose; regimen
Barnhart, 1999	DSR (0-4 scale), Profile of Mood Scale, Ham-D, SmithKline Beecham Quality of Life Self-Report Questionnaire, Buschke Immediate Recall and Delayed Recall, Symbol Copying and Digit Symbol Substitution Tests	NR	NR	NR	NR	NR	NR	NR	NR	DHEA 50 mg/day oral	Placebo
Stomati, 1999	Kupperman (0-3 scale, where 0=none and 3=marked)	NR	NR	NR	NR	NR	NR	NR	NR	DHEAs 50 mg/day oral	DHEAs 50 mg/day + Estradiol 50 mg/day trans or Estradiol 50 mg/day

Appendix F. Evidence table 6-4. Key Question 3C DHEA

	Outcomes										
Study/Year	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunc-tion**	**Quality of Life**	**Other Outcomes**
Barnhart, 1999	No significant difference between study groups	No significant difference between study groups	No significant difference between study groups	No significant difference between study groups	No significant difference between study groups	No significant difference between study groups	No significant difference between study groups	NR	No significant difference between study groups	No significant difference between study groups	Sex hormones and lipids
Stomati, 1999	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-4. Key Question 3C DHEA

Study/Year	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Barnhart, 1999	6	3	Rash (placebo) Abdominal pain/fatigue (placebo) Paresthesia (DHEA)	Subjects from both study groups had decreased total perimenopausal symptoms and improvements in components of health-related quality of life, p<0.01.
Stomati, 1999	0	0	NR	Similar significant progressive improvement in Kupperman score with all treatment groups (p<0.01). Specific components of Kupperman score not reported individually.

Key/Abbreviations

BMI = Body mass index
DB = Double blind
DHEA = Dehydroepiandrosterone
DSR = Daily Symptom Rating Calendar
HAM-D = Hamilton Depression Rating Scale
HH = Head to head
HRT = Hormone replacement therapy
NR = Not reported
P = Placebo
RCT = Randomized controlled trial
SERMs = Selective Estrogen Receptor Modifiers

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Baracat, 2002	85 in 2 groups	open RCT	HH	12 months	Postmenopausal women with intact uterus. EE/MPA mean age: 53 (45-65) Tibolone mean age: 51	Inclusion: 1. Ages 45-65 years 2. Intact uterus 3. Natural menopause > 6 months prior 4. > 4 hot flushes/day Exclusion: 1. History or presence of clinically significant physical disease, undiagnosed vaginal bleeding, hypertension, obesity, excessive smoking, alcohol or drug abuse 2. >Pap smear class III 3. Use of estrogens, progestins, androgens, Tibolone, or lipid-lowering agents within 90 days of evaluation 4. Known sensitivity to an investigational or a related drug
Benedek-Jaszmann, 1987	60 in 2 groups	DB RCT	P	12 months	Post-menopausal women attending a menopause clinic. Age 44-61	Inclusion: 1. Menopausal Exclusion: 1. Current or past h/o cancer or thromboembolic disease
Berning, 2000	94 in 3 groups	RCT	P	2 years	Post-menopausal (1-3years), non-smoking, White, with a BMI < 27. Mean age 52.7	Inclusion: 1. White 2. Non-smoking 3. BMI<27 Exclusion: 1. No disease 2. No medication that influences calcium metabolism

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Baracat, 2002	4 point scale, hot flashes calculated separately	0	1/85	NR	0	NR	NR	Excluded	CEE/MPA 25.3 Tibolone 25.0
Benedek-Jaszmann, 1987	4 point scale	NR	NR	NR	0/60	NR	NR	NR	NR
Berning, 2000	NR	0/94	0/94	NR	NR	NR	NR	NR	Median 24.3

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Baracat, 2002	Tibolone 2.5 mg/day oral	CEE/MPA 0.625/5 mg/day oral	Decreased intensity and mean number hot flashes in both groups. No significant difference between groups	Significant improvement in both treatment groups, p value not reported.	Improvement in both groups. No significant difference between treatment groups.
Benedek-Jaszmann, 1987	Tibolone 2.5 mg/day	Placebo	Improved in Tibolone group throughout study, p<.05	NR	Improved in Tibolone group at month 3 only, p<.05
Berning, 2000	Tibolone 1.25 mg/day n=36 Tibolone 2.5 mg/day n=35 Placebo n=23	Placebo	NR	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Baracat, 2002	Improvement in both groups. No significant difference between treatment groups.	Improvement in both groups. No significant difference between treatment groups.	Improvement in both groups. No significant difference between treatment groups.	NR	No significant difference between treatment groups.	Improvement in both groups. No significant difference between treatment groups.	NR
Benedek-Jaszmann, 1987	Improved in Tibolone group at month 6 only, p<.05	NR	NR	NR	NR	NR	NR
Berning, 2000	NR	NR	NR	NR	Compared to placebo, Increased number bleeders in Tibolone 2.5 mg group, p<.05. Non significantly increased number bleeders in Tibolone 1.25 mg group. Total number bleeding episodes significantly increased in Tibolone 2.5 mg compared to Tibolone 1.25 mg, p<.05 and placebo, p<.01.	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Baracat, 2002	Cholesterol levels Weight gain	CEE/MPA: 5 Tibolone: 4	CEE/MPA: 4 Tibolone: 3	HeadacheT-2.5%, CEE 6.7% Nausea Breast pain T 2.5%, CEE 11% Vaginal bleeding CEE only Pelvic pain T5%, CEE4.4%, Fatigue/HTN/leg cramps/low back pain -T2.5% CEE2.2%, Dysuria-7.5%,	4 point scale: 0 (absent) to 3 (severe). Hot flushes per cycled calculated as: sum of mean number of hot flushes per day multiplied by respective score 0 (absent) to 3 (severe).
Benedek-Jaszmann, 1987	Cholesterol, Irritability improved in Tibolone group at months 1, 6, 12, p<.05. Psychic instability improved in Tibolone group at months 1, 3, 6, 12, p<.05.	Tibolone: 6 Placebo: 11	Tibolone: 4 Placebo: 4	Weight gain (T-2, P-1) Limb pain (T-2, P-1) Skin problem (P-1) Nausea (P-1)	4 point scale: 0 (absent) to 3 (severe). Clinical parameters measured at month 1, 3, 6, 9, 12.
Berning, 2000	Estradiol levels and endometrial morphology	Tibolone 1.25: 3 Tibolone 2.5: 3 Placebo: 4	Tibolone 1.25: 2	Vaginal bleeding (T1.25-1), Skin reaction (T1.25-1)	This study not designed to assess effects of Tibolone on menopausal symptoms.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Dansuk, 2002 (Abstract only)	140 in 2 groups	RCT	HH	3 months	Hysterctomized postmenopausal women	Inclusion: 1. Women who were hysterectomized > 1 year prior Exclusion: 1. Previous estrogen use 2. Use of lipid lowering drugs
De Aloysio, 1987	124 in 3 groups	Open RCT	P	4 months	Post-menopausal women attending a menopause clinic.	Inclusion: 1. Post-menopausal Exclusion: 1. No endometriosis, fibrocystic mastitis, estrogen-related tumors, anemia, thromboembolic or liver disease, HT preceding 6 months, medications, early menopause
Egarter, 1996	129 in 2 groups	Un-blinded RCT	HH	6 months	Postmenopausal women on no HRT for at least 6 months. Mean age approximately 53.5	Inclusion: 1. Spontaneous menopause > 12 months prior 2. No use of HRT in last 6 months Exclusion: 1. Use of short-acting hormones within 3 months 2. Hysterectomy 3. Injection of long-acting estrogens within 6 months 4. Existing or suspected hormone-dependent tumors, vaginal bleeding of unknown etiology, severe liver disorders, current or previous cardiovascular or cerebrovascular disorders

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Dansuk, 2002 (Abstract only)	Kupperman	140/140	NR	NR	NR	NR	NR	0	NR
De Aloysio, 1987	NR	24/124	24/124	NR	0/124	NR	NR	No HRT in prior 6 months	Tibolone approx 23 Placebo approx 25 Control approx 25
Egarter, 1996	Kupperman Index	0/129	NR	NR	0	NR	NR	No HRT in past 6 months	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Dansuk, 2002 (Abstract only)	Tibolone 2.5 mg/day oral	E2 0.05 mg/day Transdermal	NR	NR	NR
De Aloysio, 1987	Tibolone 2.5 mg/day n=35	Placebo IM injection n=46 Control n=43	Improved in Tibolone group, p<.01	NR	No significant difference between treatment and placebo or control groups.
Egarter, 1996	Tibolone 2.5 mg/day oral	CEE 0.625 mg/day + medrogestone 10 mg/day for 12 days/month	Improvement in both groups. No difference between groups.	Improvement in both groups. No difference between groups.	Improvement in both groups. No difference between groups.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Dansuk, 2002 (Abstract only)	NR	NR	NR	NR	NR	NR	NR
De Aloysio, 1987	NR	NR	NR	NR	NR	NR	NR
Egarter, 1996	Improvement in both groups. Higher significance level in Tibolone group, p<0.001 vs. p<0.01.	NR	Overall, improvement in both groups with no significant difference between groups.	NR	NR	Improvement in both groups. Higher significance level in Tibolone, p<0.001, than CEE/medrogestone p<0.05.	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Dansuk, 2002 (Abstract only)	Cholesterol levels	0	0	NR	No difference in climacteric symptoms reported between the 2 treatment groups. Specific categories not reported.
De Aloysio, 1987	Cholesterol, BMI, BP, electrolytes, coagulation, gonadal hormones	Tibolone: 21 Placebo: 10 Control: 13	Tibolone: 5 Placebo: 2	Uterine bleeding (T-3), Weight gain (P-1), Anxiety (P-1), GI distress (T-2)	
Egarter, 1996	Endometrial thickness	Tibolone: 15 CEE/medrogestone: 18	Tibolone: 3 CEE/medrogestone: 6	Weight gain T-2, HRT-4 Bleeding HRT-4 Headache T-2, HRT-2 Leg pain T-4	Treatment groups were significantly different at baseline with regard to nervousness.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Hammar, 1998	437 in 2 groups	DB RCT	HH	48 weeks	Symptomatic menopausal women	Inclusion: 1. Physically and mentally healthy women 2. > 1 year since last menstrual bleeding 3. Menopausal complaints 4. Intact uterus 5. BMI < 30kg/m2 Exclusion: 1. Usual exclusion criteria for HRT applied
Huber, 2002	501 in 2 groups	DB RCT	HH	1 year	Postmenopausal women with intact uterus < 65. Mean age: 55	Inclusion: 1. Postmenopausal women with last period > 12 months prior 2. Under the age of 65 years 3. If date of natural menopause is unknown due to HRT use, women must be > 53 years and received HRT for > 2 years with it ending with progestin phase 4. Intact uterus 5. BMI of 18-29 kg/m2 Exclusion: 1. Presence or history of hormone-dependent malignancies, known or suspected hypercholesterolemia, hypertension, liver disease, endometrial hyperplasia, undiagnosed vaginal bleeding, prophyria, haemoglobinopathie 2. Presence or history of cardiovascular, cerebrovascular or thromboembolic disorders 3. Use of HRT during last month prior to start 4. Previous use of implantable or injectable HRT 5. Concomitant use of sex hormones or any drugs that could interfere with trial medication 6. Drinking > 4 glass of alcohol/day

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hammar, 1998	5 point scale	0/437	NR	NR	NR	NR	NR	NR	Tibolone 24.6 E2/NETA 24.3
Huber, 2002	Q-LES-Q PGWBI GCS LUCRS	0/501	NR	NR	NR	NR	< 4 alcoholic beverages per day	No HRT one month prior to trial	Tibolone 24.8 CEE/MPA 24.7

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Hammar, 1998	Tibolone 2.5 mg/day oral	E2 NETA 2 mg/day oral	Improvement with both treatments. Significantly greater decrease with E2/NETA at last visit, p<0.001.	Improvement with both treatment groups, p<0.0001.	NR
Huber, 2002	Tibolone 2.5 mg/day oral	CEE 0.625 mg/day + MPA 5 mg/day oral	No significant difference between groups on GCS	No significant difference between groups on GCS	No significant difference between groups on GCS

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Hammar, 1998	NR	NR	NR	NR	Decreased in Tibolone group, p<0.0001.	NR	NR
Huber, 2002	No significant difference between groups on PGWBI or GCS	NR	No significant difference between groups on GCS	No significant difference between groups on LUCRS	Significantly decreased in Tibolone group during cycles 1-3, p=0.002 and 4-6, p=0.004.	Significantly improved sexual interest, drive, and/or performance in Tibolone group at 12 months, p=0.017 (Q-LES-Q).	Significant differences between group in sexual drive and economic domains of Q-LES-Q only (see appropriate boxes).

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Hammar, 1998	NR	Tibolone: 54 E2/NETA: 68	Tibolone: 34 E2/NETA: 55	Breast tenderness T-44, E2-119 Edema T-72, E2-61 Nausea T-51, E2-63 Bleeding T-9, E2-37	Menopausal symptoms rated on a 5 point scale (1 = none; 5 = very severe).
Huber, 2002	Economic status score of Q-LES-Q higher at 3 months for CEE/MPA group, p=0.029.	Tibolone: 62 CEE/MPA: 50	Tibolone: 38 CEE/MPA: 33	Vaginal bleeding T-20, HRT-15 Breast tenderness T-6, HRT-43 HeadacheT-22, HRT-17; Back pain T-13, HRT-11; Body pain T-4, HRT-12; Depression T-11, HRT-10; Weight gain T-9, HRT-8; Anxiety T-8, HRT-3, Uterine bleeding T-20, HRT-15	

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Hudita, 2003	162 in 2 groups	DB RCT	P	24 weeks	Non-obese postmenopausal women with intact uterus. Mean age approximately 56 (40-65).	Inclusion: 1. Age 40-65, intact uterus 2. Amenorrhea for 12 months 3. FSH >30 mIU/ml 4. 17 beta-estradiol <50pg/ml Exclusion: 1. History of VTE disease 2. GYN cancer 3. Uncontrolled DM 4. Abnormal mammogram/pap/ lab values 5. History of kidney/liver disease 6. Use of hormones 8 weeks prior to study 7. Other criteria
Johannes, 1997 (abstract only)	770 in 4 groups	DB RCT	P	12 weeks	Non-hysterectomized post-menopausal women. Mean age: 52	Inclusion: 1. Postmenopausal women 2. Non-hysterectomized
Kö kçü, 2000 (abstract only)	50 in 2 groups	RCT	HH	1 year	Women with natural menopause. Mean age not reported.	Inclusion: 1. Women with natural menopause Exclusion: 1. Contraindication for HRT

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hudita, 2003	McCoy Sex Scale (modified), 5 point scale for menopausal symptoms	0/162	NR	NR	0/162	0/162	NR	No hormones 8 weeks prior to study	Mean approximatel y 25
Johannes, 1997 (abstract only)	NR	0/770	NR	NR	NR	NR	NR	NR	24.8
Kö kçü, 2000 (abstract only)	Questionnaire	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Hudita, 2003	Tibolone 1.25 mg/day Tibolone 2.5 mg/day	Placebo	Significant improvement in both treatment groups at 4, 12, and 24 weeks, p<.01. Greater improvement at 4 weeks with Tibolone 2.5 mg than Tibolone 1.25 mg, p<.05	Significant improvement in both treatment groups at 4, 12, and 24 weeks, p<.01. Greater improvement at 4 and 8 weeks with Tibolone 2.5 mg than Tibolone 1.25 mg, p<.05	NR
Johannes, 1997 (abstract only)	Tibolone 0.625 mg/day 1.25 mg/day 2.5 mg/day 5.0 mg/day oral	Placebo	Significant decrease in incidence with 1.25, 2.5, and 5.0 mg/d dose, p<0.05.	NR	NR
Kö kçü, 2000 (abstract only)	Tibolone 2.5 mg/day oral	CEE 0.625 + MPA 2.5 mg/day oral	NR	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Hudita, 2003	NR	NR	NR	NR	Significantly increased bleeding at week 12 in both treatment groups, p<.05	Significant improvement in both treatment groups at weeks 4, 12, and 24, p≤.05. Tibolone 1.25 mg had greater improvement at week 12 than Tibolone 2.5 mg, p<.05. Tibolone 2.5 mg had greater improvement at week 24, p<.05.	NR
Johannes, 1997 (abstract only)	NR	NR	NR	NR	Higher incidence in 5.0 mg/d group in comparison to other doses and placebo, p value not reported.	NR	NR
Kö kçü, 2000 (abstract only)	NR	NR	NR	NR	NR	Significantly increased sexual desire in Tibolone group, p<0.05.	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Hudita, 2003	Cholesterol levels	42	NR	Breast discomfort (Tibolone 1.25-2, Tibolone 2.5-4) Fluid retention (Tibolone 1.25-3, Tibolone 2.5-2) Vaginal spotting (Placebo-2, Tibolone 1.25-4, Tibolone 2.5-2) Headache (Placebo-2, Tibolone 1.25-3, Tibolone 2.5-2) Nausea (Placebo-1)	
Johannes, 1997 (abstract only)	NR	NR	NR	Bleeding	
Kö kçü, 2000 (abstract only)	Both treatment groups with significant improvement in subjective well-being and vasomotor symptoms, p<0.05.	NR	NR	NR	No significant difference in side effects between treatment groups. Specific side effects not reported.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Lam, 2004	100 in 2 groups	DB RCT cross-over	P	13 months	Postmenopausal Chinese women from Hormone Replacement Clinics. Mean age approx 50.	Inclusion: 1. Married 2. Intact uterus 3. FSH> 30 IU/L 4. Estradiol < 100 pmol/L Exclusion: 1. Breast/endometrial cancer 2. Liver/kidney disease 3. Thromboembolic disease

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Lam, 2004	GCS, GHQ, DAS (Dyadic Adjustment Scale)	0/100	NR	NR	0/100	0/100	NR	No hormones in prior 6 months	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Lam, 2004	Tibolone 2.5 mg/day	Placebo	Both groups with significantly reduced vasomotor sub score of GCS; p<.05	Both groups with significantly reduced urogential sub score of GCS, p<.05	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Lam, 2004	Significantly reduced depression sub score of GCS in treatment group, p<.05	NR	Significant reduction in somatic sub score of GCS in treatment group, p<.05	Both groups with significantly reduced urogential sub score of GCS, p<.05	NR	Both groups with significantly reduced sexual sub score of GCS, p<.05	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Lam, 2004	Marital quality of couples assessed by DAS	Tibolone: 4 Placebo: 2	NR	Muscle/bone pain (T-2; P-1) Weight gain (T-2, P-1) Headache (T-1)	Modified McCoy Sex Scale used 5 point system. GCS score significantly decreased in both treatment group, p<.05

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Landgren, 2002	775 in 5 groups	DB RCT	P	12 weeks	Healthy post menopausal women with hot flushes and sweating. Mean age approximately 52 (40-60).	Inclusion: 1. Non-hysterectomized women aged 40-60 years 2. Absence of spontaneous vaginal bleeding for > 10 months prior to start 3. > 1 moderate-severe hot flush/day 4. Body weight between 80%-130% of ideal weight Exclusion: 1. History or presence of any malignant disorder, cardiovascular or cerebrovascular disease, thromboembolism/thrombosis, hepatic or renal disease, epilepsy or classical migraine, vaginal bleeding of unknown etiology, hypertension, rheumatoid arthritis, diabetes mellitus, hyperlipidaemia, any serious disease or psychiatric disorder, hypersensitivity to oestrogen and/or progestin, disease for which exogenous hormonal steroids are contraindicated 2. Use of sex steroids within 6 weeks 3. Ethinyloestradiol within the last 6 months 4. Hormone implants at any time 5. One or more of the following drugs during the last two months: hydantion, barbiturates, primidone, carbamazepine, rifampicine, griseofulbin, drugs for treating climacteric symptoms 6. Alcohol abuse and/or drug abuse within the last 12 months 7. Smoking > 10 cigarettes/day

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Landgren, 2002	Collins and Landgren Rating Scale	0/775	NR	NR	0/775	NR	NR	NR	Placebo - 25.0 0.625mg group - 24.5 1.25mg group - 24.8 2.5mg group - 24.9 5.0mg group - 24.9

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Landgren, 2002	Tibolone 0.625 mg/day 1.25 mg/day 2.5 mg/day 5 mg/day	Placebo	Significant decrease in frequency with 1.25 mg, 2.5 mg, and 5.0 mg doses, p<0.0125	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Landgren, 2002	NR	NR	NR	NR	Dose-related increased vaginal bleeding and spotting. Highest incidence in the 5 mg/d group. Observed throughout 12 week study.	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Landgren, 2002	Sweating episodes significantly decreased in the 1.25, 2.5, and 5mg/d groups, p<0.0125.	99	36	Vaginal bleeding (T and P) others not reported	

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Lloyd, 2000	29 in 2 groups	DB RCT	P	6 months	Hypertensive post-menopausal women. Mean age approximately 61	Inclusion: 1. Women with hypertension 2. > 1 year postmenopausal Exclusion: 1. Intrinsic renal disease, insulin dependent diabetes, past history of an oestrogen dependent tumor 2. Use of sex steroid compounds, previous HRT, progesterone, Tibolone, or tamoxifen within previous 3 months
Meeuwsen, 2002	85 in 2 groups	DB RCT	P	1 year	Health women postmenopausal for 1-15 years. Mean age approximately 54.	Inclusion: 1. > 1 year but < 15 years after natural menopause Exclusion: 1. Presence or history of sex hormone dependent malignancies 2. Use of HRT or other steroid medication or muscle growth affecting drugs during last 6 months 3. Hypertension, active liver disease 4. Presence or history of endometrial hyperplasia with or without atypia, undiagnosed vaginal bleeding 5. Presence or history of cardiovascular, cerebrovascular or thromboembolic disorders 6. Consumption of > 4 alcoholic drinks/day 7. Pophyria, haemoglobinopathy 8. Use of sex hormones, anabolcs, corticosteroids, insulin, anti-coagulants or enzyme-inducing drugs 9. Participating in a clinical trial during the last 3 months 10. BMI below 18 kg/m2 or above 29 kg/m2 11. Concomitant medication that could interfere with the study

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Lloyd, 2000	GHQ	NR	NR	NR	NR	No tamoxifen within prior 3 months	3/30	No HRT within prior 3 months	Tibolone 33.9 Placebo 29.6
Meeuwsen, 2002	NHP	Tibolone: 4 Placebo: 5	0/85	NR	NR	NR	NR	No HRT 6 months prior to trial	25 in both groups

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Lloyd, 2000	Tibolone 2.5 mg/day oral	Placebo	NR	NR	NR
Meeuwsen, 2002	Tibolone 2.5 mg/day oral	Placebo	Significantly decreased in Tibolone at cycle 12 in comparison to placebo, p<0.05	NR	Significant improvement in Tibolone group in comparison to placebo, p<0.05 by NHP score.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Lloyd, 2000	NR	NR	NR	NR	NR	NR	No significant differences within or between treatment and placebo at baseline and 6 months.
Meeuwsen, 2002	No significant difference between treatment groups by NHP score.	NR	No significant difference between treatment groups in energy, pain, social isolation.	No significant difference between treatment groups.	Overall increased frequency in Tibolone group, p<0.05.	NR	No significant difference in overall NHP score between treatment groups.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Lloyd, 2000	Blood pressure and lipids	Tibolone: 2 Placebo: 2	Tibolone: 1 Placebo: 1	Headache (numbers not reported) Nausea (numbers not reported) Flushing (numbers not reported) , Uterine bleeding T-4 P-1	Primary outcome was effect of Tibolone on blood pressure and biochemical cardiovascular risk factors in hypertensive women. Quality of life reported as a secondary outcome.
Meeuwsen, 2002	NR	Tibolone: 1 Placebo: 2	Tibolone: 1 Placebo: 0	Malaise T-2 Vaginal bleeding (but no Withdrawal due to vaginal bleeding) T-16, P-4; Abnormal mammogram P-1	NHP used to assess quality of life and organized into 6 domains: emotional reactions, energy, pain, physical mobility, sleep, and social isolation.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Mendoza, 2000	76 in 2 groups	RCT	HH	1 year	Surgically menopausal women < 50. Mean age not reported	Inclusion: 1. Women who underwent a hysterectomy or bilateral oophorectomy for benign gynecologic process 2. 3-4 months from surgery to study entry Exclusion: 1. Prior use of HRT 2. Previous malignant gynecologic process, oestrogen producing tumor, endocrinological or metabolic problems, cardiovascular disease, uncontrolled hypertension, active hepatic disease, serious skin illness, intestinal sickness or chronic obstructive respiratory disease 3. Psychiatric problems or receiving anxiolytic or antidepressive drugs
Mendoza, 2002	165 in 3 groups	RCT	HH	1 year	Postmenopausal women with intact uterus amenorrhea 1-5 years. Mean age approximately 50.	Inclusion: 1. Intact uterus 2. Amenorrhea for 1-5 years 3. Under 60 years of age Exclusion: 1. Hysterectomized women 2. Use of HRT within 3 months prior to start 3. History of a malignant gynecological processes, oestrogen producing tumor, serious endocrine or metabolic disturbances, insulin dependent diabetes, obesity (BMI > 32 kg/m2), unstable hypertension, active liver disease, serious skin disease or chronic obstructive pulmonary disease 4. Psychiatric disturbance or use of anxiolytics or antidepressants

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Mendoza, 2000	Kupperman Index	76/76	76/76	NR	0	0	Alcohol: Tibolone 1/36 Estradiol 0/37 Smoking: Tibolone 11/36 Estradiol 10/37	0	NR
Mendoza, 2002	Modified Kupperman Index	0/165	NR	NR	NR	NR	No alcohol use. Smoking Tibolone 18%. Cyclic combined 23.6%. Intermittent progesterone 20%.	No HRT 3 months prior to trial.	No BMI > 32

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Mendoza, 2000	Tibolone 2.5 mg/day oral	Estradiol 50 mcg/day Transdermal	No significant difference between treatments. Both groups improved.	NR	NR
Mendoza, 2002	Tibolone 2.5 mg/day oral or Estradiol 50 mcg/day x 14 days, then Estradiol 50 mcg/day + NETA 0.25mg/day x 14 days Transdermal	Estradiol 50 mcg/day Transdermal + progesterone 200 mg 2x/week oral.	No significant difference between treatment groups (all improved)	NR	No significant difference treatment between groups.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Mendoza, 2000	No significant difference between treatments. Both groups improved.	NR	NR	NR	NR	No significant difference between treatments.	NR
Mendoza, 2002	No significant difference treatment between groups.	No significant difference treatment between groups.	No significant difference treatment between groups.	NR	NR	No significant difference treatment between groups.	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Mendoza, 2000	Lipids	NR	Tibolone: 3 Estradiol: 1	Headache E2-1 Nausea T-4, E2-1 Skin irritation Breast tenderness E2-4 Weight gain T-1, E2-2 Edema T-1, E2-1 Hirsutism T-1 Nervousness T-1 Endometriosis T-1	
Mendoza, 2002	Lipid profiles	Tibolone: 4 Intermittent progesterone: 3 Cyclic combined: 1	Tibolone: 4 Intermittent progesterone: 3 Cyclic combined: 1	Vaginal bleeding T-3, HRT-25 Headache T-4, HRT-2 Skin irritation HRT-11 Varicose veins Hypertension T-1 Stomach pain T-3 Anxiety HRT-1 Dysmenorrheal HRT-1 Mastalgia HRT-3	Symptoms on Kupperman Scale evaluated by frequency of occurrence (frequently, occasional, never). Symptoms divided into 4 categories: vasomotor, psychological, osteoarticular, and sexual behavior.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Nathorst-Bö ö s, 1997	437 in 2 groups	DB RCT	HH	48 weeks	Postmenopausal women of at least one year or using HRT more than 2 years. All participants > 53	Inclusion: 1. Healthy women 2. > 1 year postmenopausal or using HRT > 2 years 3. > 53 years old at study entry 4. Suffered from hot flushes and sweating 5. Had BMI < 30 6. Had intact uterus Exclusion: 1. Receiving HRT < 1 month prior to study 2. History of atypical endometrial hyperplasia 3. Had severe metabolic or endocrine disease
Palacios, 1995	28 in 2 groups	SB RCT	HH	12 months	Menopausal women, ages 50-60, with no history of HRT, married once, in a stable marriage	Inclusion: 1. Postmenopausal women 2. 50-60 years old 3. Intact uterus and ovaries 4. Married only once and in stable relationship 5. Normal bone densitometry Exclusion: 1. Received hormone therapy during menopause 2. Had known associated diseases
Ross, 1999	36 in 2 groups	RCT	HH	3 months	Peri- and post-menopausal women with climacteric symptoms. Mean age 52 (45-65)	Inclusion: 1. English speaking women > 45 years of age 2. Intact uterus 3. Amenorrhea > 3 months 4. No past psychotic history nor current use of antidepressants or psychotherapeutic agents 5. No contraindications to estrogen therapy

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Nathorst-Bö ö s, 1997	McCoy Sex Scale (Swedish version)	0/437	NR	NR	NR	NR	NR	437/437 discontinue d one month prior	< 30
Palacios, 1995	7 point scale	0	0	NR	NR	NR	NR	0	NR
Ross, 1999	WHQ IDA GCS	0/36	NR	NR	NR	NR	Smokers: Tibolone 9/18 CEE 14/18	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Nathorst-Bö ö s, 1997	Tibolone 2.5 mg/day oral	E2 2 mg/day + NETA 1 mg/day oral	NR	Improvement with both treatment groups. No significant difference between groups.	NR
Palacios, 1995	Tibolone 2.5 mg/day oral	Calcium 500 mg/day oral	NR	NR	NR
Ross, 1999	Tibolone 2.5 mg/day	CEE 0.625 mg/day Norgestrol 150 mg/day 12 days of cycle	No significant difference between the treatment groups on GCS.	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Nathorst-Bö ö s, 1997	NR	NR	NR	NR	NR	Greater improvement in the Tibolone group in regard to the frequency and enjoyment, p<0.05.	NR
Palacios, 1995	NR	NR	NR	NR	NR	Improved total score in Tibolone group, p<0.05	NR
Ross, 1999	No significant difference between the treatment groups (WHQ).	No significant difference between the treatment groups (WHQ).	No significant difference between the treatment groups (WHQ).	NR	No significant difference between the treatment groups (WHQ).	No significant difference between the treatment groups (WHQ).	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Nathorst-Bö ö s, 1997	NR	122	NR	NR	
Palacios, 1995	NR	4	0	NR	One primary goal of study was to demonstrate validity of sexual questionnaire designed by investigators. (10 item questionnaire scored on a 7 point scale.)
Ross, 1999		Tibolone: 2 CEE: 6	Tibolone: 2 CEE: 4	NR	

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Volpe, 1986	113 in 7 groups	RCT	P	6 months	Postmenopausal women	Inclusion: 1. Postmenopausal women 2. Physiological menopause or hysterectomy and oophorectomy 3. Last menstrual period occurred 1-5 years prior to study Exclusion: 1. Received hormone preparations < 8 weeks prior to study 2. Histories or conditions which would contraindicate oestrogen therapy
Winkler, 2000	60 in 2 groups	DB RCT	HH	24 weeks	Healthy post-menopausal women. Mean age approximately 54 (45-70)	Inclusion: 1. Healthy postmenopausal women aged 45-70 years 2. Spontaneous menopause with last period > 36 months prior or artificial menopause with FSH >30IU/L Exclusion: 1. Presence of cardiovascular, cerebrovascular or thromboembolic disorders, hypertension, hypercholesterolemia, liver, renal, thyroid, parathyroid or adrenal disorders, insulin dependent diabetes, undiagnosed vaginal bleeding, malignancy if not cured for > 10 years 2. History or presence of hormone-dependent malignancy 3. Chronic use of medication that might affect metabolism of sex steroid 4. Drug or alcohol abuse within last 12 months 5. Use of investigational drugs with the last 3 months 6. Cigarette smoking

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Volpe, 1986	4 point scale	32/113	32/113	NR	NR	NR	NR	NR	NR
Winkler, 2000	Karolinska Scale	24/60	NR	NR	NR	NR	0 smokers	NR	Tibolone 24.7 HRT 26.0

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Volpe, 1986	1. CE 0.625mg/day for 21 days/month + NETA 5mg/day for 10 days/month 2. CE 0.625 mg/day for 21days/month + CPA 12.5 mg/day for 10 days/month 3. Estradiol valerate 2 mg/day for 21 days/month + NETA 5 mg/day for 10 days/month 4. Estradiol valerate 2 mg/day for 21 days/month + CPA 12.5 mg/day for 10 days/month 5. Estnol 2-4 mg/day	Placebo	Improved in all treatment groups	NR	NR
Winkler, 2000	Tibolone 2.5 mg/day	Estradiol 2 mg/day + Estradiol 1mg/day + norethindrone acetate 1 mg/day	Improved in both groups. No significant difference between groups, p values not reported.	Improved in both groups. No significant difference between groups, p values not reported.	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Volpe, 1986	NR	NR	NR	NR	NR	NR	NR
Winkler, 2000	NR	NR	NR	NR	No significant difference between treatment groups.	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Volpe, 1986	Cholesterol levels	11	NR	NR	Hot flushes scored on 4 point scale: 0 (absent), 3 (mild), 6 (moderate), 9 (severe). All other menopausal symptoms scored on 4 point scale: 0 (absent) to 3 (severe).
Winkler, 2000	Hemostasis measurements	Tibolone: 4 HRT: 4	Tibolone: HRT: 3	Weight gain T-2 Sleep disturbance T-1 Breast tenderness T-3.4%, HRT 25.8% Vaginal bleeding HRT-1	Climacteric symptoms reported as a secondary outcome. Primary outcome was hormone effect on clotting cascade.

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	N	Study design	Comparison	Length of Trial	Population	Inclusion/Exclusion Criteria
Wu, 2001	48 in 2 groups	SB RCT	HH	3 months	Postmenopausal women with at least one climacteric symptom. Mean age 51 (38-56).	Inclusion: 1. Women who were 12-36 months postmenopausal 2. > 1 climacteric symptom
Yang, 1997 (abstract only)	40 in 2 groups	RCT	HH	6 months	Women 1-3 years post-menopause	Inclusion: 1. Postmenopausal women (1-3 years)
Yang, 1999	40 in 2 groups	open RCT	HH	6 months	Symptomatic postmenopausal women. CEE/MPA mean age: 52 Tibolone mean age: 51	Inclusion: 1. Women 1-3 years postmenopausal with significant menopausal symptoms Exclusion: 1. Any of the following: known or suspected tumor; significant bone diseases; cardiovascular, cerebrovascular or thromboembolic disorders; vaginal bleeding of unknown etiology 2. Active gastrointestinal or liver disease or gastrointestinal surgery likely to influence drug absorption 3. Diabetes, renal disease, epilepsy or history of epilepsy, rheumatic arthritis, osteoarthritis, or other arthritic processes severely restricting mobility, thyroid function disorders or adrenal disorders 4. Abuse of drugs or alcohol 5. Medication use that may affect bone/calcium metabolism 6. Uncontrolled hypertension 7. Heavy smokers

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Pre-mature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Wu, 2001	Mc Coy Sex Scale GCS	NR	NR	NR	NR	NR	NR	NR	NR
Yang, 1997 (abstract only)	GCS	NR	NR	NR	NR	NR	NR	NR	NR
Yang, 1999	GCS	NR	NR	NR	0	NR	NR	NR	Tibolone 21.5 CEE/MPA 22.5

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

			Main Outcomes		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes**	**Vaginal Dryness**	**Sleep**
Wu, 2001	Tibolone 2.5 mg/day oral	CEE 0.625 mg/day + MPA 5 mg/day	No significant difference between treatment groups.	Improved in Tibolone group, p<0.05 (GCS).	NR
Yang, 1997 (abstract only)	Tibolone 2.5 mg/day oral	Premarin 0.625 mg/day oral Provera 5 mg/day day 1-12 months oral	NR	NR	NR
Yang, 1999	Tibolone 2.5 mg/day oral	CEE 0.625 + MPA 5 mg/day 12 days/month	Improvement in both treatment groups, p<0.05	NR	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

	Main Outcomes						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Wu, 2001	No significant difference between treatment groups	NR	No significant difference between treatment groups	NR	At 3 months, Tibolone 2/16 HRT 6/16	Improved in Tibolone group, p<0.05 (McCoy Sex Scale).	NR
Yang, 1997 (abstract only)	NR	NR	NR	NR	Reported for both treatment groups, p value not reported.	NR	NR
Yang, 1999	Improvement in both treatment groups, p<0.05.	Improve-ment in both treatment groups, p<0.05	Improve-ment in both treatment groups, p<0.05	NR	NR	Improvement in both treatment groups, p<0.05	NR

Appendix F. Evidence table 6-5. Key Question 3D Tibolone

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Wu, 2001	Hormone and cholesterol levels	12	7 (3 Tibolone, 4 HRT)	Body discomfort T-3, HRT-4	
Yang, 1997 (abstract only)	Improvement of climacteric symptoms reported in both treatment groups, p value not reported.	NR	NR	NR	
Yang, 1999	Bone metabolism Bone density Cholesterol levels Effect on endometrium.	4	NR	Weight gain T-1 Uterine bleeding T-6, HRT-20 Insomnia T-2, HRT-2 Backache T-1, HRT-1 (All Effects in first 3 months)	

Appendix F: Evidence table 6-5. Key Question 3D Tibolone

Key/Abbreviations

BMI = Body mass index
BP = Blood pressure
CE = Conjugated estrogens
CEE= Conjugated equine estrogens
CPA = Cyproterone acetate
DAS = Dyadic Adjustment Scale
DB = Double blind
DM = Diabetes mellitus
E2 = Estradiol
EE = Esterified Estrogen
GCS = Greene Climacteric Scale
GHQ = General Health Questionnaire
HH = Head to head
HRT = Hormone replacement therapy
HTN = Hypertension
IDA = Irritability, Depression, and Anxiety
LUCRS = Local Urogenital Complaints Rating Scale
MPA = Medroxyprogesterone acetate
NETA=norethidrone acetate
NHP = Nottingham Health Profile
NR = Not reported
P = Placebo
PGWB-I = Psychological General Well-Being Index
Q-LES-Q = Quality of Life, Enjoyment and Satisfaction Questionnaire
RCT = Randomized controlled trial
SB = Single blind
SERMs = Selective Estrogen Receptor Modifiers
T = Tibolone
VTE = Venous thromboembolism
WHQ = Women's Health Questionnaire

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
David 1988	50	RCT	P	4 20-day courses	Patients from menopause clinic in Israel; aged 32-81; many postmenopausal for many years	NR
Evans 2005	80	RCT	P	12 weeks	Postmenopausal, symptomatic women. Recruited through newspapers, radio, direct mailings, and flyers posted in physicians' offices.	Inclusion: 1. Natural or surgical menopause 2. $\geq$ 14 hot flashes per week Exclusion: 1. Known adverse reactions to antidepressants 2. Receiving estrogens, progestins, antidepressants, or chemotherapy

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors* (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
David 1988	HF frequency; severity of perspiration; FSH, LH, testosterone, E2	NR	NR	NR	NR	NR	NR	NR	NR
Evans 2005	Modified Health Survey Short Form 36 mood scale; single-item 5-point scale about hot flashes interfrerence with daily living; daily hot flash diary (severity 1-4).	16/80	NR	NR	NR	NR	Alcohol use 14/40 in controls and 25/40 in treatment	0	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Treatment		Hot Flash Outcomes			
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Reduction in Hot Flash Frequency	Reduction in Hot Flash Severity	Reduction in Hot Flash Composite Score	Other Hot Flash Measure
David 1988	Veralipride 100mg PO qd (V)	Placebo	Pre-post comparisons only: Group 1 (V x 4): 80% reported almost complete disappearance of HF. Group 2 (Px2, Vx2): HF frequency 18 at baseline; 12 with P, almost complete resolution with V. Group 3 (Vx2, Px2): baseline 15, almost complete resolution with V; up to 6-12.	NR	NR	NR
Evans 2005	Venlafaxine XR, 37.5mg daily for 1 week, then 75mg daily	Placebo	No difference between groups.	No difference between groups.	No difference between groups. Both groups had reduction in HF score (no p-value given).	Venlafaxine 51% reduction in patient-perceived hot flush score; Placebo 15% reduction; p<0.001. (single item on interference of HF with daily living)

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Outcomes							
Study/Year	Other Outcomes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
David 1988	All groups had decrease in insomnia and depression with no significant differences.	NR	All groups had decrease in insomnia	All groups had decrease in depression	NR	NR	NR	NR
Evans 2005	NR	NR	NR	Mental health improved in tx vs. P on SF36 (p=0.005)	NR	NR	NR	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Outcomes (cont.)

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
David 1988	NR	NR	LH, testosterone, Prolactin, DHEA	3	0	NR	
Evans 2005	Possibly more sexual dysfunction in tx than P (p=0.11)	Vitality improved in tx vs. P on SF36 (p=0.005)	NR	11/40 in tx; 8/40 in P	Difficulty sleeping decreased libido, nausea and anxiety in tx group	Greater dry mouth, sleeplessness, and decreased appetite in tx than P, but dizziness, tremors, anxiety, diarrhea, and rash less in tx than P.	

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Limouzin-Lanothe, 1994	499	Non-blind RCT	HH	6 months	Enrolled by 101 physicians in France; all literate and "enjoyed a comfortable standard of living"	Inclusion: 1. Natural or surgical menopause with amenorrhea ≥ 3 months but ≤ 3 years 2. ≥4 HF/day and nocturnal sweating Exclusion: 1. HRT since beginning of menopause 2. Symptomatic TX within 1 month 3. "Estrogen-dependent pathologic characteristic"
Melis, 1988	40	DB RCT	P	30 days	Recruitment info NR; Italy	Inclusion: 1. Postmenopausal women aged 48-56 years 2. Physiologic menopause ≥1 year 3. Experiencing hot flashes Exclusion: 1. HRT within 30 days

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors* (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Limouzin-Lanothe, 1994	Women's Health Questionnaire, Psychological General Well-Being Index, Sleep Problems Questionnaire; Sexual Behavior Questionnaire. 10 symptoms on a 4-point scale	NR	NR	NR	NR	NR	Similar Education	0	NR
Melis, 1988	1. HF frequency; HF severity (0-3); and vasomotor score (frequency x severity) by diary; 2. "Objective HF" by skin temp (for 6 hours for 8 women in each group); 3. Plasma LH, FSH, PRL, E2;	NR	NR	NR	NR	NR	NR	0/40	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Treatment		Hot Flash Outcomes			
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Reduction in Hot Flash Frequency	Reduction in Hot Flash Severity	Reduction in Hot Flash Composite Score	Other Hot Flash Measure
Limouzin-Lanothe, 1994	Veralipride 100mg/day first 20 days of each month (V)	Estraderm TTS 50 and chlormandinone 1st 12 days of each month	NR	NR	NR	1 or no HF: HRT: 183/240 (81%) V: 94/239 (44%) (p<0.001); Efficacy judged to be "very good" by clinician: HRT: 128/225 (57%) V: 39/214 (18%) (p<0.001)
Melis, 1988	Veralipride 100mg/day (V)	Placebo	NR	NR	Frequency (0-3) x intensity (0-3) V: 3.0-1.0=2 (66% red) P: 3.1-2.3=0.8 (26% red) p<0.05 (note: interpreted from figure)	# of women experiencing improvement: V: 17/20 (50%) P: 10/20 (50%) p<0.05

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Outcomes							
Study/Year	Other Outcomes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Limouzin-Lanothe, 1994	Measures of quality of life, sleep, sexual function, depression, anxiety, general psychological well being, somatic complaints, cognitive difficulties, social life, family life, professional life, and vitality significantly better with HRT than V, but both groups improved over 6 months	NR	HRT group improved more than Veralipride group (p<0.001)	HRT group improved more than Veralipride group (p<0.001)	HRT group improved more than Veralipride group (p<0.01)	HRT group improved more than Veralipride group (p<0.001)	NR	7/250 in HRT group; 2/249 in V group
Melis, 1988	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Outcomes (cont.)

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Limouzin-Lanothe, 1994	HRT group improved more than Veralipride group (p<0.01)	Clinical efficacy for measures of quality of life, sleep, sexual function, depression (general psychological well being) all significantly better with HRT but both groups improved over 6 months	Attractiveness, social life, and vitality all improved more in the HRT group than in Veralipride group	No follow-up data in 10/250 of HRT and 10/249 of V; Discontinued TX: 21 of HRT and 36 of V.	NR	HRT: 67 local skin reaction, 26 systemic reaction; V: 23 systemic reactions	
Melis, 1988	NR	NR	LH levels opioids Veralipride group had increased PRL and LH	0	NR	0 in placebo group 3 mastodynia in Veralipride group	

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Stearns, 2003	165	DB RCT	P	6 weeks	Menopausal women (recruited from 17 US sites using newspaper ads, women's groups and professional referral networks)	Inclusion: 1. Women over 18 years 2. Menopausal a. Amenorrhea $\geq$ 12 months b. 6 months amenorrhea with increased FSH and E2, or c. Surgical menopause 3. 2-3 hot flashes/day or $\geq$ 14/week Exclusion: 1. Recent psychotropic medication use 2. Major depression or "significant mood or anxiety symptoms" 3. HRT within 6 weeks 4. Active cancer, current chemo or XRT 5. Active psychiatric disorder 6. Intolerance to SSRIs 7. Substance dependence
Tarim, 2002	30	DB RCT	P	5 weeks	Consecutive patients presenting to outpatient menopause clinic of U in Turkey	Inclusion: 1. Aged 35-55 years 2. Post menopausal with amenorrhea of 1 year 3. FSH $\geq$ 40 4. At least 14 hot flashes a week Exclusion: 1. CAD 2. Any psychiatric disorders

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors* (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Stearns, 2003	Daily hot flash composite score (frequency x severity; severity is 1-4); Greene Climacteric Scale 21; sleep disturbance Visual Analogue Scale; Beck anxiety inventory II; Sheehan Disability Scale; Clinical Global Impression global improvement item.	50/165	25/165	NR	12/165	12/165	NR	6 weeks prior	NR
Tarim, 2002	HF weekly severity score (frequency x severity 1-4)	NR	P: 4/9 M 150: 1/10 M 300: 4/11	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Treatment		Hot Flash Outcomes			
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Reduction in Hot Flash Frequency	Reduction in Hot Flash Severity	Reduction in Hot Flash Composite Score	Other Hot Flash Measure
Stearns, 2003	Paroxetine 12.5 Paroxetine 25	Placebo	Paroxetine 12.5 = 3.3 Paroxetine 25 = 3.2 Placebo = 1.8 (p=0.01)	NR	Paroxetine 12.5 = 62.2% Paroxetine 25 = 64.6% Placebo = 37.8% (p<0.03)	NR
Tarim, 2002	Meclopomide 150mg (M 150) or 300mg (M 300)	Placebo	NR	NR	"Weekly severity score" (frequency x severity 1-4) Mean reduction: M150: 69.8% M300: 35.0% P: 24.4%; no p-value given	Decrease of more than 50% in composite score: M150: 8/10 (80%) M300: 5/11 (45%) P: 2/9 (22%) no p-value given

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Outcomes							
Study/Year	**Other Outcomes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**
Stearns, 2003	No significant difference in sleep, depression, anxiety, sexual interest, or disability for the groups	NR	Adjusted mean difference from baseline in sleep disturbance VAS: 12.5mg: -1.38, 25mg: -1.6 P: -1.0 (not significant)	Depression (BDI-I) 12.5mg: -0.73; 25mg: -0.006; P: -0.33 (not significant); Anxiety (BAI-II) 12.5mg: -0.73 25mg: -1.23 P: -1.11 (not significant)	NR	NR	NR	NR
Tarim, 2002	NR	NR	No sleep disturbances reported by any group	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Outcomes (cont.)

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Stearns, 2003	Sexual Interest GCS 12.5mg: -0.02 25mg: -0.02 P: -0.07 (not significant)	NR	Global climacteric score improved Disability (SDS): 12.5mg: 0.83 25mg: 0.01 P: 0.06 (not significant)	12.5mg: 7/51 25mg: 14/58 P: 5/56	12.5mg: 4/51; 25mg: 8/58; P: 2/56	Headaches, dizziness, nausea, dyspnea, insomnia, constipation, lethargy, somnolence - none significant difference than placebo.	
Tarim, 2002	NR	NR	NR	1 in P and 1 in M due to somnolence	1 in P and 1 in M due to somnolence	Somnolence: 1 in each group; No dizziness, nausea, sleep disturbance	

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Wesel, 1984	43	DB RCT	HH	20 days	Women attending a OB-GYN hospital in France	Inclusion: 1. Aged 40-60 years 2. Spontaneous amenorrhea $\geq$ 6 months Exclusion: 1. Genital or mammary cancer 2. Oophorectomy 3. HRT within 30 days
Zichella, 1986	75 (5 groups of 15)	RCT	HH	20 days	Postmenopausal women Recruiting information NR Aged 45-55	Inclusion: 1. Physiologic menopause 1-2 years ago 2. Severe vasomotor symptoms. Exclusion: 1. Endocrinologically active drugs within 6 months

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors* (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Wesel, 1984	HF frequency; HF severity (1-4); HF duration (1-6);	0	0	NR	0/43	NR	NR	> 30 days discontinue	NR
Zichella, 1986	HF frequency (0-3); HF severity (0-3);	0	0	NR	NR	NR	NR	0	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Treatment		Hot Flash Outcomes			
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Reduction in Hot Flash Frequency	Reduction in Hot Flash Severity	Reduction in Hot Flash Composite Score	Other Hot Flash Measure
Wesel, 1984	Veralipride 100mg/day (V)	CEE 1.25mg	V: 54.1-15.6 = 38.5 (71% reduction) CEE: 65.2-14.0 = 51.2 (79% reduction) Not significant	NR	# x intensity (1-4) V: 73-17=56 (77% red.) CEE: 108-18=90 (83% red.) Not significant	NR
Zichella, 1986	Veralipride 100mg qd (V)	Bromocriptine 3.75; Liposom 40mg Imqd; domperidone 10mg qd	NR	NR	HF score: V: 3.5 $\pm$ 0.3 to 1.2 $\pm$ 0.1; P: 3.0 $\pm$ 0.2 to 2.4 $\pm$ 0.1 ($p<0.05$)	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

	Outcomes							
Study/Year	Other Outcomes	Vaginal Dryness	Sleep	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding
Wesel, 1984	NR	NR	NR	NR	NR	NR	NR	NR
Zichella, 1986	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-6. Key Question 3E Antidepressant drugs

Outcomes (cont.)

Study/Year	Sexual Dysfunc-tion	Quality of Life	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Wesel, 1984	NR	NR	NR	3 in CEE group	NR	V: 2 mastodynia, 2 sedation, 4 headache, 3 nausea, 1 asthenia, 1 pelvic pain, 1 venous disorder CEE: 4 sedation	3 stopped V TX due to AE; 4 stopped CEE due to AE.
Zichella, 1986	NR	NR	NR	0	0	V: mastodynia 10; galactorhea 2. 0 with placebo	Also looked at Lipisom, BCT, DOM not abstracted

Key/Abbreviations

AE = Adverse Effect
BAI-II = Beck Anxiety Inventory II
BCT = Bromocriptine
BDI = Beck Depression Inventory
BMI = Body mass index
CAD = Coronary artery disease
CEE= Conjugated equine estrogens
DB = Double blind
DHEA = Dehydroepiandrosterone
DOM = Domperidone
E2 = Estradiol
GCS = Greene Climacteric Scale
HF = Hot flash
HH = Head to head
HRT = Hormone replacement therapy
NR = Not reported
P = Placebo
RCT = Randomized controlled trial
SDS = Sheehan Disability Scale
SERMs = Selective Estrogen Receptor Modifiers
SF-36 = Modified Health Survey Short Form 36
SSRI = Selective Serotonin Reuptake Inhibitor
tx = Treatment
VAS = Visual Analogue Scale

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Andersen 1986	40	DB RCT with cross-over	P	Unclear. 1 week run-in. 2 week wash-out then cross-over. Each treatment period could last up to 8 weeks total or until "troublesome side effects".	Women experiencing hot flushes in the climacteric. Mean age 51 years (range 46-60). Duration of symptoms 0.5-16 years (mean 4 years). Norway	NR
Bergmans 1987	71	DB RCT (meds were random-ized)	P	8 weeks (4 week open study followed)	Women reporting hot flashes and sweats. No mean age reported. Patients from 3 general teaching hospitals. Netherlands.	Description of women included: All reported hot flushes and sweats with $\geq$ 1 of several other somatic complaints. Exclusion: ovariectomized patients, and several medical conditions

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Andersen 1986	Patients recorded the number of hot flashes experienced daily (run-in week and last week of each treatment period). Visual analogue scales used to denote trouble caused by hot flashes and general well-being. Interviewed about side effects and which treatment they preferred. Labs: creatinine, AST, ALT, GGT< WBC, Hgb, Direct Coombs', blood pressure, weight.	NR	NR	NR	NR	None	9/40 had previously been treated with hormones. States no treatment for hot flushes for 6 months prior to enrollment. 2 patients on topical estrogen dropped out.	NR
Bergmans 1987	Body weight, blood pressure. Symptoms rated as absent, slight, moderate, or severe. Efficacy rated by participant and investigator as poor, fair, acceptable, good or excellent.	NR	Ovariec-tomized patients excluded.	Excluded	NR	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes (corrected)
Andersen 1986	Alpha-Methyldopa 375 mg tab nightly, increased by 1 tab every 2 weeks as needed to maximum dose of 1,125 mg nightly Dose adjusted every 2 weeks if needed to maximum dose then maintained for 4 weeks.	Placebo	**Prior to crossover:** No difference in median number between M and P ($p > 0.05$). Improved number of hot flashes for both P (12/19, pNR) and M (14/17, pNR). **Summary statistics:** M group felt less troubled by hot flashes than P ($p<0.05$). General well-being was slightly disfavors M (p NR).
Bergmans 1987	Bellergal Retard (BR) 1 tablet twice daily BR = 0.6 mg ergotamine, 40 mg Phenobarbital, 0.2 mg levorotatory alkaloids	Placebo	Decrease in mean number for both BR and P. No significant difference between BR and P ($p\leq0.001$) at week 12. Decrease in severity for both BR and P. No significant difference between BR and P at week 12. Decrease in sweating for both BR and P. No significant difference between BR and P ($p\leq0.001$) at week 12.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Somatic**	**Uter-ine Bleed-ing**	**Sexual Dysfunc-tion**
Andersen 1986	No significant difference between alpha-methyldopa and placebo in median number of hot flashes. Patients on alpha-methyldopa felt less troubled by hot flashes (p<0.05).	NR	NR	NR	NR	NR	NR
Bergmans 1987	Similar number of baseline hot flashes, mean 14.48/day for BR and 14.55/day for P. The mean number of hot flushes decreased in both BR and P. The only significant difference between BR and P was noted at week 2 (p<=0.001). Hot flush severity decreased in both BR and P. The only significant difference between BR and P was noted at week 2 (p<=0.008). Sweating decreased in both BR and P. The only significant difference between BR and P was noted at week 2 (p<=0.04).	NR	Insomnia was improved for both BR (p=0.002) and P (p=0.03). Statistically significant differences between BR and P for insomnia were only seen at weeks 2 and 4. (BR	Statistically significant decreases in nervousness and hyperirritability were noted for BR and P. No significant between group differences.	Statistically significant de-crease in head-ache, pares-thesia, and dizziness noted for BR. No significant difference between BR and P.	NR	No change in loss of libido with BR, but improved with P (p=0.039). Between group difference s not significant.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Andersen 1986	No significant difference in feeling of well-being (tendency is to feel worse on M).	No significant change in blood pressure or body weight. No abnormal hematological measures.	16/40 (14 dropouts and 2 excluded because flushing not severe enough)	8/40 (4 M, 4P) drowsiness, dry mouth, headache, skin rash	"Substantially more" side effects with M. drowsiness, dry mouth, vertigo, and depression.
Bergmans 1987	NR	Overall efficacy assessed by participant and investigator at the end of the double blind and open study. BR was assessed as excellent or good in 51% of cases, placebo 21%, the difference was statistically significant in favor of BR.	33/71 5 dropped out for personal reasons prior to starting treatment, 12 dropped out from BR and 16 from P.	10/33 BR group 6/33 P group	19/33 in BR group complained of adverse reactions. 18/33 in P group complained of adverse reactions.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Andersen 1986	Distribution of symptoms appears quite different for drop-outs than for those completing the study.	Measures questionable. The authors conclude that M is efficacious for hot flashes. However, there was no difference in the number of hot flashes and overall it appears that participants tended to feel worse when on M. What is the significance of a visual analog score of the degree to which you are troubled by hot flashes? This measure and 62.5% participant preference for M is what drives the author's conclusion.	Question-able benefit for M with significant side effects noted.
Bergmans 1987	Complaints included dry mouth, dizziness, sleepiness, headache, and nausea.	Early in the study some benefit of BR over P noted but effect gone by the end of the 8 week trial.	Bellergal was not more effective than placebo.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Bolli 1975	12	DB RCT with cross-over	P	2 trials 4 weeks each; 2 weeks C or P then cross-over (n=12); 2 weeks higher dose C or P then cross-over (n=8)	Hypertensive women with menopausal flushing. Duration of flushing was 1-16 months (mean 4 months). Mean age 51 years. Dunedin Hypertension Clinic, New Zealand	NR
Carranza-Lira 2001	75 (5 groups 15 each)	SB RCT	HH	3 months	Healthy postmenopausal (≥ 1-5 years) women with vasomotor symptoms and insomnia. No hormones or other treatment for hot flushes, FSH and estradiol in the postmenopausal range. Mean age not reported. Mexico	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Bolli 1975	Daily number of hot flushes, changes in the severity and duration of hot flushes (more, same, less), severity of concomitant perspiration. Side effects.	NR	NR	NR	NR	NR	None had used HRT.	NR
Carranza-Lira 2001	Number of hot flashes per day, intensity of hot flashes on visual scale 0-10, duration in minutes, insomnia and sweating (absent or present).	NR	NR	NR	NR	NR	None had used HRT or other treatment for their symptoms.	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes (corrected)**
Bolli 1975	C 0.0375 mg tab twice daily for first trial C 0.075 mg tab twice daily for second trial	Placebo	**Prior to crossover:** NR **Summary statistics:** Results were the same for Trials 1 and 2. No significant difference in mean number between C and P. No significant difference between C and P in subjective measures.
Carranza-Lira 2001	C 0.10 mg tab every 12 hours	CEE 0.0625 mg tab daily (hysterectomized patients only) propranolol 20 mg tab every 12 hours veralipride 100 mg tab daily from Monday-Friday Placebo tab every 12 hours	

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Somatic**	**Uter-ine Bleed-ing**	**Sexual Dysfunc-tion**
Bolli 1975	Appears that data presented compares patients' Clonidine trials to their placebo trials. No significant difference in mean # of hot flashes between P and C in trial one or two, although both showed significant decrease from baseline.	NR	NR	NR	NR	NR	NR
Carranza-Lira 2001	Hot flash frequency decreased in the CEE and C groups compared to the propranolol, veralipride and placebo groups. Hot flash intensity and duration in CEE users decreased in comparison to the other four groups. Hot flash intensity was lower in C compared to propranolol and P. The presence of sweating was lower in CEE and C compared to propranolol and P.	NR	Insomnia presence was greater in the propranolol group when compared to CEE, clonidine and veralipride. Frequency of presentation of insomnia was greater in propranolol than in CEE and C.	NR	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Bolli 1975	NR	No change in blood pressure with C.	None	None	None
Carranza-Lira 2001	NR	NR	4/75 (1 CEE, 2 propranolol, 1 veralipride)	2/75 (1 CEE and 1 veralipride for drug intolerance)	

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Bolli 1975	Nausea in 1 patient on C.	Data not reported clearly. Summary states significant difference between C and P at higher dose C (150 mcg), but discussions states results of this trial did not reach statistical significance.	No difference between clonidine and placebo.
Carranza-Lira 2001	NR	Method of randomization not disclosed. States patients with contraindication to CEE were randomly distributed to the other 4 four groups. No statement that the patients were blinded. Limited information given. Summary table is essentially uninterpretable.	

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Clayden 1974	100	DB RCT with cross-over	P	9 weeks (1 week of no treatment to assess baseline then 4 weeks C or P then cross-over)	Women with menopausal flushing of sufficient severity to warrant treatment. Duration of flushing ranged from two weeks to 23 years. 42 received C first	Inclusion: 1. No other complicating illness
Edington 1980	93	DB RCT cross-over (4 weeks C or P then cross)	P	16 weeks (4 phases each 4 weeks, first 2 trials conducted by the same investigator)	Women with dilatation of blood vessels in all areas of the skin and profuse sweating. Mean age 47 years (range 27-71).	Inclusion: 1. Dilatation of blood vessels in all areas of the skin and profuse sweating. 2. $\geq$ 30 attacks per week 3. Symptoms for $\geq$ 3 months but not > 12 months. Exclusion: 1. Other interfering illness

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Clayden 1974	Patient diary recording each attack of flushing. Nine visits throughout trial. At each visit, questions were asked about frequency, severity, and duration of attacks. 5 point scale ("much more" to "much less"). Side effects question "Any problem with the tablets?" Blood pressure/pulse.	NR	NR	NR	NR	NR	States all previous medication for flushing was stopped 2 weeks before entry to trial.	Mean weight 64.6 kg (44.4 to 86.9 kg)
Edington 1980	Patient diary of the time, extent, severity and duration of flushing, and side effects. Blood pressure, pulse.	NR	NR	10/66	NR	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes (corrected)**
Clayden 1974	C 0.025 mg tabs 1 twice daily, increased to maximum of 3 tabs twice daily depending on effect or presence of side effects.	Placebo	**Prior to crossover:** No difference in mean change from baseline number to week 4 between C and P *(p=0.7)*.* **Summary statistics:** Greater reduction in number while on C (C first p<=0.05, P first p<=0.001). Compared to their own P trial, the number of patients who improved on scores of frequency, severity, and duration was greater for C first only (p=0.1, p=0.05, P=0.01). P response greater in those with flushing for <1 year (p NR).
Edington 1980	C 0.05 mg twice daily	Placebo	**Prior to crossover:** NR **Summary statistics:** Mean number of flushing attacks (averaged over all 4 trials) was significantly lower with C therapy (p<0.05). Subjective assessment of frequency, severity, and duration was noted as much less or less in (50-89%) of all participants after each crossover.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Somatic**	**Uter-ine Bleed-ing**	**Sexual Dysfunc-tion**
Clayden 1974	Appears that data presented compares patients' Clonidine trials to their placebo trials, rather than doing the two trials separately. Reduction in number of hot flashes was greater during clonidine period than placebo period (C first p<=0.05, P first p<=0.001). During first treatment period, more patients on C than P improved in scores of frequency, severity, and duration (p values listed by week). During the second treatment period, there was no difference between C and P. Greater placebo response noted in those with flushing for less than 1 year.	NR	NR	NR	NR	NR	NR
Edington 1980	Mean number of flushing attacks (averaged over all 4 trials) was significantly lower with C therapy (p<0.05).	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Clayden 1974	NR	Blood pressure and pulse. No significant changes over the study period (p NR).	14 excluded for several reasons (Table 1). 4/14 were for side effects	3C,1P	
Edington 1980	NR	Blood pressure and pulse. No significant changes over the study period (p NR).	27/93 6 due to symptoms, 1 nonmedical, 8 lost to follow up, 12 patients did not keep proper diaries	6/93	2/93 on P withdrew (1 headache, 1 double vision), 4/93 on clonidine withdrew (1 respiratory infection, 1 depression, 2 headaches, 1 nausea)

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Clayden 1974	56 participants reported side effects. 34 while on C, 36 while on P. Effects nonspecific (Table V) and "well distributed" between C and P except dry mouth which was more frequent on C.	No stats provided prior to cross-over.	No significant difference between C and P prior to crossover. After cross-over, C was more effective than P in reducing number of hot flashes.
Edington 1980	Headache 12C, 10P Dry mouth 11C, 4P Insomnia 8C,4P Fatigue 3C, 5P Nausea 2C, 3P Other 30C, 28P (p NR)	Study done in 4 trials of 4 weeks each. Trial 3 was a single-blinded placebo only trial. "The findings were averaged" from the 4 trials. I don't think this study can be used.	Clonidine was more effective than placebo. However, statistical method is questionable.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Gerdes 1982	38 (15/38 de-faulted) There were also 10 asymp-tomatic controls	DB RCT	HH	20 weeks	Menopausal women with symptoms. No mean age noted. Climacteric Clinic Johannesburg Hospital	Inclusion: 1. Elevated FSH (>18mIU/ml) and LH (> 15mIU/ml) 2. Hot flushes Exclusion: 1. Several medical conditions

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Gerdes 1982	South African Personality Questionnaire, Leckie-Withers Test of Liability to Depressive Illness, Bem Sex Role Inventory, Items from Uken Motherliness Test, Mini-Biography Questionnaire, subjective assessment concerning pretreatment to post treatment change on 5 point scale.	NR	NR	NR	Excluded	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes (corrected)
Gerdes 1982	Opposed Estrogen group: CEE 1.25 mg daily for 21 days + medrogestone 5mg daily from day 16 to 21, then 7 days off, + placebo C 2 tab twice daily for 28 days	C group: placebo CEE daily 21 days + placebo medrogestone days 16-21, then 7 days off, + C 0.025 mg 2 tab twice daily for 28 days	Reported in Sonnendecker 1980

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	Hot Flashes	Vaginal Dryness	Sleep	Mood	Somatic	Uter-ine Bleed-ing	Sexual Dysfunc-tion
Gerdes 1982	Reported in Sonnendecker 1980	NR	NR	Significant de-crease in MBQ depression score for CEE compared to C ($p<0.05$). A significant de-crease in indirect and direct de-pression, MBQ depression and anxiety scores was seen in CEE but not C ($p<0.05$).	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Gerdes 1982	NR		38 women entered the study but 15 defaulted (7 from estrogen and 8 from clonidine group) leaving only 23 remaining.	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Gerdes 1982	NR	10 asymptomatic postmenopausal controls (not included in n)	Only estrogen/progesterone combination was associated with improvement in measures of depression and anxiety ($p<0.05$).

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Guttuso 2003	59 (246 screened 187 were ineligible)	DB RCT	P	12 weeks (followed by a 5 week open-label treatment phase)	Postmenopausal women with hot flashes. Mean age 52.7 G, 53 P. Randomization was stratified by surgical menopause status. Recruited by advertisement. New York	Inclusion: 1. Average $\geq$ 7 hot flashes/day accompanied by sweating 2. Amenorrhea for > 12 months or 6-12 months with FSH>40 mIU/mL and estradiol<20 pg/mL or status post bilateral oophorectomy for 2 months. Exclusion: multiple
Hammond 1984	10	DB RCT with cross-over	P	14 weeks (1 week baseline, 4 weeks study drug, 1 week baseline, 4 weeks alternate medication)	Menopausal women with vasomotor symptoms. Mean age 45.6 years (range 36-54). 7 natural menopause, 3 surgical menopause (6 months to 6 years post menopause). North Carolina	All women had $\geq$ 30 vasomotor flushes/week and serum FSH $\geq$ 40 mIU/ml. States women were "normotensive, in good health, and had no medical contraindication to M."

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Guttuso 2003	4 patient clinic visits, bimonthly phone calls and patient diaries. Serum FSH and estradiol, LH, CBC with differential, platelets, chemistry-14 panel, phosphate. Vitals signs, height, weight. Hot flash diary of frequency and severity (scale 1-7) symptoms noted at occurrence. Composite hot flash score, Pittsburgh Sleep Quality Index, Profile of Mood States, Short Form-36 Health Survey, Patient Global Impression of Change Scale. Adverse events.	NR	NR	8/30 G 6/29 P	NR	1/30 G 5/29 P	States could not be on HRT, leuprolide, or tamoxifen for 2 months prior to study.	BMI NR only weight. Mean weight in pounds 158.7 G and 152.8 P.
Hammond 1984	Diary of number of vasomotor flushes and objective 5 hour study periods of continuous temperature monitoring and sampling for serum LH.	NR	NR	NR	NR	NR	States no HRT used for 6 months prior to study.	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes (corrected)
Guttuso 2003	G 300 mg tab 3 times daily (900 mg daily). Participants allowed to decrease dose if side effects. In the open label trial the dose of G could be increased to maximum of 2700 mg/day.	Placebo	Statistically significant decrease between G and P in frequency at weeks 4 (p=0.03) and 12 (p=0.02) and composite score at weeks 4 (p=0.01) and 12 (p=0.01). Results not altered by adjusting for baseline group differences in duration of hot flashes and Total Mood Disturbance scores.
Hammond 1984	Methyldopa 250 mg tab twice daily, increased after 1 week to 3 times daily	Placebo	**Prior to crossover:** Both M and P resulted in decrease in hot flashes (pNR). No significant difference in mean decrease in number between M and P. **Summary statistics:** Compared to baseline, significant decrease in number for M (p<=0.02). No significant difference in objective measures of skin temperature.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	Hot Flashes	Vaginal Dryness	Sleep	Mood	Somatic	Uter-ine Bleed-ing	Sexual Dysfunc-tion
Guttuso 2003	Statistically significant decrease between G and P in hot flash frequency at weeks 4 (p=0.03) and 12 (p=0.02) and composite score at weeks 4 (p=0.01) and 12 (p=0.01). Results not altered by adjusting for baseline group differences in duration of hot flashes and Total Mood Disturbance scores.	NR	Pittsburgh Sleep Quality Index improved with G at week 4 (p=0.01) but not at week 12 (p=0.09).	No significant difference between G and P in Profile of Mood States.	NR	Onset of menses in 3 P and 2 G.	NR
Hammond 1984	In the first study period (i.e. before crossover) there was no significant difference between M and P in mean decrease of hot flashes. In the second study period there was a significant decrease in vasomotor flushes for M but not P (p<=0.02). Objective measures of hot flashes by skin temperature changes did not show any significant difference in either treatment phase.	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Guttuso 2003	No significant difference between G and P in Short Form-36 Health Survey.	No significant difference between G and P in Patient Global Impression of Change Scale. Several lab studies done. Significant differences were seen in albumin, total protein, total bilirubin, blood urea nitrogen, and platelets.	5 withdrawals from double-blind study, 4 withdrawals from open-label study	4/30 in G (dizziness, rash, heart palpitations, and peripheral edema) 1/29 in P (diarrhea) Two withdrawals for AE's from the open- label study (dizziness, peripheral edema).	
Hammond 1984	NR	Statistically significant decrease in the mean number of LH peaks per hour during M therapy (p<=0.05).	1/10	1/10	No side effects noted for P. 1 patient on M developed a lupus-like rash. Fatigue, weakness, dizziness and nausea were noted by 50% of patients. Bradycardia 2 patients, orthostatic hypotension 1 patient.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Guttuso 2003	Somnolence, dizziness, rash and peripheral edema were reported in G but not P. 15 (50%) in G and 8 (27.6%) in P reported at least one adverse event.	A few patients were taking raloxifene or antidepressants during the study. 81.5% of patients requested to continue G after completion of the open-label study.	G was more effective than P throughout the study.
Hammond 1984	"Significant side effects occurred in 6/10 patients receiving methyldopa."	Authors conclude that "because of significant side effects and minimal symptomatic improvement, M is not likely to be an acceptable therapy."	No significant effect of M. Significant side effects.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Lindsay 1978	100	DB RCT with cross-over	P	13 weeks (6 weeks P or C then cross-over, 1 week free in between)	Menopausal women with symptoms. States all experienced "natural" menopause. Mean duration of symptoms 1.6 years (1 month-5 years). Mean age 46.4 years (35-60) Patients selected from referrals on a random basis. Glasgow.	NR
Nagamani 1987	30	DB RCT	P	10 weeks (2 weeks to assess baseline, 8 weeks C or P)	Symptomatic women (6 spontaneous menopause, 24 surgical). Mean age 41 (range 25-58) Texas	Exclusion: 1. Previous treatment with oral C, 2. Other medical exclusions listed
Nappi 1991	35 (5 groups of 7 each)	RCT	HH	4 weeks	Menstruating women undergoing TAH-BSO for benign indications. Mean age 43.5 years (range 30-50)	Not more explicitly specified.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Lindsay 1978	No diaries. Interviews at weeks 4, 7, and 12. Blatt Menopausal Index (4 points scale). Flushing attacks assessed separately (4 point scale). Kellner and Sheffield rating scale for psychological symptoms.	NR	NR	NR	NR	NR	# NR, states all treatment of symptoms stopped at least 4 weeks before entry	NR
Nagamani 1987	Patient diary noting occurrence of hot flashes and side effects of treatment. At visit, patients were questioned about frequency, severity (decrease or same), and duration (decrease or same) of hot flashes. Blood pressure, pulse, LH levels.	NR	NR	24/30	NR	NR	NR, states no treatment for symptoms for at least 30 days before inclusion	NR
Nappi 1991	Plasma LH and FSH. Patient diaries of frequency (0, <5/day, >5-<10/day, >10/day scored 0-3) and intensity of hot flushes (0, mild, moderate, severe scored 0-3).	None	35/35	35/35	NR	NR	NR	BMI 23.1 $\pm$ 1.5

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes (corrected)
Lindsay 1978	0.025 mg tab, 2 tablets twice daily, increased to 2 tabs three times daily after 1 week if needed	Placebo	**Prior to crossover:** Significant decrease in Blatt score for C ($p<0.05$) and P ($p<0.05$) and in flush score for C ($p<0.005$) and P ($p<0.001$). No significant difference between C and P on Blatt or flush score. **Summary statistics:** After crossover, no significant improvement in scores for either C or P, no difference between C or P.
Nagamani 1987	C Transdermal 0.1 mg/day, patch changed weekly	Placebo	No significant difference between C and P in mean change at weeks 4 *(p=0.28)** and 8 *(p=0.25)**. Significant decrease in mean number for C ($p=0.002$) and P ($p=0.04$) at week 8. Proportion of women reporting a decrease in subjective frequency ($p<0.04$), severity ($p<0.04$), and duration ($p<0.03$) was greater for C than P.
Nappi 1991	C 0.075 mg tab twice daily	Sodium Valproate 200 mg tab twice daily Lisuride 0.2 mg tab twice daily Transdermal 17B estradiol 0.050 mg daily placebo	Hot flash frequency and intensity were lower in the estradiol, clonidine, and Lisuride treated groups compared to P ($p<0.01$).

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	Hot Flashes	Vaginal Dryness	Sleep	Mood	Somatic	Uter-ine Bleed-ing	Sexual Dysfunc-tion
Lindsay 1978	Blatt Menopausal Index. Significant decrease in first 6 weeks for C ($p<0.05$) and P ($p<0.05$). No difference between C and P. "Flushing attacks". Significant decrease in first 6 weeks for C ($p<0.005$) and P ($p<0.001$) No difference between C and P.	NR	NR	Kellner and Sheffield initial scores higher in women with menopausal symptoms for >1 year ($p<0.01$) compared to those with symptoms for < 1 year	NR	NR	NR
Nagamani 1987	Mean number of hot flashes significantly decreased from baseline at each weekly assessment ($p<0.001$-0.03) for C and only at weeks 5 ($p<0.05$), 6 ($p< 0.05$), and 8 ($p<0.04$) for P. (Results for direct comparison of C and P NR, graphic display only.) Subjective comparison of frequency (decrease or same) ($p<0.04$), severity ($p<0.04$), and duration ($p<0.03$) of hot flushes significantly decreased in the clonidine compared to the P groups.	NR	NR	NR	NR	NR	NR
Nappi 1991	Hot flash frequency and intensity were lower in the estradiol, clonidine, and Lisuride treated groups compared to P ($p<0.01$).	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Lindsay 1978	NR	NR	62/100	2	2 withdrawals for nausea, dry mouth and insomnia on C
Nagamani 1987	NR	LH levels measured in 2 participants without C and after 2 weeks of C. No change in LH pulsatile secretion noted with C. No significant changes in blood pressure and pulse.	1/30 (excluded from analysis, dropped out after 2 weeks of treatment)	None	None
Nappi 1991	NR	FSH, LH levels	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Lindsay 1978	2 reported nocturia on C, 1 reported nausea on P	100 initially to be included. States only 41 completed treatment in the trial. Three additional withdrawals noted, one did not return after initial assessment, 2 withdrew because of side effects. Results are reported for the remaining 38.	No difference between clonidine and placebo.
Nagamani 1987	Skin reactions (erythema and/or itching) 4C, 3 P (no dryness of mouth or dizziness reported)	How useful are the results of limited subjective measures?	C was more effective than P in subjective measures but not for mean decrease in number of hot flashes.
Nappi 1991	NR	All treatments started on the first day after surgery. Method of randomization not disclosed. No report of blinding. One small paragraph on hot flash results, more time spent discussing LH/FSH results.	Estrogen, clonidine, and Lisuride decreased hot flash frequency and intensity compared to placebo.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Nesheim 1981	40	DB RCT with cross-over	P	Not clearly stated but inferred; 1 week baseline; 30 day M or P then 14 day washout then cross-over	Women with menopausal hot flushes. Mean age or age range NR. Patients referred by General Practitioners in Akershus County, Norway.	Exclusion: 1. Use of antihypertensive, antidepressants, or sedating drugs
Salmi 1979	40	DB RCT cross-over (not true RCT, medica-tion packs made in random order)	P each patient is her own control	12 weeks, cross-over at 6 weeks	Women with menopausal symptoms. 10 still menstruating, 18 spontaneous menopause. Mean age 50.5 years (range 41-57). Mean duration of symptoms 21.5 months (range 1-131 months). Outpatients from Department of Ob/Gyn, University Central Hospital, Finland.	Inclusion: 1. Hot flushes, sweating, menopausal symptoms

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Nesheim 1981	Patient recorded number of hot flashes per day. Patients were contacted weekly by phone and asked to use a VAS to record degree they were troubled by hot flashes. Blood pressure.	NR	NR	NR	NR	NR	Participants were not allowed to take estrogen for 4 weeks before the study.	NR
Salmi 1979	Patient records and visits (3). Frequency of sweating episodes/hot flushes (none, <5, >5, >10) Incidence of insomnia and depression, occurrence of possible anxiety states (none, less than before the medication, the same as before, more than before) Blood pressure, pulse, AST, cholesterol. Side effects.	2/37	7/37	NR	1 of the patients was excluded at the beginning because of cancer in a mammary node.	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes (corrected)**
Nesheim 1981	l-methyldopa 250 mg tab twice daily increased if needed to maximum of 2 tabs twice daily	Placebo	**Prior to crossover:** NR **Summary statistics:** Median reduction in number 38% P (pNS), 65% M (p<0.05). Between groups M superior to P (p=0.06 M first, p=0.01 P first). 22 M, 15 P improved. Overall, greater reduction in number for M (p=0.004) Median improvement on VAS score 5 M, 2.4 P (p=0.002). Median improvement 77% M, 30% P.
Salmi 1979	0.025 mg tab twice daily, increased every 2 weeks by 1 tab twice daily, if needed, to max 0.075 mg twice daily	No concurrent use of HRT, psychopharmaceutics or antihypertensive.	**Prior to crossover:** No significant difference between C (14/20) and P (16/17) in number asymptomatic at 6 weeks *(p=0.0975)**. **Summary statistics:** No significant difference between C and P in alleviation of symptoms (p NR).

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Somatic**	**Uter-ine Bleed-ing**	**Sexual Dysfunc-tion**
Nesheim 1981	Median number of hot flashes per week prior to medication was 58 (14-315). 16 participants received M first, 12 P first. Median number of hot flashes for M first was 42 (14-140 and for P first was 70 (28-315). (Not reported if this was significantly different at baseline.) Hot flash frequency was reduced by both M and P, favoring M in both the first phase (p=0.06) and the second phase (p =0.01) Combined results from both phases favors M (p=0.004). Median VAS score prior to treatment 8.4 cm (2.9-10) Improvement in score was greater with M than P (p=0.002) (patients compared to themselves). Median improvement 77% with M, 30% with P.	NR	NR	NR	NR	NR	NR
Salmi 1979	Sweating and hot flushes (day and night). No statistical difference (p NR) between C and P.	NR	Insomnia. No statistical difference (p NR) between C and P.	Disturbances of depression and anxiety states. No statistical difference (p NR) between C and P.	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Nesheim 1981	NR	No significant change in blood pressure.	12/40 (various reasons reported) 2 additional patients were unable to keep record of their hot flashes, only VAS data available	2/40 (specific effects not stated)	
Salmi 1979	NR	No changes in blood pressure and pulse during the trial.	3 were excluded from initial 40, unclear if this was prior to randomization. 1 for cancerous node, 1 for psychiatric treatment, 1 for interruption of medication.	none	None

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Nesheim 1981	Tiredness 15 M, 3 P Dry mouth 10 M, 7P Slight edema 3 M Diarrhea 1 M, 1P Exanthem and Arthralgia 1 M	Some results appeared to be combined across both treatment periods (i.e. patients compared to themselves).	
Salmi 1979	No significant differences between C and P in side effect occurrence. (Various side effects listed Table 1)	Serum aspartate amniotransferase and cholesterol readings were done in all and there were no elevated values noted.	No difference between clonidine and placebo.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	N	Type of Trial	Com-pari-son	Length of Trial	Population	Inclusion/exclusion criteria
Sonnendecker 1980	38 (15/38 de-faulted)	DB RCT	HH	20 weeks	Menopausal women with symptoms. No mean age noted. Climacteric Clinic Johannesburg Hospital	Inclusion: 1. Elevated FSH (>18mIU/ml) and LH (> 15mIU/ml) 2. Hot flushes Exclusion: 1. Several medical conditions
Wren 1986	19	DB RCT with cross-over	P	10 weeks (2 weeks placebo, then 4 weeks C or P then cross-over)	Postmenopausal women with symptoms (all spontaneous menopause). Mean age 50.6 (range 46-56) Menopause clinic at the royal Hospital for Women, New South Wales	Inclusion: 1. Spontaneous menopause 2. Symptoms $\geq$ 3 months but not > 12 months. Exclusion: 1. Hysterectomy 2. Previous C or anti-hypertensive use

Appendix F. Evidence table 6-7. Key Question 3F other drugs

		Specific Characteristics of Population						
Study/Year	Measures	Hyster-ectomy +/- UO (#/n)	Hyster-ectomy BSO (#/n)	BSO (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Recent discontinuation of HRT (#/n)	High or Low BMI (#/n)
Sonnendecker 1980	Mammography, hot flushes in number per day, FSH, LH, 17B-estradiol, progesterone, prolactin.	NR	NR	NR	Excluded	NR	NR	NR
Wren 1986	Frequency, severity, and duration of vasovagal symptoms. Patient diaries of number of flushes/sweats, insomnia, anxiety, libido, headache, irritability, and depression. Exam and biochemical investigation every 2 weeks.	Excluded	Excluded	NR	NR	NR	Excluded if previous use C, anti-hypertensive, HRT or sedative, tranquilizer, or hypnotic drugs	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Treatment		
Study/Year	**Main Drug type; dose; regimen**	**Other Drugs type; dose; regimen**	**Hot Flashes (corrected)**
Sonnendecker 1980	Opposed Estrogen group: CEE 1.25 mg daily for 21 days + medrogestone 5mg daily from day 16 to 21, then 7 days off, + placebo C 2 tab twice daily for 28 days	C group: placebo CEE daily 21 days + placebo medrogestone days 16-21, then 7 days off, + C 0.025 mg 2 tab twice daily for 28 days	Mean change in number from pre- to post-trial follow up decreased significantly with CEE ($p<0.05$) but not C. No significant difference in mean change between CEE and C.
Wren 1986	C 0.025 mg tabs 2 twice daily	Placebo	**Prior to crossover:** NR **Summary statistics:** No significant difference in mean number between C and P (p NR). No data reported for severity and duration.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

	Main Outcomes						
Study/Year	**Hot Flashes**	**Vaginal Dryness**	**Sleep**	**Mood**	**Somatic**	**Uter-ine Bleed-ing**	**Sexual Dysfunc-tion**
Sonnendecker 1980	Number of hot flashes experienced daily was decreased significantly in the estrogen group ($p<0.05$) but not in the clonidine group.	NR	NR	NR	NR	NR	NR
Wren 1986	Crossover design, each patient is her own control. No significant difference in mean # of hot flashes. (p NR)	No change with C or P	No change in insomnia or tiredness with C	No change in anxiety, panic, or irritability with C	NR	NR	NR

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Main outcomes (cont.)

Study/Year	QoL	Other Outcomes	Withdrawals	Withdrawals due to AEs	Withdrawals due to Adverse Effects
Sonnendecker 1980	NR	FSH, LH, and estradiol, progesterone and prolactin levels were assessed. Mammography was performed.	38 women entered the study but 15 defaulted (7 from estrogen and 8 from clonidine group) leaving only 23 remaining.	NR	NR
Wren 1986	NR	No change in blood pressure or gonadotropin levels	5/19 (not included in analysis, states withdrawal due to frustration with lack of benefit)	None	No adverse affects reported.

Appendix F. Evidence table 6-7. Key Question 3F other drugs

Study/Year	Adverse Effects Reported	Comments	Overall findings
Sonnendecker 1980	NR		Only estrogen/progesterone combination was effective for decreasing hot flashes.
Wren 1986	NR	No p values reported in this paper	No difference between clonidine and placebo. Statistical method is question-able.

Appendix F: Evidence table 6-7. Key Question 3F other drugs

Key/Abbreviations

*p value not reported by the authors
AE = Adverse Effect
BMI = Body mass index
BR = Bellergal Retard
BSO = Bilateral Salpingo Oophorectomy
C = Clonidine
CEE = Conjugated Equine Estrogens
DB = Double-blind
ECOG = Eastern Cooperative Oncology Group Scale
G = Gabapentin
HH = Head to head
HRT = Hormone replacement therapy
M = Methyldopa
MBQ = Mini-Biography Questionnaire
NR = Not reported
P = Placebo
QoL = Quality of Life
RCT = Randomized Controlled Trial
SERMs = Selective Estrogen Receptor Modifiers
TAH = Total abdominal hysterectomy
UO = Unilateral Oophorectomy
VAS = Visual Analogue Scale

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Aiello, 2004	173	RCT	HH	12 months	Postmenopausal women recruited from the greater Seattle area (50-75 years of age) through mass mailings and media placements. Average age 60.7 and 60.6 SD (6.6 and 6.7years). Approximately 60% had some menopausal symptoms.	Inclusion: 1. Sedentary at baseline (<60 min/week of moderate-to vigorous exercise) 2. BMI>25.0 or over 24.0 with body fat>33% Exclusion: 1. Taking HRT 2. Smoker
Albertazzi, 1998 &1999	104	RCT	P	12 weeks	Mean age 53, range of 48-61. Women postmenopausal requesting treatment for severe hot flushes.	Inclusion: 1. $\geq$ 6 months since the last menstrual period or $\geq$ 6 weeks since bilateral oophorectomy was performed 2. Seven moderate to severe hot flushes, including night sweats/24 hours during at least the last 2 weeks of the 4 week prestudy period 3. FSH>50 and estradiol <35 Exclusion: 1. HRT or any other drug for the treatment of climacteric symptoms, such as Vitamin E, clonidine, veralipride.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Aiello, 2004	Adherance to exercise via daily activity logs, food frequency questionnaire, information on menopause symptoms and their severity was collected at 0,3,6,9, and 12 months with a self-administered questionnaire, which was a modified version of a questionnaire used by the Women's Health Initiative, DEXA was conducted at baseline and 12 months for leanness	13-18%	NR	NR	NR	NR	NR	35-38% had taken in the remote past	Average was 30.5 and 30.6 in each group
Albertazzi, 1998 &1999	Daily diary; Kupperman Index	NR	NR	NR	NR	Allowed	NR	Had to be off at least 6 weeks	Mean was 25.9 for both groups with range from 18-36

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Aiello, 2004	45 minutes of moderate-intensity exercise, 5 days/week for 12 months	Control was invitation to attend 45 minute weekly stretching session for 12 months	No change in frequency over the year	NR	No change in either group over the year
Albertazzi, 1998 &1999	Casein 60 grams daily for 12 weeks	Soy powder (Supro Brand Protein Technologies, St. Louis, MO) 60 grams/day; this contained 76 mg of isoflavones (aglycone units)	Hot flash reduction was seen in both group (43.6 % reduction in soy group compared with 31.3% reduction in placebo group). Soy group had greater reduction than casein group at 12 weeks ($p<0.01$)	Vaginal maturation indices did not increase in the soy group, but did significantly increase in the casein group	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Aiello, 2004	No change in depressive feelings in either group over the year (only 13% had a baseline)	No change in either group over the year; when analyzed by time since menopause those within 5 years of menopause had a significant decrease in memory problems in the exercise group compared to the controls (OR at 6 mo=0.2; 95% CI, 0.08-0.6). This was sustained at 9 and 12 months.	NR	NR	NR	NR	NR
Albertazzi, 1998 &1999	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Aiello, 2004	When analyzing the subset of moderate/severe menopausal symptoms (n=11 exercisers, 10 controls), a significant decrease in hot flashes was seen over the year in the control group (p=0.02 but not in the exercisers)	6/87 in the exercise group; 2/86 controls	None	None	Mind-body	Only RCT looking at exercise
Albertazzi, 1998 &1999	Kupperman index values as a whole did 'not change'	25/51; 11 in the soy group and 14 in the casein group	14 patients, 7 in each group dropped due to gastrointestinal side effects; lack of efficacy caused 3 patients in the casein group and 1 person in the soy group to withdraw	Gastrointestinal - constipation 48%	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Anarte, 1998	73	RCT	HH	6 months	45-55 year old postmenopausal women with less than 3 years evolution, no previous treatment; all attending a Menopause Unit in Southern Spain	None reported other than population definition except that patients in whom hormonal treatment was contraindicated were excluded
Atkinson, 2004	205	DB RCT	P	1 year	Women recruited from a breast clinic in Cambridge, UK	Exclusion: 1. History of breast cancer, major breast surgery 2. Use of HRT

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Anarte, 1998	Kupperman Index, plus the emotional alternation, anxiety and depression scales of the Granada Gynecological Questionnair of Salvatierra et al.	NR	NR	NR	Those with contraindic ation to HRT excluded	NR	NR	No previous	NR
Atkinson, 2004	28 day menopausal symptom diary at baseline and 12 months; severity and frequency of 21 symptoms associated with menopause	NR	NR	NR	Excluded	NR	NR	NR	Measure d but not reported

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Anarte, 1998	Transdermal estrogen with cyclical progesterone	HRT plus Psychological counseling (Education, counseling and behavioral element)	In both groups there was significant improvement in vasomotor symptoms (p<0.0001	NR	Insomnia significantly improved in the combined group (HRT + counseling) p=0.0001 from baseline and 0.0022 between groups. Insomnia was not significantly improved in HRT group.
Atkinson, 2004	Promensil 1/day; 26 mg biochanin, 16 mg formononetin, 1 mg genistein, 0.5mg diadzein derived from red clover	Placebo	Interaction between treatment group and menopausal status for changes in menopausal symptom score and number of hot flashes was not statistically significant p<0.05	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Anarte, 1998	Combined treatment group has significant benefit in nervousness (p=0.0001), anxiety, depression, emotional alteration, melancholia (p=0.0001) over HRT only group, however, both groups had significant improvement in these parameters from baseline. HRT only nervousness (p=0.0001) and anxiety (p=0.0002); combined group both had p = 0.0001.	NR	NR	NR	NR	NR	NR
Atkinson, 2004	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Anarte, 1998	Weakness and fatigue improved in combined group over HRT alone group (p=0.0001); same with palpitations. Neither group had improvement in joint and muscle pain or headache symptoms.	NR	NR	NR	Mind-body	
Atkinson, 2004	NR	16/102 withdrew from Promensil group and 12 /103 from placebo withdrew	None reported; most withdrew to go on HRT	None	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Baber, 1999	51	DB RCT	P	7 months	Unpaid female volunteers	Inclusion: 1. Aged 45-65 2. > 3 hot flushes/day Exclusion: 1. Intercurrent medical problems 2. HRT or antibiotics in previous 3 months 3. FSH<30 4. Menstruation in previous 6 months 5. Hysterectomy 6. Vegetarian (>10g legumes per day)
Baird, 1995	97	RCT	Control Usual care	4 weeks	Volunteers recruited through newspaper ads, flyers, and radio	Inclusion: 1. Age less than 65 2. No menses for $\geq$ 2 years 3. No use of estrogen or antibiotics $\geq$ 6 months 4. No use of prescription drugs known to effect outcomes, such as corticosteroids.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Baber, 1999	Greene Climacteric Scale	Excluded	NR	NR	NR	NR	Vegetarian > 10g legumes/ day excluded	None for 3 months	Weight reported in kg with mean 67-71 kg +/- 11.0-12.8
Baird, 1995	Health habits and history questionnaire, Luteinizing hormone, follicle stimulating hormone, vaginal cytology, urinary phytoestrogen	NR	NR	NR	NR	NR	NR	None for 6 months	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Baber, 1999	Promensil (Novogen Ltd, Sydney); Promensil is a standardized isoflavone supplement prepared from red clover extract in 500mg tablet form containing 40 mg/tablet; contains genistein, daidzein, biochanin, and formononetin	Placebo	Greene score and flush frequency decreased in both placebo and active groups during the 3 months of treatment (p=0.003); no difference between groups	NR	NR
Baird, 1995	1/3 of calories to come from soy flour	Control was usual care diet	NR	No change in vaginal maturation index	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Baber, 1999	NR	NR	NR	NR	NR	NR	NR
Baird, 1995	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Baber, 1999	Significantly different (p=<0.001) in urinary isoflavones between baseline and 3 months in the supplemented group; not the case in the placebo group	8/51 withdrew	7 withdrew for personal reasons; 1 withdrew for medical reasons not related to the study	NR	Biologically based therapies	After urine isoflavone analysis was performed, it became apparent that many subjects in the placebo group displayed high urinary isoflavone excretion
Baird, 1995	No change in FSH, LH,	6/97 withdrew, 3 were found ineligible after screening, 2 from other family emergencies and 1 could not tolerate soy foods	None	None	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Balk, 2002	27	RCT	P	6 months	Postmenopausal women were recruited from clinics and private gynecology, family practice, and internal medicine offices in Pittsburgh. Advertisements were placed in newspapers, on radio, and on the web site for Magee-Women's Research Institute home page.	Inclusion: 1. Over 40 years, postmenopausal, no vaginal bleeding for 1 year or >30 years old with BSO or POF 2. Omnivore 3. Intact uterus Exclusion: 1. HRT in past year 2. Use of SERMs

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Balk, 2002	Endometrial biopsy Menopausal Symptoms Questionnaire by Brzeginski, et al	NR	NR	NR	NR	Excluded	NR	Over 1 year to be eligible	Mean was average

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Balk, 2002	100 mg soy/cereal/day	N/A	No difference	No difference	Soy had more insomnia

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Balk, 2002	No difference (depression)	N/A	N/A	No difference	N/A	No difference (decreased libido)	N/A

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Balk, 2002	Headache, palpitation, night sweats, no difference	2/13 from placebo and 6/14 from the soy group	Yes Number not stated	Flatulence, poor taste - no improvement	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Bellipanni, 2001	79	RCT	P	6 months	No relevant pathologies, taking no drugs, hormones or herba preparation and conducting a normal lifestyle with typical Mediterranean diet rich of carbohydrates and fresh vegetables	Inclusion: 1. Age 42-62

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Bellipanni, 2001	Questionnaire in which life habits, physiological data, data concerning previous pathologies, treatment-related side-effects, treatment-induced alterations, effects on perimenopausal symptoms (neurovegetative, sleep, psychological) werer recorded at time 0 and at 3 and 6 months. Questions concerned duration and character of their menstrual cycle and/or psychosomatic, peri- and menopause related symptoms such as irritability, morning mood and depreession, insomnia, night sweatings, headache, stypsis, amnesia, hot flushes, palpitations, and body weight increase.	NR	NR	NR	NR	NR	All non-smokers and no alcohol abuse	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Bellipanni, 2001	3 mg melatonin/day	Placebo	No significant difference between groups	NR	No significant difference between groups

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Bellipanni, 2001	After analysis of all answers, the evaluation of different typical perimenopause or menopause-related symptoms or alternations did not disclose a clear-cut difference between the two groups, with the notable exception of a very significant improvement of mood and complete disappearance of morning depression in the melatonin-treated women.	NR	NR	NR	Only episodical improvement of regularity and duration of menstrua cycles were reported. Six menopausal women (at 1 and 2 years after total cessation of the menses) reported a re-acquisition of normal (bleeding and duration) menstrual cycles	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Bellipanni, 2001	Information on LH, thyroid and FSH results	NR	NR	NR	Biologically based	Poor study

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Blatt, 1953	748	DB RCT	5 arms with controls and placebo	3 years	Climacteric women	NR
Boblitz, 2003 (Abstract Only)	179	RCT	P	6 weeks	Women with menopausal symptoms	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Blatt, 1953	Menopausal index, a validated scale that represents a numerical conversion of the severity of the 11 most common menopausal symptoms.	NR	NR	NR	NR	NR	NR	NR	NR
Boblitz, 2003 (Abstract Only)	Kupperman Menopause Index; CGI scores for anxiety, impaired drive, depressive mood and nervousness/irritability	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Blatt, 1953	Vitamin E 50-100mg tid (n=82) vs. ethinyl estradiol 0.05mg (n=107) vs. conjugated equine estrogen 1.25mg (n=173) vs. phenobarbital 15mg tid (n=88).	Placebo (n=298)	All results reported by menopausal index of which several questions pertain to vasomotor symptoms. No p values are given in paper due to date of publication. However, 66.5% of both estrogen groups had an excellent response to treatment (as compared to 13.4% of Vitamin E, 23.6% of phenobarbital and 15.6% of placebo patient)	NR	NR
Boblitz, 2003 (Abstract Only)	Remifemen Plus; 20 mg black cohosh, 250 mcg of hypericin	Placebo	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Blatt, 1953	NR	NR	NR	NR	NR	NR	NR
Boblitz, 2003 (Abstract Only)	In all Greene Climacteric Index items referring to psychological symptoms, Remifemin Plus was superior to placebo ($p<0.001$)	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Blatt, 1953	NR	NR	NR	NR	Biologically based	
Boblitz, 2003 (Abstract Only)	A decrease in Kupperman Index total score demonstrated significant superiority of the active to placebo ($p<0.001$)	NR	6 withdrew in each group due to adverse events, none serious	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Brzezinski, 1997	145	RCT	Control Israeli diet (usual care)	12 weeks	Women who were peri and postmenopausal (43-65 years) with climacteric complaints from the outpatient menopause clinic at Hadassah Medical Center, Jerusalem, Israel	Inclusion: 1. Natural or surgical menopause (≥ 3 months of amenorrhea) 2. FSH>30, LH>20, and low plasma estradiol level (<200) 3. ≥ 1 of the following symptoms: hot flashes, night sweats, insomnia, depression, vaginal dryness, or dyspareunia Exclusion: 1. Evidence of acute medical illness 2. Use of gonadal hormones or any medication known to influence menopausal symptoms or endocrine variabels 3. Known or suspected allergic reaction to specific food items.
Burke, 2003	241	DB RCT	HH	24 months	Women aged 45-55 were recruited from the community and seen at Wake Forest University. White: 88% Married: 79% High school diploma: 96% ≥$30,000 annual income: 79%	Inclusion: 1. Perimenopausal (only 1 period in preceding 3 months) 2. At least 1 vasomotor symptom a day 3. No use of HRT for 3 months prior to study entry Exclusion: 1. Acute myocardial infarction or stroke within 6 months 2. History of breast or endometrial cancer 3. History of invasive cancer within 5 years 4. Active thromboembolic disease 5. Previous osteoporosis fractures being treated with hormones 6. Low bone density 7. Previous exposure to diethylstilbestrol 8. An endometrial biopsy showing hyperplasia

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Brzezinski, 1997	Menopause symptoms questionnaire (MSQ); evaluates hot flashes, night sweats, palpitations, headache, depression, vaginal dryness, urinary discomfort, insomnia, and decreased libido on a four point scale. Serum phytoestrogen concentrations	Included	Included	NR	NR	NR	NR	Could not be taken at the time of study	26.24 ± 0.48 for PE group and 25.82 ± 0.87 in control group
Burke, 2003	Self report in symptom diaries.	56/241	NR	NR	Excluded	NR	NR	180/241	0/241

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Brzezinski, 1997	Phytoestrogen rich diet, approximately 1/4 of their calories (PE group)	Regular Israeli diet; told to avoid soy products and flax seed	Significantly reduced in PE group over controls (p=0.004)	Significantly reduced in PE group over control (p=0.005)	NR
Burke, 2003	25g of soy with 42mg a day of isoflavones or 25g of soy with 58mg a day of isoflavones	25g of soy, alcohol washed to remove isoflavones (Control)	Rapid reduction in all groups, including control. No difference between groups. Significant reduction for all groups from baseline (p<0.0001) but no difference between groups (p=0.10).	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Brzezinski, 1997	NR	NR	NR	NR	NR	NR	Total score of menopausal symptomatology (MSQ score) was reduced greatly in both groups during the study groups, but the difference between the groups was not significant
Burke, 2003	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Brzezinski, 1997	Average of 100-fold increase in the phytoestrogen serum levels of the PE group; no change in the control group	31/145	4/95 in the PE group due to intolerance of diet; 2/95 in soy group and 7/50 in control group withdrew due to unbearable menopausal symptoms; other dropouts were due to personal reasons	NR	Biologically based therapies	Interesting as came from food, tofu, soy milk, and flax seed largely
Burke, 2003	NR	NR	NR	NR	Biologically based therapies	170/241 used OC

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Bygdeman, 1996	40	RCT	HH	3 months	Postmenopausal women complaining of vaginal dryness (aged 43-76, mean 58.28 years)	Exclusion: 1. Hormonal-dependent tumors 2. Known or suspected other serious diseases, abnormal genital bleeding, past history of active thromboembolic disorder, vaginal infection 3. HRT in the last 3 months 4. Vaginal use of any douche or lubricant
Cagnacci, 2003	80	RCT, open	HH	3 months	Women (age 47-53) in perimenopause referred to the Menopause Center were enrolled; mean age was 50.2, 51.5 and 51.8	Exclusion: 1. Organic or neurological pathologies 2. Used hormones, neuroactive or psychotropic drugs in the 3 months preceeding

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Bygdeman, 1996	Self diary and vaginal dryness index (Bachmann)	NR	2/40	NR	NR	NR	NR	NR	NR
Cagnacci, 2003	State Trait Anxiety Inventory, Self-Evaluations Depression Scale, Greene's Climacteric Scale	NR	NR	NR	NR	NR	NR	NR	Mean 26.0, 26.9 and 26.7

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Bygdeman, 1996	Replens: 1 vaginal application three times/week for 3 months	Dienoestrol vaginal cream (0.01%) 0.5mg daily for 2 weeks then three times a week for 3 months	NR	Both groups resulted in a significant increase in the vaginal dryness index with compared to baseline values	NR
Cagnacci, 2003	Kava-Kava (KK) 100m/day (15 women) vs. Kava-Kava 200mg/day (19 women)	Control was 1000mg Calcium/day (34 women)	Both KK groups had significant decline in Greene's score from baseline, but not significantly different from control group.	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Bygdeman, 1996	NR	NR	NR	NR	NR	NR	NR
Cagnacci, 2003	Anxiety; significant decrease compared to control in both KK groups ($p<0.009$); Depression scores were significantly decreased from baseline in KK groups, however, not significant from controls	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Bygdeman, 1996	NR	1/40	NR	NR	Biologically based	
Cagnacci, 2003	NR	12/80; 6 in the control group, and 5 in the 100mg KK group and 1 in the 200mg KK group	2 for nausea and gastric pain	nausea and gastric pain	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Carranza-Lira, 2001	30	DB RCT	P	1 month	Postmenopausal women who attended the Climacteric Clinic of the hospital studied	Inclusion: 1. No current or previous exposure to HRT 2. FSH >30 and estradiol <30
Chen, 2003	52	RCT	HH	16 weeks	Non-hysterectomized postmenopausal women, aged 45-65 with climacteric complaints were recruited from outpatients attending this Taiwan Hospital	Inclusion: 1. Last menstruation $\geq$ 6 months previously 2. No HRT for $\geq$ 6 months Exclusion: 1. Severe metabolic, endocrine, or GI disease, concomitant heart disease, uncontrolled hypertension (>160/95), diabetes, endometriosis, undiagnosed vaginal bleeding and psychiatric illness 2. Surgically induced menopause 3. Previous or current estrogen-dependent tumors, other current malignant or life-threatening disease, 4. Previous or concomitant serious or chronic medical conditions. 5. Taking tranquilizers or antidepressants

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Carranza-Lira, 2001	Modified Kupperman Index	NR	NR	NR	NR	NR	NR	Never received	No difference between groups (average BMI is 28)
Chen, 2003	Greene Climacteric Scale	Excluded	Excluded	Excluded	Excluded	NR	NR	None within 6 months	52-56 kg

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Carranza-Lira, 2001	Phytoestrogen cream 4mg/day aloe vera; wild yam root extract; almond oil; cartamo oil; jojoba oil; tocopheryl acetate; chamomile extract; sheepshkin root extract oil of ass herb; siberian ginseng extract; to alternating forearms/day	Cold cream control	A significant decrease in Kupperman Index Score was found in both groups at the end of treatment ($p<0.001$), no other significant differences between groups	NR	NR
Chen, 2003	JWSYS (Sun Ten Pharmaceutical Co., Taipei, Taiwan); 4 grams tid; includes angelica Radix, Atractylodis rhizoma, Paeoniae Radix; Bupleuri Radix; Hoelen; Glycyrrhizae Radix; Moutan Bark; Gardeniae Fructus; Zingiberis Rhizoma, Menthae Herba	Premelle 0.625/2.5 (Wyeth Medica, Newbridge, Co. Kildare, Ireland); one tablet q d	JWSYS had significant reduction ($p<0.01$) in vasomotor symptoms on Greene scale and Premelle did not.	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Carranza-Lira, 2001	NR	NR	NR	NR	NR	NR	NR
Chen, 2003	Both groups had significant improvement in anxiety and depression (p<0.01)	NR	Both groups had significant improvement from baseline (p<0.01)	NR	See withdrawals	Premelle group had significant improvement (p<0.01), but JWSYS group did not	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Carranza-Lira, 2001	A significant decrease in KI was found in both groups at the end of the treatment (p<0.001) in both groups from baseline	NR	NR	NR	Biologically based therapies	
Chen, 2003	Both JWSYS and Premelle induced a significant reduction of prevalence and severity of menopausal symptoms. (p<0.01)	13/37 JWSYS; 11/25 HRT	3/37 from Chinese herb group due to vaginal bleeding and abdomenal disturbances; 5/25 from HRT group due to vaginal bleeding and breast tenderness	See withdrawals	Biologically based therapies	No true control; high drop out rate

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Chenoy, 1994	56	DB RCT	P	6 months	56 women were recruited from the general gynecology clinic of North Staffordshire Hospital Center, London; from general practitioners' surgeries, and by self referral of volunteers.	Inclusion: 1. Menopausal women who had hot flushes at least three times/day 2. Elevated FSH and LH or had amenorrhea for at least 6 months, or both. Exclusion: 1. Received estrogen replacement or essential fatty acid supplements in the previous 2 months. 2. Taking any form of HRT or other drug for menopausal symptoms during the study, or systemic steroids, non-steroidal anti-inflammatory agents, anticonvulsants, clonidine, and phenothiazides.
Chiechi, 2003	187	RCT	Usual care	6 months	Healthy postmenopausal asymptomatic woman aged 39-60, living in Southern Italy; mean age was 52.7 years	Inclusion: 1. Spontaneous menopause of $\geq$ 6 months 2. FSH>30, or bilateral oophorectomy Exclusion: 1. Age >60 2. Heavy drinkers 3. Treatment with HRT, cholesterol-lowering, antiosteoporotic or other interfering drugs (i.e. tibolone) 4. Diabetes or history of cancer 5. In vegetarian or macrobiotic diet 6. Presence of menopausal symptoms requiring therapy

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Chenoy, 1994	Self reported symptom diary	Excluded	NR	NR	NR	NR	NR	None for 2 months prior	NR
Chiechi, 2003	Karyopycnotic index and maturation value of the vagina, FSH, estradiol, urinary daidzein, vaginal smears	Included	NR	NR	NR	NR	NR	NR	27.06-28.9 mean

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Chenoy, 1994	Six months of treatment with either four 500mg evening primrose oil with 10mg natural Vitamin E	Placebo was 500mg liquid paraffin; four capsules twice daily	All women given placebo showed a significant positive difference between control cycle and last cycle ($p<0.05$). Women given gamolenic acid, however, did not show a significant improvement between the control cycle and last available treatment cycle except for a reduction in the maximum number of night time flushes (p-0.014).	NR	NR
Chiechi, 2003	Women were given soy increased diet, adding a soy food every day, and two meals twice/week based on phytoestrogen rich food; isoflavone intake of 20-30mg/day	Usual care; and HRT	These women were asymptomatic	Statistically significant improvement from baseline in vaginal indices in both the HRT ($p<0.01$) and soy groups ($p=0.03$), most in the HRT group; not seen in control group	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Chenoy, 1994	NR	NR	NR	NR	NR	NR	NR
Chiechi, 2003	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Chenoy, 1994	NR	11/28 from placebo and 10/28 from gamolenic acid group	2/11 from placebo due to nausea; however main reason stated was lack of clinical response	Lack of clinical response	Biologically based therapies	Significant response to placebo but not to gamolenic acid
Chiechi, 2003	NR	22 out of control group; 44 out of diet group; 31 out of HRT group	NR	NR	Biologically based therapies	Too high of drop out rate to be reliable

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Cleary, 1994	30	RCT	P	15 weeks	Women age 50-60 years with menopausal symptoms recruited through local and national newspapers	Inclusion: 1. < 4 periods in the previous 12 months 2. Abnormal FSH/LH analysis Exclusion: 1. Current or past HRT in last 18 months 2. Any debilitating medical condition 3. Any facial or spinal surgery 4. Taking medication likely to affect their hormonal or sympathetic systems, such as thyroxine, or beta-blockers 5. Any past or present patient of the researcher
Cohen, 2003	18	RCT	HH	12 weeks	Women were recruited by flyers and by advertisements in local newspapers in a New England ; 11/17 women had ceased having menstrual cycles within the past 2 years and the remaining 6 women had not had a period in 3-4 months; Mean age was 47.3 years (43-53)	Inclusion: 1. Ability of self-identification of menopausal hot flushes 2. Ceased previous treatment of menopausal symptoms with hormones, other medications, herbs, or acupuncture at least 3 months prior to enrollment in the study to allow for a sufficient cleansing period Exclusion: 1. Women with hormonal supplementation, other pharmacologic therapies, herbal remedies, or acupuncture (including acupressure).

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Cleary, 1994	1. Weekly 1-10 scale Symptom questionnaire during study 2. Pre-, Week 5, and Week 15 blood levels of estradiol, FSH, LH, thyroxine, testosterone, sex hormone binding globulin, prolactin, cortisol, IGF/1, TSH, and GH	NR	NR	NR	Excluded	NR	NR	At least 18 months	NR
Cohen, 2003	4 scale daily symptom diary	NR	NR	NR	NR	NR	NR	Excluded at least 3 months prior	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Cleary, 1994	The spine and pelvis of each subject was treated by a low-force osteopathic technique developed by Fox, and the cranium by cranial techniques following mechanical principles weekly for 10 weeks, followed by a 5 week observation period.	Placebo: low-force technique delivered to a joint adjacent to a restricted joint, where it will have no effect; force is so low in both groups that they are unaware they have received treatment weekly for ten weeks followed by five week observation period	Reduction in study group of hot flashes (p=0.016) at ten weeks and (p=0.007) at 15 weeks; Reduction in study group of night sweats (p=0.021) at ten weeks and (p=0.016) at 15 weeks	NR	Reduction in insomnia vs control group (p=0.098) at ten weeks and (p=0.018) at 15 weeks
Cohen, 2003	9 week acupuncture treatment protocol consisting of 1/week for 3 weeks then once every other week for a total of 6 treatments followed by 3 nontreatment weeks (20-30 minutes/ treatment) (EA group)	UB15, 23, 32; GV 20, H7; pericardium 6; SP6, 9; L3 for experimental group; comparison is general tonic (shen mein) L4;K7 and ear points (7)	EA group showed a decrease in mean monthly hot flush severity (30%) for site-specific acupuncture from baseline to month 2 (p=0.05), baseline to month 3 (p=0.005) and baseline to posttreatment month 4 (p-0.019). The comparison acupuncture treatment group had no change in severity from baseline over the treatment phase.	NR	Sleep disturbances in the EA group declined over the study and reached a statistically significant difference (0.05) from baseline in posttreatment month. This also accured in the comparison group.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Cleary, 1994	Reduction in depression in study group compared to controls (p = 0.042) at ten weeks and (p=0.290) at 15 weeks; Reduction in irritability is study group compared to controls (p = 0.184) at ten weeks and (p=0.271) at 15 weeks	NR	NR	Reduction in urinary frequency in study group over controls (p=0.021) at ten weeks and (p=0.168) at 15 weeks	NR	NR	Average symptom score decreased in the study group compared to the control group over the study (p=0.005)
Cohen, 2003	Mood changes decreased in both groups between baseline and posttreatment month of the study; EA group p=0.05; comparison acupuncture group (0.056)	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Cleary, 1994	Of the 11 hormones studied there was a significant difference in testosterone levels (decreased in study group) (p=0.028); Reduction in pain was greater in the study group: (p=0.04) for neck pain, and (p=0.06) for back pain	NR	NR	NR	Manual Medicine	
Cohen, 2003	NR	1/18	Withdrew prior to randomization	None	Alternative Health Systems	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Crisafulli, 2004	90	RCT	P, HH	1 year	Healthy, ambulatory women, referred by the Department of Internal Medicine and the Department of OB/GYN at University of Messina, Italy, age 47-57	Inclusion: 1. No surgical menopause patients 2. No period for 12 months, FSH>50 and estradiol level <100. Exclusion: 1. Clinical or lab abnormalities suggesting cardiovascular, hepatic, renal disorders, coagulopathy 2. Use of oral or transdermal estrogen, progestin, androgen or other steroids in the preceeding year 3. Smoking >10 cigarettes/day
Dalais, 1998	52	DB RCT	HH	7 months	52 postmenopausal women were recruited	Inclusion: 1. Age 45-65 2. FSH > 40 3. > 14 hot flashes/week 4. 12 months of amenorrhea 5. No antibiotic or hormone replacement therapy use for the preceding 3 months 6. Non-smoker and non-vegetarian

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Crisafulli, 2004	Self-reported diary of the number of hot flushes, 14 days before each assessment; only number used, not severity	Not allowed	Not allowed	NR	NR	NR	Not allowed if smoked > 10 cigarettes/ day	None for 12 months	Average for all groups was 23-24
Dalais, 1998	Hot flush diary	NR	NR	NR	NR	NR	Non smokers; non vegetarians	None for 3 months prior	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Crisafulli, 2004	1mg/day estradiol combined with noresthisterone; genistein (n=30) at 54mg/day	Placebo	Estrogen group, flush score decreased by 53% ($p<0.001$) compared to placebo at 3 months. This was maintained at 6 and 12 months. Genistein group decreased by 22% ($p<0.01$) after 3 months; 29% at 6 months ($p<0.001$) and 24% at 12 months ($p<0.01$) compared to placebo. The difference between the estrogen group and the genistein group was significant at all measurements ($p<0.05$)	NR	NR
Dalais, 1998	45 grams of soy (high phytoestrogen), linseed (high phytoestrogen), or wheat diet; dosage of isoflavones (daidzein, genistein) was 52.64 $\pm$ 8.68 mg/day	Wheat diet	In women consuming linseed and wheat, a significant decrease in hot flush rate was observed following 12 weeks of ingestion (41% decrease, $p<0.009$; 51% decrease, $p<0.001$ respectively) compared to baseline. No significant decrease in hot flush rate was detected during soy ingestion.	Women ingesting soy showed signicant increase in vaginal cytology maturation index (p-0.03); none for other two groups	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Crisafulli, 2004	NR	NR	NR	NR	NR	NR	NR
Dalais, 1998	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Crisafulli, 2004	NR	7	None	None	Biologically based therapies	Funding source not reported; important study due to length.
Dalais, 1998	Urinary excretion of daidzein, genistein, enterodiol and enterolactone increased significantly (10-30 fold) during soy and linseed ingestion, respectively ($p<0.01$). No such changes in wheat group	8/52	Personal reasons	NR	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Davis, 2001	55	DB RCT	P	12 weeks	Women, age 45-70 years were recruited through the Jean Hailes Foundation Newsletter, newspapers, radio station interviews and the medical unit of the Jean Hailes Foundaion	Inclusion: 1. Non-Asian women who had lived in Australia for at least ten years 2. Postmenopausal (>12 months amenorrhea and FSH >25) 3. Reported at least 14 hot flushes or night sweats/week Exclusion: 1. Use of HRT, Chinese medicinal herbs (CMH), or other natural therapies during the eight weeks before baseline 2. Preexisting gastrointestinal, renal, or liver disease, diabetes mellitus requiring treatment, uncontrolled hypertension, undiagnosed vaginal bleeding, systemic glucocorticosteroid use 3. Undergoing cancer therapy 4. Women who had consumed a high phytoestrogen diet for the four weeks before baseline

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Davis, 2001	Daily diary of the frequency of hot flushes and night sweats for four weeks before treatment and for the entire 12 weeks of the study period. The Menopause Specific Quality of Life Questionnaire (MENQOL) and urinary phytoestrogen excretion	NR	NR	NR	NR	NR	NR	44.4% of placebo group had previously used HRT, and 53.6% of CMH has previously used HRT	Body mass index was 26.1 (24.3, 27.9) in placebo group; and 25.7 (23.9, 27.5) in CMH group

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Davis, 2001	Both placebo and CMH produced by Ningbo Daekang Herbs Co Ltd (Ningbo, China)	Placebo was cornstarch with a bitter taste enhancer	Frequency of vasomotor symptoms were reduced in both CMH and placebo groups. Difference between groups was not significant (p =0.09) A progressive decline in the frequency of vasomotor symptoms with treatment duration was seen in both groups	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Davis, 2001	NR	NR	NR	NR	NR	NR	A reduction in score was seen in all four domains of the MENQOL scores. 'This was significant only for the physical, vasomotor, and sexual domains in the CMH group, and the physical domain in the placebo group. The difference between the two treatment groups was not significant for any of the four domains

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Davis, 2001	Women with more than four years of ammenorrhea had a significantly greater response to placebo than to CMH; significant greater reduction in score was seen with CMH compared with placebo in the vasomotor domain of the MENQOL for age <55, BMI <25, and previous nonusers of natural therapies (p<0.05)	14/42 in Chinese herbal group; 9/36 in placebo group.	Most withdrew in the first week after randomization due to the taste of both products	In CMH group, two became asymptomatic before study began and withdrew, and on started HRT; 7 withdrew due to taste intolerance, 2 were lost to follow-up, and 2 withdrew due to other illness; in placebo group, one withdrew before the study commenced due to lack of symptoms, 2 withdrew due to no benefit, one withdrew due to other illness, one was lost to follow-up and 3 withdrew due	Biologically based therapies (specifically comments in article that this is not assessing TCM)	Herbs in CMH = rehmannia glutinosa, Cornus officinalis, Dioscorea opposita, Alisma orientalis, Paeonia suffruticosa, Poria cocos, Citrus reticulata, Lycium chinensis, Albizzia julibrissin, Zizyphus jujuba, Eclipta prostarata, Ligustrum lucidum

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Duffy, 2003	36	DB RCT	P	12 weeks	36 postmenopausal women aged 50-65 were recruited by circular email at King's College London from a database of those who had previously participated in a study on bone mineral density at Guy's Hospital.	Inclusion: 1. No menstruation for the previous 12 months Exclusion: 1. Had used HRT in previous 12 months 2. Use of antibiotics in the previous 3 months 3. Current illness or use of psychoactive medication. Three subjects were excluded during the course of the treatment, two because they started treatment with amitryptiline and one because she started HRT
Faure, 2002	75	DB RCT	P	4 months	Postmenopausal women requesting treatment for hot flushes.	Inclusion: 1. $\geq$ 6 months out from last menses 2. FSH >40 3. $\geq$ 7 moderate to severe hot flashes per 24 hours 4. $\geq$ 6 weeks since last HRT use

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Duffy, 2003	Hospital Anxiety & Depression Scale; Greene Climmacteric Scale; Stanford Sleepiness Scale; Epworth Sleepiness Scale; paced Auditory Serial Addition test; plus short-term memory test from the Weschler Memory Scale; plus samples from the Cambridge neuropsychological Test Automated Battery 'list all the animals they could think of in 1 minute'	13-22%	Included	NR	NR	NR	All nonsmokers; caffeine and alcohol assessed, plus diet; alcohol intake significantly less in soy group ($p<0.05$); high IQ in both groups (118 and 115)	None in past 12 months	NR
Faure, 2002	Self report by diary.	NR	NR	NR	NR	NR	NR	At least 6 weeks	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Duffy, 2003	Soya isoflavone supplement used was Solgen 40 (Solbar Plant Extracts, Ashdod, Israel). Each capsule contained 30 mg total isoflavone equivalents. Dose was two capsules/day for 12 weeks	Identical looking placebo capsules; told to avoid Soya foods and food products containing Soya for the duration of the study, and for the two weeks prior	No significant effects of treatment on any of the menopausal symptoms assessed by the Greene Climacteric Scale	NR	No difference
Faure, 2002	70mg/day of Genisten and Diadzin (Phytosoya) 325mg four/day = 70mg of G/D	Placebo	The Intention-to-treat analysis indicated treatment effect on the change in frequency of hot flashes for the intervention group (p=0.01).	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Duffy, 2003	No difference	Significant improvement in memory in Solgen group (delayed recall of pictures ($p<0.03$); immediate story recall ($p<0.06$); corrected for practice effect; also learning the reversal of the simple discrimination rule ($p=0.05$)	No difference	NR	NR	NR	NR
Faure, 2002	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Duffy, 2003	Improved time to learn complex tasks greater in Solgen group than placebo (p<0.05 and <0.003)	3/36	None	None	Biologically based therapies	
Faure, 2002	NR	6 soy group 14 placebo	NR	NR	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Freedman, 1992	33	RCT	HH	4 weeks	33 women were recruited from newspaper advertisements; mean age in years was 50.7 ± 8.6 in paced respiration group; 53.1 ± 6.0 in muscle relaxation group; and 53.9 ± in alpha wave feedback group	Inclusion: 1. Amenorrheic ≥ 1 year 2. ≥ 5 hot flashes/day
Freedman, 1995	24	RCT	HH	4 weeks	Women recruited from newspaper advertisement; age was 52.5 years ± 1.6 for paced respiration group; 52.7 ± 1.6 years for alpha feedback group	Inclusion: 1. Amenorrheic ≥ 1 year 2. ≥ 5 hot flashes/day

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Freedman, 1992	Ambulatory monitoring of sternal skin-conductance level and abdominal and thoracic ventilation; in addition thoracic and abdominal ventilation were recorded on two additional channels of the Medilog using inductance plethysmography (Respitrace); serum epi	Included	Included	NR	NR	NR	NR	None for 1 year	NR (mean weight with variation recorded in pounds)
Freedman, 1995	Ambulatory monitoring of sternal skin-conductance level and abdominal and thoracic ventilation; in addition thoracic and abdominal ventilation were recorded on two additional channels of the Medilog using inductance plethysmography (Respitrace); serum epinephrine and norepinephrine	Included	Included	NR	NR	NR	NR	None for 1 year	NR (mean weight with variation recorded in pounds)

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Freedman, 1992	8 1-hour biweekly treatment sessions of paced respiration training	8 1-hour treatment sessions of alpha-EEG biofeedback, or Patients were taught muscle relaxation by a research assistant using previously published methods	Hot flash frequency declined significantly ($p<0.02$) for the paced-respiration group but not for the muscle relaxation ($p>0.2$) or alpha wave feedback group ($p>0.5$).	NR	NR
Freedman, 1995	8 1-hour biweekly treatment sessions of paced respiration training	8 1-hour treatment sessions of alpha-EEG biofeedback	Hot flash frequency declined significantly ($p<0.001$) for the paced-respiration group but not for the alpha wave feedback group.	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Freedman, 1992	NR	NR	NR	NR	NR	NR	NR
Freedman, 1995	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Freedman, 1992	Analysis of vafriance on respiration rate showed a significant ($p<0.02$) Group x Pretreatment/Posttreatment interaction effect. Simple effects tests showed a significant pretreatment/posttreatment increase in tidal volume for the paced respiration group ($p<0.03$) but not for the muscle relaxation group ($p>0.8$) or alpha wave feedback ($p>0.5$)	NR	NR	NR	Mind-body interventions	
Freedman, 1995	The 24-hour patern of skin-conductance level of significantly altered for the paced respiration group ($p<0.001$); no significant change in any of the biochemical measures	NR	NR	NR	Mind-body interventions	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Germaine, 1984	26	RCT	HH	6 months	Menopausal women, 44-61 years (Mean=50.3 years); 12 premenopausal women, all reporting regular menstrual periods from 22-45 served as controls	Inclusion: 1. ≥ 2 hot flashes/day 2. No HRT 3. No periods
Han, 2002	82	DB RCT	P	5 months	Women, age 45-55 years	Inclusion: 1. Intact uterus 2. FSH > 25 3. Estradiol < 20 4. Presence of hot flashes 5. 'in menopause' at least 12 months Exclusion: 1. Using lipid-lowering drugs, antidiabetic medications, soybean-derived products, or herbal supplements 2. History of uncontrolled hypertension, stroke or TIA 3. Cancer diagnosed less than 5 years ago 4. Previous myocardial infarction

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Germaine, 1984	Heat stress test (HST); this is 2 circulating water pads maintained at 42° C to the subjects torso whild supine on a bed in a 23° C room. Subjects were instructed to signal the earliest perception of a hot flash by pushing a hand-held button; following the HST 1 the 14 menopausal women were randomly assigned to receive 6 weekly sessions of progressive musle relaxation or alpha EEG biofeedback; HSTs were then administered 1 week later and then final test at the end of training.	NR	NR	NR	NR	NR	NR	NR	NR
Han, 2002	Kupperman Index; height, weight, blood pressure, lipid, and hormone levels, transvaginal sonography	Excluded	NR	NR	Excluded if within past 5 years	NR	All exercised less than three times/week ; 30% smokers in placebo group; 20% smokers in isoflavone group;	None allowed for 12 months	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Germaine, 1984	Progressive muscle relaxation (PMR)	Alpha EEG biofeedback	Increase in heart rate during the heating period, whereas premenopausal women declined in heart rate. Significant reduction in PMR group compared to controls during third HST (Significant test p<0.0003, and Group X Test p<0.002) were found. Also time was significantly longer (p<0.01) for onset of hot flush in the PMR group compared to control group. This change was significant between HST 2 and HST 3 for the PMR group but not the control group (p<0.01).	NR	NR
Han, 2002	Soy isoflavone 83.3 mg/day; soy protein 50.3 mg and isoflavone 33.3mg. Genistein, daizein, and glycitein in aglycone form 23.3.mg, 6.2mg, and 3.8 mg, respectively.	Placebo was 83.3 mg composed of purified soy protein 50.3mg without isoflavones and glucose 33.3mg	Isoflavone group declined more than placebo group (p<0.01)	NR	Insomnia score decreased in isoflavone group more than placebo group (p<0.01)

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Germaine, 1984	NR	NR	NR	NR	NR	NR	NR
Han, 2002	Isoflavone group improved score over placebo in melancholia, nervousness ($p<0.01$)	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Germaine, 1984	NR	NR	NR	NR	Mind-body interventions	Novel way of confirming the presence of hot flushes
Han, 2002	All measures of Kupperman scale (vasomotor, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia and myalgia, headache, palpitation, formication) showed individual statistical improvement in isoflavone group over placebo ($p<0.01$)	1 out of 41 in each group; 1 for 'poor response' and 1 for 'nausea'	NR	NR	Botanically based	Soy isoflavone obtained from eugenbio Co. Ltda, Seoul, South Korea

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Hartley, 2003	34	DB RCT	P	1 week	Postmenopausal women aged 53-65 were recruited from those responding to articles in national and local press	Inclusion: 1. No period for 12 months and healthy. Exclusion: 1. Use of HRT within the previous 12 months 2. Smoking more than 20 cigarettes/day 3. Current illness or use of psychoactive medication, including soya supplements, Ginkgo or ginseng (herbs were allowed)
Hirata, 1997	71	DB RCT	P	24 weeks	Women (mean age 52.4 $\pm$ 6 years) were solicited through radio, television, and newspaper and magazine information; age range was from 44.7-69.3 years in the placebo group and from 44.5 to 59.6 years in the dong quai group.	Inclusion: 1. FSH > 30 2. 'troublesome' hot flushes >14/week 3. 'post menopausal' for $\geq$ 6 months 4. No HRT for 3 months Exclusion: 1. Weight >30% or < 15% of ideal weight 2. Previous hysterectomy, serious illness 3. Use of herbal therapy during the previous 3 months 4. Gastrointestinal disorders that resulted in chronic diarrhea or malabsorption 5. History of breast cancer, pelvic irradiation, 6. Tobacco use, or consumption of > 2 alcoholic drinks per day 7. Active liver disease 8. Chronic use of antibiotics 9. Use of vaginal creams or corticosteroids

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hartley, 2003	National Adult Reading Test-Revised version; Hospital Anxiety and Depression Scale, Greene Climacteric ScaleStanford Sleepiness Scale, Epworth Sleepiness Scale, Immediate and delayed paragraph recall from the Weschler Memory Scale-Revised, and several other brain function measures	Included	Included	NR	NR	NR	Smokers included	None for 12 months prior to study	Mean 66kg
Hirata, 1997	Kupperman Index; symptom diary; serum estradiol, estrone, and sex hormone-binding globulin levels; vaginal cells, endometrial ultrasounography	Excluded	NR	NR	Excluded	NR	Smokers excluded; more than 2 alcohol drinks/day excluded; 57% were regular exercisers	No HRT allowed for previous 3 months	Excluded for weight >30% or < 15% of ideal weight

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Hartley, 2003	Ginkyo One-A-Day 120mg tablet/day containing 25% Ginkgo flavonoids and 6% terpenoids	Placebo	No significant effect of treatment on any of the menopausal symptoms assessed by the Greene Scale, however all improved from baseline ($p<0.001$)	NR	No effect
Hirata, 1997	4.5 grams/day of dong quai from root material	Maltodextrin placebo	29.4% of the placebo group and 33.3% of the dong quai group reported good or excellent control of their vasomotor symptoms	40% of subjects complained of moderate to severe vaginal dryness at baseline; 12 weeks later, about 30% still had this symptom	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Hartley, 2003	No difference between groups	Not significant between groups	NR	NR	NR	One parameter of Greene's scale that did not improve over time	NR
Hirata, 1997	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Hartley, 2003	NR	3	One in the placebo group because of brief menstrual period and two in the Ginkgo group because testing was too demanding	NR	Biologically based	
Hirata, 1997	Both groups has significant decrease in Kupperman scale from baseline at 6, 12, and 24 months (p<0.0001); No significant changes were seen in serum estradiol level, estrone level, SHBG level, blood pressure, or weight were seen during the study	6/36 in the placebo group; 4/35 in dong quai group	Placebo: 2 dropped due to lack of efficacy; 2 developed 'minor side effects'; 1 lost interest; 1 developed 'other health problems'; dong quai; 2 due to lack of efficacy; 1 due to minor side effects and 1 due to other health problems	Side effects: burping, gas, and headache in both groups, with no statistically significant difference between groups	Botanically based	Dong quai was extracted from the crushed root of Angelica sinensis by East Earth Herbs, Inc (Eugene, OR). Potency of the study drug material was standardized to 0.5mg/kg of ferulic acid. Oil of orange was added to all study drug material to disguise the aroma of the dong quai.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Hochanadel, 1999	11	DB RCT	P	12 weeks	Naturally postmenopausal women over age 45	NR
Hudson, 1998	13	DB RCT	P	3 months	Women recruited from a one sentence article in The Oregonian (local newspaper)	Inclusion: 1. Hhot flashes and one additional menopause symptom 2. No HRT for the previous 3 months 3. Natural physiologic menopause with no menses for > 3 months 4. No serious acute or chronic disease 5. No cariovascular disease and normotensive
Hunter, 1999	86	RCT	P	5 years	All women were over 50 years who had been randomized to two 90 minute education groups or no intervention at age 45;	Inclusion: 1. Premenopausal at age 45, from the age/sex registers of five general practices in south London Detailed exclusion/inclusion criteria outlined in Maturitas 1998:29:215-24

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hochanadel, 1999	Somatic symptoms, mood and verbal learning performance of naturally post-menopausal women were measured	Excluded	NR	NR	NR	NR	NR	NR	NR
Hudson, 1998	Self-reported symptom diary (frequency and severity)	NR	Excluded	NR	NR	NR	NR	No HRT for 3 months previously	NR
Hunter, 1999	1. Sociodemographic and health information survey 2. Knowledge about menopause questionnaire 3. Menopause Representation Questionnaire (MRQ) 4. Women's Health Questionnaire (WHQ)	NR	NR	NR	NR	NR	Smokers & exercisers	29% taking HRT	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Hochanadel, 1999	100 mg/day of encapsulated soy isoflavone	Placebo	No improvement	No improvement	NR
Hudson, 1998	Botanical formula that contained 500mg combined dry herb: burdock root (2 part), licorice root (2 part), motherwort (1 part), Dong Quai root (2 part) and Mexican wild yam root (1 part) 2 capsules tid	Rice bran placebo with similar smell and appearance also 2 tid.	100% improvement in severity symptom score in verum group (n=7) and 67% improvement in placebo group (n=6). 71% in verum group had improvement in number of symptoms and 17% had improvement in number of symptoms in placebo group. One sided Z-test showed p<0.03, but two-sided Z test did not reveal this to be statistically significant	NR	NR
Hunter, 1999	Education	N/A	HRT users reported fewer hot flashes (p<0.04).	No difference	No difference

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Hochanadel, 1999	No significant difference between groups	No significant differences between groups	No significant differences between groups	No improvement	NR	No improvement	NR
Hudson, 1998	NR	NR	NR	NR	NR	NR	NR
Hunter, 1999	No difference in depression or anxiety	Significant difference in knowledge of menopause (p<0.01)	Control group more likely than intervention group to believe aches & pains (p<0.01) & skin problems (p<0.05) are due to menopause, no difference as a category	NR	No difference	Improved sexual function in intervention group (p<0.06) Controls had lost interest in sex more (p<0.02)	HRT users in comparison to non-users reported that menopause had a greater impact on their lives (p<0.04).

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Hochanadel, 1999	None of the statistical comparisons between the active and placebo conditions yielded findings in support of the hypothesis that soy isoflavones may be useful fo the treatment of these post-menopausal cognitive or somatic changes	NR	NR	NR	Botanically based	Poster. Don't have actual paper
Hudson, 1998	NR	None	None	NR	Botanically based	Size of study was too small
Hunter, 1999	Women in intervention group maintained better knowledge & did not attribute so many things to menopause. Women in prepared group took more exercise ($p<0.01$) and had lower prevalence of HRT ($p<0.01$).	NR	N/A	N/A	Mind-body interventions	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Hyde, 1983 (Abstract Only)	30	RCT	HH	NR	Menopausal women	NR
Irvin, 1996	45	RCT	HH, P	10 weeks	Postmenopausal women from the greater Boston area recruited through media sources of public service announcements and newspaper advertisements, and through posted notices at appropriate medical sites, age 44-66	Inclusioin: 1.General good health 2. $\geq$ 6 months without a menstrual period 3. Experiencing $\geq$ 5 hot flashes per 24 hours 4. Willingness to monitor flashes and abide by the protocol

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Hyde, 1983 (Abstract Only)	Menopausal symptoms checklist for frequency, intensity and duration of menopausal symptoms; Galvanic skin responses	NR	NR	NR	NR	NR	NR	NR	NR
Irvin, 1996	Spielberger State-trait Anxiety Inventory; Profile of Mood States; daily hot flash diary	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Hyde, 1983 (Abstract Only)	12 contingent Galvanic Skin Response feedback conditioning sessions and progressive relaxation training	12 non-contingent feedback sessions and were told simply to relax	Both groups improved; No significant difference between groups was observed	NR	NR
Irvin, 1996	Relaxation group (RR); reading group (R) which served as the placebo intervention group, or the charting group which was the control group	Reading group was instructed to read leisure material; relaxation group instructed in diaphragmatic breathing and breath awareness; both 20 minutes/day	All three groups had a change in flash frequency, but these did not reach statistical significance. The RR group did have a significant decrease ($p<0.046$) in intensity of hot flashes from baseline.	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Hyde, 1983 (Abstract Only)	NR	NR	NR	NR	NR	NR	NR
Irvin, 1996	On the POMS the RR group demonstrated a significant decrease in tension-anxiety ($p<0.044$) and depression-dejection ($p<0.013$)	The reading group showed significant decrease in confusion-bewilderment ($p<0.013$) on the POMS	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Hyde, 1983 (Abstract Only)	NR	NR	NR	NR	Mind-body interventions	
Irvin, 1996	NR	12/45	4 left because they found charting to be too intrusive in their lives, 3 dropped out due to snow; 2 because they started their menses again, 2 lack of interest, and 1 who went on estrogen treatment	See withdrawals	Mind-body interventions	Inclusion: 1. Postmenopausal women symptomatic, having $\geq$ 3 flushes/day 2. $\geq$ 6 months of amenorrhea or bilateral oophorectomy, FSH >40 Exclusion: 1. HRT within the previous 6 weeks 2. Allergy to foodstuffs known to contain isoflavones 3. Current history of active bowel, liver or gall bladder disease 4. Diabetes requiring drug therapy 5. Malignancy (excluding skin cancers) 6. Contraindications to HRT use, vegetarians and/or regular soy product users.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Jeri, 2002	30	DB RCT	P	16 weeks	Nonvegetarian Peruvian women who had been postmenopausal for more than 1 year; median age was 52 ± 0.7 years for treatment group and 51 ± 0.8 years for control group	Inclusion: 1. < 60 with FSH>30, having ≥ 5 hot flushes/ day averaged for more than 1 week 2. Not using HRT, antidepressants, or other medication or soy or other estrogen-active plan products
Knight, 1999	37	DB RCT	HH, P	12 weeks	Women, age 40-65, were recruited through the University Department of OB/GYN at St. George Hospital, Sydney, Australia	Inclusion: 1. Postmenopausal women symptomatic, having ≥ 3 flushes/day 2. ≥ 6 months of amenorrhea or bilateral oophorectomy, FSH >40 Exclusion: 1. HRT within the previous 6 weeks 2. Allergy to foodstuffs known to contain isoflavones 3. Current history of active bowel, liver or gall bladder disease 4. Diabetes requiring drug therapy 5. Malignancy (excluding skin cancers) 6. Contraindications to HRT use, vegetarians and/or regular soy product users, 7. Receiving medications that result in liver enzyme induction

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Jeri, 2002	Self reported diary of frequency and severity of hot flushes	NR	NR	NR	NR	NR	NR	Excluded	NR
Knight, 1999	Greene Menopause Scale;self-reported diary of hot flushes	NR	Included	NR	Excluded	NR	NR	None within 6 weeks	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Jeri, 2002	Promensil (40 mg standardized isoflavones (genistein, daidzein, formononetin and biochanin))/day	Placebo	Reduction in both frequency and severity of hot flushes was reported by women in the treatment group; 14 Promensil women had a 48% reduction from baseline in frequency of hot flashes ($p<0.001$), controls had a 10.5% reduction. P value not given between groups or for control group; Regarding severity index, 47% reduction in Promensil group from baseline ($p<0.001$) and no change in placebo form baseline.	NR	NR
Knight, 1999	Placebo vs. 40mg of Promensil vs. 160mg of Promensil	Promensil is a standardized isoflavone supplement prepared from red clover extract, in tablet form; each tablet contains 40 mg of total isoflavones; genistein (4.0), daidzein (3.5mg) and their methylated precursors biochanin (24.5mgg) and formononetin (8.0mg)	Flushing frequency decreased in all groups over the 12 week trial period. There was not difference in flushing frequency between the active and placebo groups. (average 29-34% reduction)	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Jeri, 2002	NR	NR	NR	NR	NR	NR	NR
Knight, 1999	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Jeri, 2002	Significant reduction in FSH in Promensil group from baseline (59.27 to 48.60) P<0.001)	1/15 Promensil group	NR	NR	Biologically based	
Knight, 1999	None of the biological parameters of estrogen activity measured, including FSH, SHBG and climacteric symptom scores, showed any change with time, compared to placebo. (average 26% -160mg group to 46% - placebo group reduction in Greene Score over the twelve weeks)	2/37	Intervention by their general practitioner	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Knight, 2001	24	DB RCT	P	12 weeks	24 subjects were recruited through the University Departments of Obstetrics and Gynecology , Sydney Australia	Inclusion: 1. Postmenopausal women, having $\geq$ 3 hot flushes/day; amenorrhea for 6 months, FSH >40 or bilateral oophorectomy 2. Aged 40-65 Exclusion: 1. HRT within the previous 6 weeks 2. Current history of active bowel, liver or gall-bladder disease; diabetes requiring drug therapy; malignancy; contraindications to HRT use 3. Vegetarians and regular soy-product users.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Knight, 2001	Daily flush diary; Green Menopause Scale	Included	Included	NR	Excluded	NR	NR	None within 6 weeks	Mean of 66.1-70.2 kg

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Knight, 2001	Isoflavone powder, TakeCare, 60g/day; isoflavones 134.4mg/day; (aglycone formulations 77.4mg/day)	Casein based powdered drink	Flushing frequency decreased in both groups, but there was not difference in flushing frequency between the active and placebo groups; no difference in Greene Menopause Symptom Scores	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Knight, 2001	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Knight, 2001	NR	4/24	3/12 in the isoflavone group..could not tolerate taste	None	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Komesaroff, 2001	50	DB RCT	P	3 months	Healthy menopausal women 45-60 years, currently experiencing symptoms of the menopause, recruited from the Baker Institute Menopause Clinic, and from the local community by advertisements placed in local newspapers and discussion in the electronic media. Mean age was 53.3 $\pm$ 1.1 years	Inclusion: 1. No HRT for $\geq$ 6 weeks 2. Last period > 12 months before, FSH>30 or estradiol <130 Exclusion: 1. Significant cardiac, renal or hepatic disease, psychiatric disease, inflammatory conditions or active thyroid disease, diabetes, or a history of breast cancer

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Komesaroff, 2001	Symptom diary self reported including number of episodes of flushing and scores for specific symptoms. Symptom scores were combined to produce values for 'total', flushing', and total non-flushing' scores. This approach made possible analysis of specific scores relating to mood, breast symptoms, libido and energy levels.	3/50	NR	NR	NR	NR	NR	None within 6 weeks	Mean of 27.3 ± 0.8

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Komesaroff, 2001	Wild yam preparation (Biogest) supplied in 100gram tubs. Participants were asked to apply one teaspoonful twice daily to the arms, legs or abdomen (manuractures claim that each 1 gram of bioGest contains Dioscorea villosa extract 100mg, Linum usitatissmum oil 2 grams, Perlargonium graveolens oil 100mg, Salvia officinalis oil 100mg and alpha tocopheryl acetate 10mg in a vegetable cream base).	Placebo	No significant difference between the yam cream and placebo in any of the three cases	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Komesaroff, 2001	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Komesaroff, 2001	NR	19/25 in the Biogest group attributed to unrelieved symptoms and unspecified personal circumstances. 8/25 in the placebo group for same reasons	No adverse effects	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Kotsopoulos, 2003	94	DB RCT	P	3 months	Women were recruited from a larger trial. Average age: 59-60 years	Inclusion: 1. Aged 50-75 years 2. Non smokers 3. Non vegetarians 4. ≥ 12 months amenorrheic 5. FSH >20 Exclusion: 1. On HRT in previous 12 months 2. On phytoestrogens or soy based proteins 3. On antibiotics in previous 3 months
Kritz-Silverstein, 2003	56	DB RCT	P	6 months	Women were recruited through mass mailings based on voter registration lists, newspaper ads, and presentations at local organizations. Average age: 61 years Average age at menopause: 49 years	Inclusion: 1. Postmenopausal women aged 55-74 years
Leonetti, World Congress on Fertility, 1998 (Abstract Only)	90	RCT	P	1 year	5 years of menopause, surgical or natural	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Kotsopoulos, 2003	Validated questionnaire of menopause-associated symptoms (measure not stated by name).	NR	NR	NR	NR	NR	0/94	0/94	0/94
Kritz-Silverstein, 2003	Beck Depression Inventory (BDI) The Mini-mental Status Examination (MMSE) Trials A & B of the Halstead-Reitan Neuropsychological Test Battery Category Fluency Logical Memory and Recall	NR	NR	Yes exact number not stated	NR	NR	2/56 drink soy beverages every day	Yes exact number not stated	NR
Leonetti, World Congress on Fertility, 1998 (Abstract Only)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Kotsopoulos, 2003	118mg Isoflavones	Placebo	No change between groups.	No change between groups. Intervention group had a significant improvement (p=0.01).	NR
Kritz-Silverstein, 2003	110mg/day of Isoflavones	Placebo	NR	NR	NR
Leonetti, World Congress on Fertility, 1998 (Abstract Only)	20mg/day of natural progesterone cream	Placebo	83% of natural progesterone cream patients had improvement or resolution of vasomotor symptoms compared with 14% of placebo group (p<0.001)	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Kotsopoulos, 2003	No change within groups for psychological outcomes	NR	No change between groups	No change within groups.	NR	No change between groups, both intervention and placebo groups improved (p=0.009 and p=0.015, respectively).	NR
Kritz-Silverstein, 2003	NR	Women in the treatment group showed improvement on four of five tests compared to controls (p=0.03)	NR	NR	NR	NR	NR
Leonetti, World Congress on Fertility, 1998 (Abstract Only)	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Kotsopoulos, 2003	Both intervention and placebo groups had a significant improvement in facial hair (p=0.04 and p=0.014, respectively) and dry skin (p=0.0027 and p=0.011, respectively).	19/94 10 in treatment group 9 in placebo group	Gastrointestinal side effects All were due to AEs (19)	None serious Treatment group: 7 - intolerable; 1 - weight gain; 1 - menopausal symptoms; 1 - unrelated Placebo group: 6 - intolerable; 2 - constipation; 1 - allergies	Biologically based	
Kritz-Silverstein, 2003	NR	NR	NR	NR	Biologically based therapies	Outcome was significant improved performance on category fluency
Leonetti, World Congress on Fertility, 1998 (Abstract Only)	NR	NR	NR	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Lewis, 2002 (Abstract Only)	99	DB RCT	HH, P	16 weeks	Postmenopausal women	NR
Lindh-Astrand, 2004	75	RCT	HH	12 weeks	75 postmenopausal sedentary women with vasomotor symptoms, 48-63 years of age, recruited by advertisement in the local papers and at the gynecological outpatient clinic of a hospital in Sweden; mean age of exercise group was 54 years with BMI of 24.6; estrogen treated women had mean age of 50.9 years and BMI of 25.6	Inclusion: 1. Spontaneous menopause $\geq$ 6 months previously Exclusion: 1. Severe endocrine, metabolic or thrombo-embolic disease, uncontrolled hypertension, or daily use of sedatives, anxiolytic or antidepressant medication 2. Exercising regularly more than 1 hour/week

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Lewis, 2002 (Abstract Only)	Menopause Specific Quality of Life (MENQOL), plus daily diary of frequency and severity of hot flashes	NR	NR	NR	NR	NR	NR	NR	NR
Lindh-Astrand, 2004	Number of flushes during the last day and night in a log-book which was filled in at bedtime for two weeks before and during the 12 week treatment. Also measured the severity of flushes (0-10); also completed questionnaires on aspects of quality of life at baseline, 4,8,12, and 24 weeks, Kupperman Index, VAS to general summary of the total climacteric symptom intensity and distress, MOOD Scale, SCL-90	4	None	NR	NR	NR	NR	None previous	See populatio n

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Lewis, 2002 (Abstract Only)	Flaxseed muffin vs. soy flour muffin	Wheat flour muffin	NR	NR	NR
Lindh-Astrand, 2004	3 times weekly exercise (15 women); also compared to 8 wait listed women and 4 women being observed in a parallel study on hot flushes in women with breast cancer	Oral estrogen (15 women); 45 other women randomized to three additional arms (2mg/day)	The severity of flushes decreased significnatly p=0.041 in the 5 exercising women, who continued the complete follup-up time of 36 weeks (exercising the entire time period). In the estrogen group the mean number of flushes decreased (p<0.001) after 12 weeks and remained at this level; in the waiting list group of 12 untreated women the number of flushes did not change during a period of 8 weeks.	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Lewis, 2002 (Abstract Only)	NR	NR	NR	NR	NR	NR	NR
Lindh-Astrand, 2004	NR	NR	NR	NR	NR	NR	Kupperman's Index and Mood Scale only changed significantly in the estrogen group ($p<0.01$), although SCL-90 improved in both exercise and estrogen group ($p<0.01$)

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Lewis, 2002 (Abstract Only)	ANOVA on 4 domains showed no significant time by dietary group interaction in quality of life: vasomotor, psychosocial, sexual, physical or in combined score, hot flash frequency of hot flash severity. No MENQOL domains or hot flash symptoms showed significant group differences: however, all groups showed improvement with time	7/33 from flax, 3/33 from soy;3/33 from wheat	NR	NR	Biologically based therapies	
Lindh-Astrand, 2004	SCL-90, Kupperman's and VAS all changed significantly p<0.01) at 36 weeks, and mood scale only in the estrogen group	5/15 in the first 12 weeks, 5/15 additional in the second 12 weeks in the exercise group; 6/15 in the first 12 weeks from the estrogen group; 0/15 in the second 12 weeks	1 from estrogen group	Vaginal bleeding	Mind-body interventions	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Makkonen, 1993	30	DB RCT	P	6 months	Women, mean age of 52.3 ± 2.7 years for guar gum group; mean age of 53.6 ± 4.0 in placebo group	Exclusion: 1. Uncontrolled hypertension, diabetes mellitus, liver disease or thromboembolic disease 2. Hormone therapy taken during previous three months
Murkies, 1995	58	DB RCT	HH	14 weeks	Women were recruited from interested patients in a general practice in Melbourne, Australia and newspaper advertisements	Inclusion: 1. ≥ 12 months of amenorrhea, and FSH>25, 2. Hot flushes > 14/week 3. Non-smokers 4. Stopped antibiotics or hormonal replacement ≥ 3 months prior
Nachtigall, 1994	30	RCT	HH	12 weeks	Post menopausal women	Inclusion: 1. > 1 year past their last menstrual period 2. Not on any other HRT 3. Cancer free 4. Experiencing vaginal discomfort or dyspareunia.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Makkonen, 1993	Kupperman Index, weight, height, blood presuure, serum estrone, estradiol, testoserone, androstenedione, FSH, LH, SHBG, TSH, total cholesterol, HDL cholesterol, triglycerides and fasting blood glucose	NR	NR	NR	NR	NR	3 were smokers in guar gum group; none in placebo	At least 3 months off	Weight recorded in kilograms
Murkies, 1995	Diet diary; flush diary to record daily number of flushes; subjective four point scale of 'general menopause symptoms' (flushes, sweats, palpitations, headache, sleep disturbance, depression, tiredness, irritability/nervousenss, frequency/urge to urinate, vagninitis, loss of libido, dyspareunia; vaginal smears	NR	NR	NR	NR	NR	Non smokers	None for 3 months	26.5 $\pm$ 0.76 for soy group; 25.6 $\pm$ 0.68 for wheat group
Nachtigall, 1994	Pap smear done every 4 weeks with specific criteria for atrophy; Vaginal fluid pH; Vaginal health index	NR	NR	NR	NR	NR	NR	Not allowed	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Makkonen, 1993	Guar gum (Guarem, Orion Pharmaceutica, Espoo, Finland) 5 grams 3 times daily for 6 months	Placebo was wheat flour granules	Both groups improved significantly on the Kupperman scale ($p<0.001$) at 3 and 6 months from baseline. No difference between groups	NR	NR
Murkies, 1995	45 grams of 'soy flour'	45 grams of refined wheat flour	At 6-weeks there was a significant decrease in hot flashes and general symptom score from baseline in the soy treated group ($p<0.05$). At 12-weeks there was a significant decrease in hot flashes and general symptom group in both groups ($p<0.05$) and no significant difference between the 2 flour groups.	Vaginal maturation score did not change within or between flour groups	NR
Nachtigall, 1994	Replens (a nonhormonal bioadhesive local vaginal mosturizer) 3 times/week for 12 weeks	2 grams of Premarin Vaginal cream daily for 12 weeks	NR	Vaginal moisture showed significant improvement in both groups at 12 weeks ($p<0.005$)	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Makkonen, 1993	NR	NR	NR	NR	NR	NR	NR
Murkies, 1995	NR	NR	NR	Urinary daidzein excretion increased signifiantly over 12 weeks in the majority of women in the soy group with signicant difference between groups (p<0.001)	NR	NR	NR
Nachtigall, 1994	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Makkonen, 1993	See note under hot flashes regarding Kupperman Index scores	3 withdrawals from the placebo group, one due to depression and exhaustion, and two due to travelling. No withdrawals from the guar	NA	NA	Biologically based therapies	
Murkies, 1995	No change in lipid panels between groups	5/28 withdrew from soy group; 6/30 withdrew from wheat group	NR	NR	Biologically based therapies	Soy Products of Australia donated debittered soy and unbleached refined wheat flour
Nachtigall, 1994	Vaginal elasticity improved in both groups ($p < 0.02$) from baseline; vaginal pH and vaginal fluid volume improved from baseline ($p<0.05$)	None	None	None	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Nassef, The 10th World Congress on the Menopause. 2002 (Abstract Only)	37	RCT	P	3 months	Postmenopausal Egyptian females	NR
Penotti, 2003	62	DB RCT	P	6 months	Women patients attending the outpatient Menopause Clinic at the University of Mulan	Inclusion: 1. High FSH and low BE2 2. LDL < 160 3. ≥ 7 hot flashes/day 4. Post menopausal for ≥ 6 months 5. Aged 45-60 years 6. T score > -2.5 Exclusion: 1. Osteoporosis

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Nassef, The 10th World Congress on the Menopause. 2002 (Abstract Only)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Penotti, 2003	Daily diary for hot flash recording	NR	NR	NR	NR	NR	NR	NR	23.2 both groups

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Nassef, The 10th World Congress on the Menopause. 2002 (Abstract Only)	Cimicifuga rhizome 40mg/day	Placebo	No difference (p>0.05) between groups	NR	NR
Penotti, 2003	36mg Soy Isoflavones a day	N/A	No change between groups, both groups had a 40% reduction in hot flashes	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Nassef, The 10th World Congress on the Menopause. 2002 (Abstract Only)	NR	NR	NR	No difference in dysuria or stress urinary incontinence between groups (p>0.05)	NR	NR	NR
Penotti, 2003	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Nassef, The 10th World Congress on the Menopause. 2002 (Abstract Only)	Bone aches were significantly improved in phytoestrogen group (p<0.001); no significant difference between groups in vaginal cytology, bone mineral density, or endometrial thickness (p>0.05)	NR	NR	NR	Biologically based	
Penotti, 2003	NR	6 in soy group 7 in placebo group	1 from soy group due to diarrhea Persistent hot flashes in the rest	Diarrhea	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Rachev, 2001	64	DB RCT	P	60 days	Women age 40-60 from the 'maternity ward' of the University Hospital in Sofia, Bulgaria; mean age was 51.5 in LF group and 49.5 in placebo group.	Inclusion: 1.Evident anxious-depressive symptoms associated with physiological menopause lasting for at least one year 2. No treatment with phospholipids $\geq$ 4 weeks prior 3. No antidepressant or anxiolytic therapy during the study Exclusion: 1. Sensory organ deficiency not properly corrected by artificial aids 2. Signs or symptoms of foci of cerebral lesions, 3. Signs or symptoms of other neurological and/or psychiatric diseases requiring treatment with neuroleptic drugs and/or other antidepressants 4. Liver or kidney impairment, severe cardiovascular diseases, past or ongoing neoplastic diseases, other sever ongoing internal or surgical pathologies 5. Proven hypersensitivity to phospholipid
Rankin, 1989	40	RCT	No treatment	2 weeks	Women, age 40-60 who stated they were experiencing menopausal symptoms; referred to the study by other health professionals and recruited from church groups and various women's organizations. Mean age was 49.3 years, range from 40-58	Inclusion: 1. Understand and write English

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Rachev, 2001	Hamilton Anxiety Scale (HAMA) and the Climacteric Index	NR	NR	NR	NR	NR	NR	NR	Weight was expressed in kilograms, mean of 71.3 for LF group and 79.0 for P group
Rankin, 1989	Neugarten-Kraines Menopausal Index Scale, Sound Wave Audiotapes	41%	NR	NR	NR	NR	NR	5 (2/sound, 3/control) had taken HRT for 1-12 years	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Rachev, 2001	Liposom Forte (phospholipid liposomes) 28mg/2ml as a single intramuscular injection every other day for a period of 60 days	Placebo injection every other day for 60 days	Significant decline in the climacteric index in LF and P groups from baseline (p<0.001); however more significant decline in LF group (p=0.0013) than P group (NOTE: did include questions of asthenia (p=0.05), dizziness (p=0.024) and restlessness (p=0.019)	NR	NR
Rankin, 1989	20 minute long low frequency sound wave audiotape developed by Halpern (1978); 3 times/week for 2 weeks	No treatment	The sound wave group has significant improvement over no treatment in decreased frequency of symptoms (p=0.01), somatic symptoms were decreased (p=0.03) and psychological symptoms were decreased (p=0.029).	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Rachev, 2001	Decrease in the total HAMA score in both groups was noted (p<0.001); however significantly greater decline in the LF group than the P group (p<0.001); specifically anxious mood (p=0.006), tension (p=0.024) and fear (p=0.009) were significant between groups as well.	NR	NR	NR	NR	NR	See climacteric index scores under hot flashes
Rankin, 1989	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Rachev, 2001	NR	6/64	Allergy = 1 anxiety = 1; asthenia = 1; drowsiness = 2; hypertension = 1; petechia = 1; increased sweating = 1; paroxysmal tachycardia = 1; weight increase = 1	NR	Biologically based therapies	Not sure that they did a good job of confirming symptoms were related to menopause
Rankin, 1989	NR	6/20 in sound group; 7/20 in the control group	4 completed the protocol late, others did not follow instructions, or did not have time.	None	Mind-body	Poor study

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Rao, 2003	30	RCT	P	2 months	Women with menopausal symptoms	NR
Russo, 2003	50	DB RCT	P	3 months	Women who were referred to a clinic in Rome, Italy. Average age: 53 years Average age at onset of menopause: 51 years	Inclusion: 1. Aged 48-54 years 2. Recent menopause (1-2 years LMP) 3. Symptomatic 4. Caucasian 5. Negative PAP test Exclusion: 1. Currently on HRT or off <6 months 2. Arterial hypertension or cardiovascular pathologies 3. Endocrinological pathologies 4. Nicotinism 5. Obesity 6. Alcohol or drug abuse

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Rao, 2003	Menopause-specific Quality of Life	NR	NR	NR	NR	NR	NR	NR	NR
Russo, 2003	Self report questionnaire.	NR	NR	NR	Excluded	NR	Smokers excluded	≥ 6 months discon-tinuation	Obesity excluded

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Rao, 2003	Biogest cream (wild yam)	Placebo	Significant effects were noted with symptoms of hot flushes, night sweats, and emotional symptoms with dramatic reductions in these symptoms occurring in the BioGest group when compared with placebo.	NR	NR
Russo, 2003	32mg/day of Soy (Fitormil)- Specific formulation described in paper	Placebo	11/25 in soy group and 6/25 in placebo group described improvement in symptoms ($p<0.05$)	No significant reductions for either group.	No significant reductions for either group.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Rao, 2003	NR	NR	NR	NR	NR	NR	NR
Russo, 2003	No significant reductions for either group on anxiety.	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Rao, 2003	NR	NR	NR	NR	Biologically based	Abstract only available
Russo, 2003	NR	3	1 due to spotting after 15 days	Spotting	Biologically based	Cross over study, only using data from first 3 months before cross over.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Salmaggi, 1993	80	DB RCT	P	30 days	Age 45-59 (mean age is 51) women patients consecutively referred to an Ob/Gyn department in Italy	Inclusion: 1. Major depression within 6 to 36 months following surgical or natural menopause 2. Free of antidepressants for $\geq$ 1 week Exclusion: 1. Considered at risk for suicide 2. On estrogen therapy 3. Major medical illness or bipolar illness
Sammartino, 2003	70	RCT	HH	12 cycles of 28 days	Women attending Menopause Clinic. Average Age: 51 years Average time since menopause: 17 months Average BMI: 24-26	Inclusion: 1. At least 12 months after spontaneous menopause 2. FSH > 40 3. Estradiol < 20 4. At least 7 hot flashes of moderate to severe severity in 24 hours during last 2 weeks Exclusion: 1. Neoplastic, metabolic and infectious diseases 2. Concomitant use of any drug 3. BMI < 30 4. Past or concomitant use of HRT or other drug used for treatment of climacteric symptoms 5. Endometrial thickness of >5mm or endometrial abnormalities

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Salmaggi, 1993	HAM-D-21 (Hamilton Depression Rating Scale) and the RDI (Rome Depression Inventory); MMPI (Minnesota Multiphasic Personality Inventory); CGI-I (Clinical Global Impression Improvement Scale)	Included	Included	NR	NR	NR	NR	Not included if on estrogen	NR
Sammartino, 2003	Kupperman scale - Baseline and 6, 12 months	0	0	0	0	NR	NR	Excluded	Excluded if >30

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Salmaggi, 1993	1600mg SAMe per day divided into 4 doses	Placebo	NR	NR	NR
Sammartino, 2003	36mg/day of Genistein	Calcium supplements	Significant decline in Kupperman Score for Genistein group ($p<0.05$).	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Salmaggi, 1993	HAM-D-21 decreased significantly (p<0.01) at both day 10 and 30 compared to placebo; also found in RDI (p<0.01), CGI-I (p<0.01) and depression and psychoasthenia scale of MMPI (p<0.01) compared to placebo.	NR	Questions 11-16 on the HAM-D-21 pertaining to somatic symptoms improved significantly from placebo at both day 10 and 30 (p<0.01)	NR	NR	NR	NR
Sammartino, 2003	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Salmaggi, 1993	NR	10/40 from each group due to poor compliance	NR	NR	Biologically based	
Sammartino, 2003	All women in Genistein group had decreased climacteric symptoms (but not specified by symptom).	3 in Genistein 4 in Calcium	None	None	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Sandberg, 2002	30	RCT	HH	14 weeks, Follow-up at 6 months	Women age 48-60, natural menopause of at least 6 months were recruited through advertisements in the local press and at gynecological outpatient clinics.	Inclusioin: 1. FSH and estradiol levels confirms postmenopausal state 2. Natural menopause of $\geq$ 6 months 3. Aged 48-60 years Exclusion: 1. Severe metabolic, thromboemboic, endocrine or malignant disease, uncontrolled hypertension 2. Use of medication that could interfere with vasomotor symptoms
Scambia, 2000	39	DB RCT	P	12 weeks	Women who were outpatients at Italian hospital (mean age was 54 $\pm$ 7.1 years)	Inclusion: 1. Spontaneous amenorrhea $\geq$ 12 months 2. Surgical or early menopause 3. Normal endometrial thickness by ultrasound, negative mammography, and metabolic and biochemical index within normal range

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Sandberg, 2002	Visual Analog Scale (VAS) SCL-90	Unclear	Not included	Not included	NR	NR	Similar rates of smoking & exercise	NR how recent, not taken during study	26.7 vs. 25.6
Scambia, 2000	Vasomotor symptoms were evaluted usina a special score card and the Greene climacteric scale. Special score card was filled out daily to evaluate the number and severity of hot flushes and brought it to each visit	NR	1/50	1/50	NR	NR	NR	NR	BMI = 26.2 $\pm$ 1.7

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Sandberg, 2002	Electro acupuncture (EA)	Extremely superficial needle insertion	Both groups showed improvement in VAS at 3 and 6 months	NR	NR
Scambia, 2000	Standardized soy extract containing 12% isoflavones and 35% saponins in a tablet which was 200mg SOYSELECT 2/day which would correspond to 50mg/day of isoflavones. After 6 weeks of treatment Premarin was also given to each participant at a dose of 0.625 for 4 weeks	Placebo tablet containing lactose	In the first 6-weeks of treatment, participants who were taking the standardized soy extract had a significant reduction ($p<0.01$) in the mean number of hot flushes/week as compared with placebo. Once the Premarin was started both groups had a decrease in hot flushes and there was no significant difference between groups.	After 6 weeks of treatment, the group that was taking the standardized soy extreact had a significant reduction ($p<0.001$) in the mean point values 19 and 20 of Greene scale (hot flushes and night sweats) compared with placebo.	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Sandberg, 2002	Significant improvement in mood at 12 weeks in EA group compared to baseline Both groups improved in SCL-90	NR	NR	NR	NR	NR	NR
Scambia, 2000	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Sandberg, 2002	NR	4/15 Superficial needle insertion 4/15 EA	Hot flashes	Hot flashes	Alternative health care systems	
Scambia, 2000	NR	20 were analyzed in soy extract group suggesting no withdrawals	Nausea in 1 placebo member	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Simkin-Silverman, 2003	535	RCT	Lifestyle vs. assess-ment only	5 years	Women were recruited from the WHLP clinical trials and were seen at the Health Studies Clinic at the University of Pittsburg.	Inclusion: 1. Aged 44-50 years 2. Premenopausal by self report 3. Not taking HRT 4. BMI was 20-34 Exclusion: 1. Women taking lipid-lowering medication, antihypertensive medication, insulin, thyroid medication, or psychotropic medications
St. Germain, 2001	69	RCT	Placebo	24 weeks	Telephone interviews of age 42-62 year old women;	Inclusion: 1. $\geq$ 10 hot flushes and/or night sweats/week, within 12 months of their last menstrual cycle 2. Free from chronic diseases (cardiovascular disease or osteoporosis) or chronic medication use 3. Not taking HRT or ERT at the time of the study or 12 months previously 4. 1 or both ovaries remaining 5. BMI 20-31 6. FSH>30.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Simkin-Silverman, 2003	Weight, BMI and body fat were measured. Paffenbarger Activity Questionnaire The Block Food Frequency Questionnaire	NR	NR	NR	NR	NR	NR	NR	58/535 High BMI
St. Germain, 2001	5 day Menopausal Index (modified from the Blatt instrument, 1953) at baseline, week 12 and week 24	11 with intact ovaries	Excluded	NR	NR	NR	Non smoking	None for 12 months prior to study	20-31

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Simkin-Silverman, 2003	Behavioral, dietary and physical activity intervention	N/A	NR	NR	NR
St. Germain, 2001	SPI+ (Supro 675 HG; Protein Technologies International, St. Louis, MO = 80.4 mg/day aglycone components which are the unconjugated parent forms of isoflavones)	SPI- (Supro 675 IF; Protein Technologies International) = 4.4 mg/day aglycone components; Group 3 consumed whey protein (control) produced by ProMod; Ross Laboratories, Columbus, Ohio	No treatment effect on the change in frequency of hot flushes; time of study from baseline did have a significant effect on hot flush frequency in all groups (p.0.003)	No significant difference among the three groups at any time point	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Simkin-Silverman, 2003	No signs of increased stress or depressive symptoms in intervention group	NR	NR	NR	NR	NR	NR
St. Germain, 2001	No significant difference among the three groups at any time point	NR	NR	No significant difference among the three groups at any time point	NR	No significant difference among the three groups at any time point	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Simkin-Silverman, 2003	Women lost significantly more weight in the intervention group ($p<0.001$), remained more active ($p<0.001$) and consumed fewer calories ($p<0.01$) than the control group.	14/260 Intervention 12/275 Control	NR	NR	Mind-body	5 year program showed that intense exercise encouragement (cognitive restructuring program) and low fat diet showed decrease of weight and waste circumference
St. Germain, 2001	NR	1/69	None	NR	Biologically based therapies	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Teoman, 2004	81	RCT	Control Usual care	6 weeks	Volunteer postmenopausal women (average age 51.0 ± 3.9 years)	Inclusion: 1. Natural menopause 2. Taking HRT ≥ 1 year (0.625 mg estrogen and 2.5 mg medroxyprogesterone/day) 3. Aged 45-65 years old 4. No health problems that may prevent from doing exercise 5. No high cardiac risk
Thompson, 2002 (Abstract only)	53	DB RCT	P	16 weeks	Women with breast cancer with menopausal symptoms	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Teoman, 2004	6 minute walking test, vertical jump test, static back extension test, sit up test, side bending test, sit and reach test, balance test, quality of life using the Nottingham Health Profile	NR	Excluded	NR	NR	NR	NR	Must be on for 12 months	27.0 ± in exercise group and 25.4 ± 4.0 in control group
Thompson, 2002 (Abstract only)	Measure Yourself Medical Outcome Profile (MYMOP), Hospital Anxiety and Depression score, European Organization for Research and Treatment in Cancer Quality of Life Score, Menopausal Symptom Scale	NR	NR	NR	Included	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Teoman, 2004	6 weeks aerobic exercise programme	Non-exercise control group	NR	NR	NR
Thompson, 2002 (Abstract only)	Homeopathic intervention	Placebo	Both groups showed significant improvement over the study period by an average of 80%. No statistically significant difference betweeen groups	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Teoman, 2004	NR	NR	NR	NR	NR	NR	At the end of the 6 weeks, there was a statistically significant change in the exercise group according to NHP, indicating an improvement in the quality of life (<0.05). Only the increase in social isolation parameter was not statistically significant.
Thompson, 2002 (Abstract only)	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Teoman, 2004	NR	NR	NR	NR	Exercise Mind/body	Turkey
Thompson, 2002 (Abstract only)	NR	8/43	NR	NR	Biologically based therapies	Abstract only; included as only homeopathic RCT that could be found.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Tice, 2003	252	DB RCT	HH	12 weeks	Women were recruited from 3 academic clinical research sites in Oakland, CA; Minneapolis, MN, and Iowa City, Iowa from the general population through newspaper and radio advertising, flyers posted in clinics and at health fairs, and directed mailings	Inclusion: 1. Age 45-60 years old 2. Experiencing $\geq$ 35 hot flashes/week 3. FSH > 30 4. $\geq$ 2 consecutive months of amenorrhea prior to enrollment with $\geq$ 6 months of amenorrhea in the year prior to entry, or documented bilateral oophorectomy. Exclusion: 1. Vegetarians 2. Consumed soy products more than once/week 3. Took medications affecting isoflavone absorption (antibiotics, antacids) or hormonal preparations during the three months prior to enrollment 4. Significant gastrointestinal disease 5. > 2 alcoholic beverages/day 6. Allergic to red clover 7. Regular users of dietary supplements containing isoflavones 8. Consumed less than 80% of the expected study tablets during the 2-week placebo run-in period
Unfer, 2004	376	DB RCT	P	5 years	Healthy voluntary postmenopausal women; mean age was 49 $\pm$ 4.3 years in soy group; 50 $\pm$ 3.9 years in placebo group	Inclusion: 1. Intact uterus 2. Absence of menses for $\geq$ 12 months 3. FSH >30 4. Body weight range within 20% of normal Exclusion: 1 Use of medication containing estrogens, progestins, or androgens within 8 weeks of the beginning of the study 2. Presence of endometrial hyperplasia

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Tice, 2003	Greene Climacteric Scale; used the psychological (anxiety and depression), somatic, vasomotor, and sexual desire; hot flash diary cards	NR	Allowed	NR	NR	NR	Excluded if drank >2 alcoholic beverages/ day	None for 3 months prior	26.3 ± 5.1 in Promensil group; 25.6 ± 4.2 in Rimostil group; 26.5 ± 5.4 in placebo group
Unfer, 2004	Endometrial biopsies at the beginning of the study, after 30 months, and at the end of the study	Excluded	Excluded	NR	NR	NR	NR	None for 8 weeks	67 kg ± 10.2 kg in soy group; 65.8 ± 10.7 kg in control group

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Tice, 2003	Promensil contains an average of 41.0 mg of total isoflavones/tablet (red clover containing a higher proportion of biochanin A and genistein); Rimostil contains average of 28.6 mg of total isoflavones and a higher proportion of formononetin and daidzein. Participants took two tablets daily.	Placebo that had less than 0.04 mg total isoflavone	Decrease in hot flush count was significant for all three groups ($p<0.001$), however, the hot flash reductions in the phytoestrogen groups were not statistically different from placebo at 12 weeks ($p>0.20$).	NR	NR
Unfer, 2004	Soy tablets (3/day) equaled 150mg/day of isoflavones; isoflavones were 40-45% genistein, 40-45% diadzein, and 10-20% glycitein	Placebo	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Tice, 2003	NR	NR	NR	NR	NR	NR	NR
Unfer, 2004	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Tice, 2003	Greene Symptom Scales; over the 12-week treatment period, there were significant improvements from baseline in all three groups, but there was no statistically significant differences between groups on any of the Greene scales	6/252 withdrew 2 from each of the 3 arms; 84 participants were in Promensil group; 83 participants were in Rimostil group; 85 participants were in placebo group	1 from the Rimostil group	There was no statistically significant association of either of the dietary supplements with adverse events	Biologically based	
Unfer, 2004	No cases of endometrial hyperplasia or malignancy were detected at 30 months; at 5 years, 6 cases of endometrial hyperplasia were detected in Group A (soy), none in Group B (p<.05) (control)	7 withdrew at 30 months; and 50 more withdrew by 5 years	NR	NR	Biologically based	Significant for length of study..5 years

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Upmalis, 2000	177	DB RCT	P	12 weeks	Postmenopausal women age ≥ 50 years	Inclusion: 1. Overall good health 2. Body weight within +/- 35% range for body mass index 3. FSH >40 4. Estradiol levels of 25 pg/mL or less 5. Average of ≥ 5 vasomotor symptoms/day 6. No menses for at least 6 months 7. Discontinued HRT use at least 60 days before study entry Exclusion: 1. History of breast cancer, hyperplasia, endometrial carcinoma, or cervical neoplasia 2. Positive pregnancy test 3.Undiagnosed abnormal vaginal bleeding 4. Bilateral oophorectomy or hysterectomy 5. Thromboembolic disorders 6. History of cardiovascular disease 7. Liver disease 8. History of chronic alcoholism 9. Medication hypersensitivity, or allergy to dietary supplement ingredients 10. Uncontrolled addiction or severe depression 11. Acute systemic infection 12. Abnormal laboratory values
Valente, 10 world congress on the menopause, 2000 (Abstract Only)	100	RCT	HH	NR	Menopausal women	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Upmalis, 2000	Daily symptom dairy cards for recording the number and severity of hot flushes and night sweats	Excluded	Excluded	NR	Excluded	NR	NR	Discontinue ≥ 60 days prior	See inclusion criteria
Valente, 10 world congress on the menopause, 2000 (Abstract Only)	Neurovegetative symptoms, vaginal dryness, endometrial pattern, lipids, bone density	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Upmalis, 2000	Soy isoflavone extract tablet. The extract was standardized for total content of genistin and daidzin (approximately 50% each). The dose contained in two tablets taken once daily was approximately 50mg in total of genistin and daidzin	Placebo	There was a significant ($p<0.05$) change from baseline in both the number and the severity of hot flushes in both treatment groups. Analysis showed a statistically significant reduction ($p=0.01$) in average hot flush severity over the 12 weeks in the soy isoflavone extract tablet group compared with the placebo group. Marginally significant ($p=0.078$) reduction in the number of hot flushes in the soy isoflavone extract tablet group compared with the placebo group; No statistically significant difference between the two groups at 12 weeks ($p>0.05$) in frequency of night sweats	NR	NR
Valente, 10 world congress on the menopause, 2000 (Abstract Only)	50 women treated with phytoestrogens (25 with oral and 25 with patch, 75mg/day)	50 with HRT, patch (Estradiol 2.5mg and Levonorgestrel 1mg)	"Phytoestrogen therapy cannot be considered as valid as HRT"	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Upmalis, 2000	NR	NR	NR	NR	NR	NR	NR
Valente, 10 world congress on the menopause, 2000 (Abstract Only)	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Upmalis, 2000	NR	31/90 those randomized to soy group withdrew; 24/87 withdrew from placebo group	Failure to meet inclusion/exclusion criteria; protocol violations; voluntary discontinuation;	NR	Biologically based therapies	Odd study design in that randomization occurred prior to screening for inclusion/exclusion criteria
Valente, 10 world congress on the menopause, 2000 (Abstract Only)	NR	NR	NR	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
van de Weijer, 2002	30	DBRCT	P	12 weeks	Symptomatic postmenopausal women, age 49-65	Inclusion: 1. ≥ 5 hot flushes/day 2. ≥ 12 months amenorrhea Exclusion: 1. HRT or antibiotics within 12 weeks of study entry 2. Undiagnosed vaginal bleeding, active liver or renal disease 3. History of allergy for foodstuffs 4. Previous history of malignancy, cardiovascular disease or thromboembolism
Washburn, 1999	51	DB RCT	HH	6 weeks then cross-over	Perimenopausal women aged 45-55 years; women were recruited through advertisements in a local newspaper	Inclusion: 1. Presence of menopausal symptoms (≥ one hot flush or night sweat daily) 2. Not currently using HRT (or any HRT in the past 6 months) 3. Missing ≥ 3 menstrual periods in the last 12 months and having last menstrual period not > 12 months before participating in the study

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
van de Weijer, 2002	Greene Climacteric Scale; self-reported diary Urinary isoflavone levels	NR	NR	NR	Excluded	NR	NR	None for 12 weeks prior to study	BMI was 24.8 ± 3.0 for placebo group and 26.4 ± 5.4 for Promensil group
Washburn, 1999	Self reported symptom diary of hot flashes and night sweats; both frequency and severity; A health related quality of life questionnaire was administered at baseline and at the end of each 6 week intervention period. Using the health related quality of life questionnaire data, an overall symptoms core was calculated by using the Likert scale information for the following content specific areas: estrogenic symptoms, general health, sleep disturbances, and gastrointestinal symptoms. Specifically, the estrogen symptom score was calculated to provide a continuous estimate of the intensity/frequency of symptoms known to be estrogen-dependent (vasomotor symptoms, vaginal dryness, sleep disturbances, breast tenderness, mood	NR	NR	NR	NR	NR	NR	≥ 6 months discontinuation	Mean weight was 163.4lbs

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
van de Weijer, 2002	Red clover (Promensil) 80 mg/day	Identical placebo	No difference in the hot flush count between the 2 groups at baseline 1. At week 12 there had been a significant decline in hot flushes in the isoflavone users (p=0.0154)	NR	NR
Washburn, 1999	Group 1: 20 grams complex carbohydrated supplement containing no phytoestrogen; Group 2: 20 grams of soy protein supplement containing 34 mg phytoestrogen/day; Group 3: 20 grams soy protein supplement containing 34 mg phytoestrogens split into two equal doses consumed twice daily.	All supplements were provided by Protein Technologies International, St. Louis, Missouri. All identical appearing packets	No significant differences were observed in the number of hot flushes or night sweats/week; however, severity of hot flashes was lower in the soy groups vs. the carbohydrate group (p<0.001)	NR separately	No significant difference between groups

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
van de Weijer, 2002	NR	NR	NR	NR	NR	NR	Greene scores differences did not reach significance
Washburn, 1999	NR	NR	NR	NR	NR	NR	General health score was not significantly different between groups

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
van de Weijer, 2002	Isoflavone urinary excretion increased significantly for women in the active treatment group (p=0.027). (p=0.0005) from baseline of 4 week washout period	3/16 red clover group; 3/14 control group	Zero Withdrawals were due to lack of efficacy	N/A	Biologically based therapies	Red clover was manufactured from three varieties of red clover using a standardized extraction and blending process to obtain a proprietary ratio of daidzein, genistein, biochanin and formononectin.
Washburn, 1999	Estrogenic symptom score' was significantly different from the comparison group (p<0.05)	9/51	5 had personal reasons; 1 did not want to use aspartame, 1 remembered she was allergic to soy and 1 had a recurrence of acne rosacea	NR	Biologically based	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Wiklund, 1999	384	DB RCT	P	16 weeks	Women were recruited through advertisements in newspapers. Women seeking medical assistance due to climacteric symptoms were asked to participate in the trial as well.	Inclusion: 1. Healthy postmenopausal women, aged 45-64 2. No HRT for the previous 2 months 3. No bleeding during the previous 6 months 4. 6 episodes of hot flushes during at least 3 of the past 7 days. Exclusion: 1. Previous or concomitant serious or chronic medical conditions 2. Uncontrolled hypertension (>160/95) 3. Psychiatric illness 4. Unable to understand and complete the QoL questionnaires 5. Taking tranquilizers
Williamson, 2002	80	RCT	HH	19 weeks	Women age 45-60 with no period for 3 months. Recruited by means of notices placed in primary care surgeries.	Exclusion: 1. Current HRT use or psychoactive medications 2. Severe pathology of feet 3. Previous reflexology treatment 4. Current CAM treatment for menopausal symptoms or 5. History of severe psychological illness

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Wiklund, 1999	Women's Health Questionnaire; Psychological General Well-being Index; Visual Analog Scales (VAS); self-reported diary	NR	NR	NR	Excluded	NR	NR	None for 2 months	Reported in kg, with mean 71.1 (11.6) for ginseng group (n=193) and 69.9 (11.5) for placebo group (n=191)
Williamson, 2002	Women's Health Questionnaire; VAS for severity of flushes and night sweats, MYMOP, a validated, self-completed measure of quality of life	NR	NR	NR	NR	NR	NR	Required	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Wiklund, 1999	Standardized ginseng extract (Ginsana, containing 100mg of the standardized ginseng extract G115; Pharmaton SA, Lugano, Switzerland); 2 capsules/day	Placebo	Both treatments improved vasomotor symptoms compared with baseline ($p<0.05$), with no indication that the ginseng was superior to placebo; No statistically significant difference between treatments was observed in vasomotor symptoms even though a considerable decrease in these symptoms was noted for both treatments	NR	NR
Williamson, 2002	Reflexology weekly for 6 weeks then monthly for 3 months	N/A	No change between groups	NR	No change between groups

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunction**	**Quality of Life**
Wiklund, 1999	Statistically significant differences ($p<0.05$) were detected for depression, well-being and health subscales of the PGWB in favor of the ginseng extract compared to placebo	NR	NR	NR	NR	NR	With regard to the primary endpoint (total score of the PGWB index) only a tendency for slightly better overall symptomatic relief ($p<0.1$) was seen in subjects taking the ginseng extract.
Williamson, 2002	Anxiety Depression no change between groups	No change between groups on memory/ concentration	No change between groups	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Wiklund, 1999	NR	3/193 ginseng group; 2/191 placebo group	1/193 in the ginseng group due to nausea and lack of efficacy	See withdrawals	Biologically based	
Williamson, 2002	Feelings of attractiveness no change. p>0.2 for time-group interaction. p<0.001 - strong time effect evidence	5/38 control 6/42 reflexology	No reasons stated	None reported	Energy Therapy	

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Woo, 2003	136	RCT	HH	3 months	50-65 year old women with no periods for the past 12 months; contacted as part of a territorywide survey and random sampling of housing estates, and participants who are registered with the Family Medicine clinic of the Chinese University of Hong Kong	Inclusion: 1. No period for 12 months Exclusion: 1. Hypertension, ischemic heart disease, stroke, dementia, diabetes, thyrotoxicosis, breast lump/malignancy, or abnormal Pap smear 2. Taking lipid lowering drugs or HRT
Wuttke, 2003	62	DB RCT	HH, P	12 weeks	NR	Inclusion: 1. Postmenopausal women, 40-60 years of age 2. BMI < 30 3. Last menstrual bleeding at least 6 months ago 4. FSH>25 5. $\geq$ 3 hot flushes/day 6. Menopause rating scale (MRS) items 1-6, sum of scores >1.7 at visits 1 and 2; MRS item 1 (hot flushes) >0.3 at visits 1 and 2.

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Woo, 2003	Menopausal symptoms questionnaire; MMSE, plus four neuropsychological tests covering measurement of memory (Hong Kong List-Learning test, attention (Trail Making test), motor speed (Finger Tapping Test), and word-finding ability (Boston Naming Test), quality of life (SF36), Food Frequency Questionnaire; lipid profile; urinary deoxypyridinoline; dietary phytoestrogen intake and urinary phytoestrogen; estradiol; FSH and LH	24%	18%	NR	Excluded	NR	100% non smokers	Not allowed	24
Wuttke, 2003	Menopausal rating scale	NR	NR	NR	NR	NR	NR	NR	Excluded if >30

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Woo, 2003	Pueraria lobata (PL) Isoflavone 100mg/day; plus a control group where women were given no treatment	HRT; Premelle (Wyeth) containing conjugated equine estrogen (o.625 mg) for first 14 days followed by 14 days of combination of estrogen plus progesterone (5mg)	No significant change in menopausal symptoms between baseline and 3 months in any of the groups	NR	NR
Wuttke, 2003	Cimicifung racemosa (CR BNO 1055) brand name Klimadynon/Menofem, correlating to 40mg herbal drug/day; and placebo	Conjugated estrogen 0.6mg/day	MRS items 1-3 (#1 related to hot flashes) were significantly reduced by the CE compared to placebo (p=0.0461). CR BNO 1055 showed a marked difference to placebo, without reaching the level of significance.	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Main Outcomes (cont.)

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Woo, 2003	NR	1. No change in any group except MMSE increased for both HRT & PL 2. Delayed recall improved in HRT vs. control 3. Attention span better in HRT & PL 4. Performance in flexible thinking best in PL group	NR	NR	NR	NR	SF-36, no differences in any groups
Wuttke, 2003	NR	NR	Factor 3 (questions 7-10 on the MRS scale) which relate to urinary and sexual symptoms did show significant improvement with the black cohosh vs placebo (p=0.0218); CE approached significance (p=0.0503)	NR	NR	NR	MRS score (items 1-10) demonstrates an obvious placebo effect over the 12-week treatment period, which was outmatched by CR BNO 1055 and CE. These effects approached significance, p=0.0506 and p=0.0513

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Woo, 2003	NR	5/48 HRT 2/47 PL 2/41 control	HRT = abdominal pain, distension, and acne or too busy; PL group = urticaria and being too busy; control group = being too busy	Abdominal pain, distention, acne, too busy, urticania	Biologically based	p values not clear in article regarding cognitive changes, probably <0.05
Wuttke, 2003	NR	NR	NR	NR	Biologically based	This study is often quoted as the one study that shows black cohosh as effected as conjugated estrogen for menopausal symptoms. Clearly this is a misquote as the data did not show statistically significance between any on the 1-10 MRS scale, and only conjugated estrogen was significant in MRS 1-3

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Wyon, 1995	24	RCT	P	3 months	"Ordinary" women patients who attended the outpatient clinic because of vasomotor symptoms and were primarily interested in HRT Median age was 54 with a range from 47-62	Inclusion: 1. Healthy women with vasomotor symptoms 2. Natural menopause at least 1 year previously Exclusion: 1. Severe metabolic, thromboembolic, or endocrine disease 2. Uncontrolled hypertension (>95mg Hg diastolic)
Wyon, 2004	45	RCT	HH, P	12 weeks with 6 month followup	Local newspaper and gynecological clinic in Sweden	Inclusion: 1. Healthy women with vasomotor symptoms 2. Age 48-63 years 3. Natural menopause $\geq$ six months prior (4 had hysterectomy, however, none had bilateral oophorectomy) Exclusion: 1. Severe metabolic, thrombo-embolic, or endocrine disorders 2. Severe hypertension (>95mg Hg diastolic) 3. Use of sedatives, anxiolytics, or antidepressants, or narcotics.
Yoles, 2002 (Abstract Only)	102	RCT	P	6 months	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Wyon, 1995	Daily symptom dairy; Psychological General Well-Being Index; Sleep Dysfunction Test; modified Kupperman Index	Excluded	Excluded	Excluded	NR	NR	NR	Not allowed	NR
Wyon, 2004	Kupperman Index; visual analog scale; self-reported daily symptom diary of frequency and severity of menopausal symptoms	4/45	Excluded	NR	NR	NR	Excluded if exercised > 1 hour/week; 20-31% smokers	NR	19.5-36.6; average 25.6 - 26.4
Yoles, 2002 (Abstract Only)	Detailed questionnaire regarding patients 15 variables of patients menopausal complaints	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Wyon, 1995	Acupuncture to VB 15, 23, 32; GV20; H7; P6; LIV3; SPG, Each treatment given twice a week for 2 weeks and once week for 6 weeks for 30 minutes each.	Superficial needle insertion	No significant differences were found between groups on any measure, before, during, or 3 months after treatment; Number of hot flushes/day decreased significantly in both groups from before to the first as well as the second treatment period (p=0.013 and 0.0033 in the EA group, p = 0.005 and 0.0093 in the SNI group)	NR	NR
Wyon, 2004	Electro acupuncture (EA) 14 treatments over 10 weeks sites BL 15, 23, 32, HT 7, SP 6, 9 LR 3, PC 6, GV 20	Conjugated estrogen 0.625mg/day vs. superficial needle insertion (SNI) (sham acupuncture) at Baseline, Week 15, 23, and 32	Hot flushes decreased in all 3 groups over the 12 weeks (p<0.001); these results persisted at the 6 month followup.	NR	NR
Yoles, 2002 (Abstract Only)	Tofu based concentrated phytoestrogen	Placebo	Hot flushes decreased in 76% of the patients treated by phytoestrogen vs 19% of placebo group (p<0.001)	NR	Sleep disturbance improved in 69% taking phystoestrogen vs 16% placebo (p<0.001)

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

	Main Outcomes (cont.)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunction	Quality of Life
Wyon, 1995	PGWB index did not change significantly in any group during treatment	NR	NR	NR	NR	NR	NR
Wyon, 2004	NR	NR	NR	NR	NR	NR	NR
Yoles, 2002 (Abstract Only)	Nervousness improved in 56% taking phytoestrogen vs 14% placebo ($p<0.001$)	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	NCCAM Category	Comments
Wyon, 1995	Visual analog scale decreased significantly in the EA group but not the SNI group (p=0.008); Kupperman Index decreased significantly in both groups (p<0.05) and persisted for 3 months after treatment	3/24 due to noncompliance with log books	None	None	Alternative Health Systems	
Wyon, 2004	All 3 groups had significant improvement in Kupperman Index and visual analog scale (p<0.001); these results persisted at the 6 month followup	4/15 in electroacupunc-ture group; 3/15 in superficial needle insertion group; 6/15 in estrogen group	None	None	Alternative Systems	
Yoles, 2002 (Abstract Only)	77% decrease in PE group vs 17% in placebo group (p<0.001); no change in endometrial thickness	NR	NR	NR	Biologically based	Done in Israel

Appendix F: Evidence table 6-8. Key Question 3G-I complementary and alternative therapies

Key/Abbreviations

AE = Adverse effects
BDI = Beck Depression Inventory
BMI = Body mass index
BSO = Bilateral Salpingo Oophorectomy
CAM = Complimentary and Alternative Medicine
CE = Conjugated estrogen
CGI = Clinical Global Impression Improvement Scale
CMH = Chinese medicinal herbs
DB = Double blind
EA = Electro acupuncture
ERT = Estrogen replacement therapy
G/D = Genisten and Diadzin combination therapy
GI = Gastrointestinal
HAMA = Hamilton Anxiety Scale
HAM-D-21 = Hamilton Depression Rating Scale
HH = Head to head
HRT = Hormone replacement therapy
HST = Heat stress test
KK = KavaKava
LF = Liposom Forte (phospholipid liposomes)
LMP = Last menstrual period
MENQOL = Menopause Specific Quality of Life Questionnaire
MMPI = Minnesota Multiphasic Personality Inventory
MMSE = Mini-mental Status Examination
MRQ = Menopause Representation Questionnaire
MRS = Menopause rating scale
MSQ = Menopause symptoms questionnaire
MYMOP = Measure Yourself Medical Outcome Profile
NA = Not applicable
NHP = Nottingham Health Profile
NR = Not reported
OC = Oral Contraceptives
P = Placebo
PE = Phytoestrogen
PGWB-I = Psychological General Well-being Index
PL = Pueraria lobata
PMR = Progressive muscle relaxation
POF = Premature ovarian failure
POMS = Profile of Mood States
QoL = Quality of life
R = Reading
RCT = Randomized controlled trial
RDI = Rome Depression Inventory
RR = Relaxation
SAMe = S-adenosyl-L-methionine
SD = Standard deviation
SERMs = Selective Estrogen Receptor Modifiers
SNI = Superficial needle insertion
TCM = Traditional chinese medicine
TIA = Transient ischemic attack
VAS = Visual Analogue Scale
WHLP = Women's Healthy Lifestyle Project
WHQ = Women's Health Questionnaire

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Barton, 1998	125	RCT cross-over	P	9 weeks	Women over age 18 with a history of breast cancer.	Inclusion: 1. Hot flashes for $\geq$ 1 month with a frequency of $\geq$ 14 times per week. 2. Life expectancy $\geq$ 6 months. 3. ECOG performance status of 0 or 1. 4. Tamoxifen allowed Exclusion: 1. Current or planned therapy with corticosteroids, progestational agents, estrogens, androgens, chemotherapy, any other agen used for treating hot flashes, or more than 60 IU of vit E daily. 2. Pregnant or lactating women. 3. Women with a history of bleeding tendencies, immune deficiencies or thrombophlebitis.
Barton, 2002 (abstract)	80	Open trial	HH	4 weeks	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Barton, 1998	Documentation of hot flashes number and severity using a diary questionnaire (cites Bergman, Loprinzi studies).	NR	NR	NR	100%	54%	Vitamin use in Table 1	NR	NR
Barton, 2002 (abstract)	Hot flash diary: frequency and score (daily frequency x score)	NR	NR	NR	100%	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Barton, 1998	Vitamin E succinate 800 IU daily for 4 weeks followed by placebo	Placebo for 4 weeks followed by vitamin E	At the end of 4 weeks, HF frequency decreased 25% in vitamin E group as compared to 22% in the P (p=0.90). HF score decreased 28% with vitamin E and 20% with P (p=-0.68). Both groups had statistically significant within group decreases by Wilcoxon's sign rank. At the end of 9 weeks, vitamin E/P group had decrease in HF frequency and HF score that was greater than the P/vitamin E group, P<0.05, no data given	NR	NR
Barton, 2002 (abstract)	Venlafaxine, nefazodone, citalopram, mirtazapine		Venlafaxine decreased HF score to 47% of baseline (n=47) Nefazadone decreased HF score to 37% of baseline (n=6) Citalopram decreased HF score to 40% of baseline (n=14) Mirtazapine decraesed HF score to 38% of baseline	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Barton, 1998	NR	NR	NR	NR	NR	NR	NR
Barton, 2002 (abstract)	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Barton, 1998	102 women responded to question about preference at the conclusion of the study: 32% preferred vitamin E; 29% preferred placebo; 38% did not have a preference.	4 prior to initiation of drug.	None	No significant differences in reporting of: 1. headaches16/120 in vitamin E; 17/120 in P (p=0.85) 2. nausea 11/120 in vitamin E; 11/120 in P (p=0.99) 3. fatigue 20/120 in vitamin E; 25/120 in P (p=0.31) 4. other: 18/120 in vitamin E; 13/120 in P (p=0.43).	125 women randomized; 5 in the placebo group withdrew before starting their medication. RCT cross-over tiral, but stratified by age (18-49 vs 50 and older), current tamoxifen use, duration of hot flashes (>/< 9 mo), average frequency of flushes and current MVI use.
Barton, 2002 (abstract)	"these antidepressants appear to ameliorate other menopausal related symptoms such as difficulty sleeping, anger and depression."	NR	NR	NR	Pilot of 4 anti-depressant medications (venlafaxine, nefazadone, citalopram, mirtazapine)

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Bertelli, 1999 (abstract)	71	Open label Randomized	HH	6 weeks	NR	71 post-menopausal breast cancer survivors with at least 7 HF/week.
Carpenter, 2002	15	RCT cross-over	P	72 hours ecah arm followed by 2 days observation period and 10 day wash-out	Postmenopausal women ≥18 years (some postmenopausal at early age due to chemotherapy)	Inclusion: 1. Women ≥ 18 years 2. 1st time diagnosis of breast cancer 3. No other type of cancer 4. Currently free of cancer or competing treatment 5. > 12 months of ammenorrhea 6. Expereincing HF 7. Able to speak, write, and read English Exclusion: 1. Contraindication to magnets (i.e. implanted devices) 2. Concurrent use of magnets for other symptoms 3. Concurrent use of other HF treatments

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Bertelli, 1999 (abstract)	HF frequency and score	NR	NR	NR	100%	NR	NR	NR	NR
Carpenter, 2002	1. HF monitor - ambulatory sternal skin conductance monitoring 2. HF diary (number of HF, date/time, severity 0-10, degree of bothered 0-10) 3. HF related daily interference scale (HFRDIS) - 10 item scale measures degree to which HF interferes with 9 daily activities and overall quality of life	NR	NR	NR	100%	NR	NR	NR	Mean 28.8 (SD 5.7)

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Bertelli, 1999 (abstract)	Depot IM medroxyprogesterone acetate (MPA) 500 mg IM on days 1, 14, and 28 vs oral megestrol acetate (MA) 40 mg/day for 6 weeks.	MPA vs MA	HF frequency was reduced by 87% and HF score was reduced by 89% as compared to baseline, with no significant diffferences between groups. Response (>50% reduction in HF) observed in 28/37 (75%) off MPA and 22/34 (64%) of MA groups, p=0.7 Follow-up 6 months after randomization: 25/28 (89%) of MPA vs 10/22 (42%) MA maintained response (p<0.001).	NR	NR
Carpenter, 2002	6 magnetic devices attached to participants skin over accupuncture/accupressure sites used to balance energy and treat HF. Accupressure sites located by 2 licensed accupuncturists. Study nurses affixed devices and covered with gauze and tegaderm magnetic device (hard plastic outer layer with 4 separate magnets of alternating polarity (+,-,+,-). Magna Bloc.	Placebo was identical in size, shape and weight (but blinding was not possible due to the distinctive magnetic properties of the treatment devices).	HF frequency decreased from 9.55 $\pm$ 6.7 to 8.27 $\pm$ 6.56 in the magnet group and from 10.45 $\pm$ 5.89 to 6.64 $\pm$ 5.82 in the P group (p=0.02). HF severity showed no significant difference between groups. HF botherersome decreased from 4.18 $\pm$ 2.41 to 4.07 $\pm$ 2.68 for the magent group and from 4.4 $\pm$ 2.34 to 3.21 $\pm$ 2.85 in the P group (p=0.02) HF interference scale was reduced in both groups, but no signficicant differences were found between groups.	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Bertelli, 1999 (abstract)	NR	NR	NR	NR	NR	NR	NR
Carpenter, 2002	NR	NR	NR	NR	NR	NR	Overal quality of life was not significantly different between groups.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Bertelli, 1999 (abstract)	NR	NR	NR	"less side effects were reported with MPA than MA" 2 MPA vs 7 MA pts had vaginal bleeding. 0 MPA vs 6 MA stopped treatment early for toxicity.	
Carpenter, 2002	NR	Only 11 participants (of 15) completed both arms of the study.	Reasons for 4 not completing the 2nd arm of the study. Perspiration (unable to keep device attached to skin) = 1 Lack of interest = 2 Itching from tape = 1	Several problems were reported in both placebo and magnet arms in first week (27%) 1 - Perspiration 1 - Redness 1 - Itching By end of 2nd week 6 reported itching. Willingness to continue with placebo was 8.2 vs. treatment at 9.3	Data not presented prior to cross-over. No wash out period reporte between arms of cross-over.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Ganz, 2000	76	RCT	Usual Care	4 months	Mean age: 54.5 years Disease-free, female breast cancer patients between 8 months and 5 years after diagnosis of stage I or II disease	Inclusion: 1. Perimenopausal or postmenopausal (defined by ammenorrhea > 6 months) 2. All chemotherapy or radiation therapy completed ≥ 4 months prior to enrollment, but could be taking tamoxifen 3. Presence of ≥ 1 target symptom that was moderate to severe in intensity 4. Willing to accept behavioral or pharmacologic treatment for ≥ 1 target symptom Exclusion: 1. History of other cancers except non-melanoma skin cancer 2. Serious medical conditions that might influence the assessment of helath related quality of life 3. An abnormal Pap smear showing dysplasia or more severe changes 4. curent symptoms of majoy psychiatric illness that were not being treated or were not being controlled with medication. 5. Inability to read and write English 6. Active alcohol or substance abuse 7. Use of ERT within the past 3 months 8. Major cognitive impairment or inability to provide informed consent

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Ganz, 2000	1. Menopausal Symptom Scale Score adapted from the Breast Cancer Prevention Trial Symptom Checklist 2.Vitality Scale from the RAND 36 Item Health Survey 1.0 (also known as the Medical Outcomes Study SF-36) 3. Sexual Summary scale from the Cancer Rehabilitation Evaluation System (CARES)	NR	NR	NR	100%	40 (56%) on Tamoxifen	NR	Excluded if any ERT use within last 3 months.	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Ganz, 2000	NP counselling, tailored therapy and support. 1. Assessment: symptom diary, in-depth interview focused on symptoms and influencing factors, and a standardized psychosocial evaluation. 2. Symptom Management: With help of nurse, patient chose 1 of 3 symptoms to focus on, developed an individualized plan of care that included education, counseling and specific pharmologic and/or behavioral interventions (for HF: pharmacologic = bellergal, clonidine patch, or megestrol; behavioral = slow abdominal breathing; for vaginal dryness: moisturizer or lubricant; for SUI: behavior = Kegel's; pharm = replens, phyenylpropanolamine; for psychosocial problems = referral for counseling or group support 3. Follow-up: telephone call 2 weeks after intervention, visits at 2 months and 4 months. Patients had ability to change or alter treatment until symptom relief achieved.	Usual Care (UC)	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Ganz, 2000	NR	NR	NR	NR	NR	Intervention group had significantly higher change score in CARES sexual functioning scale both unadjusted and adjusted (unadjusted mean change score 0.11 UC vs 0.46 Int, p=0.03)	No differenece in the mean change score for the RAND vitality scale between UC and INT groups (UC 2.3 vs INT 0.8, p=0.72). Same results after adjustment, and after adjustment using clonidine as a covariate.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Ganz, 2000	Change in overall menopause symptom scale was significantly greater in the intervention group (reduced symptoms) as compared to the usual care group (true both for unadjusted scores and score adjusted for age, tamoxifen use, prior chemotherapy, race, partner status ad RAND score): unadjusted mean change score: 0.09 UC vs 0.57 INT, p<0.0001	4 people dropped out, all from the intervention group: 2 had family member's illness, 2 developed metastatic disease and became inelligible	None	NR	1. Groups were random, but not equivalent at baseline: intervention group had lower urinary symptom scores and higher RAND vitality scores (p=0.05 for both). 2. Also, cannot distinguish interventions, as participants could choose from a menu and change within the course of the 4 months. 3. There was contamination of the usual care group: up to 31% started some kind of therapy for symptoms.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Goldberg, 1994	116	DBRCTX	P	9 weeks (1week of P to assess baseline 4 weeks C or P then X)	Adult women on tamoxifen for breast cancer with hot flashes. Median age 54 years (30-76). Stratified by age, duration of tamoxifen use, duration of hot-flash symtpoms, and average frequency /severity of hot flashes.	Inclusion: 1. Hot flashes present >1 month and $\geq$ 7 per week 2. Life expectancy of $\geq$ 6 months 3. ECOG performance status of 0 or 1. Exclusion: 1. Many listed
Hernandez Munoz, 2003	136	RCT	HH	12 months	Women > 35 years attending a breast cancer clinic in Venezuela	Inclusion: 1. Women > 35 years who were premenstrual 2. Diagnosis of ER+ breast cancer treated with tamoxifen 3. Hot flush symptoms

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Goldberg, 1994	Self administered question-naires of number of hot flashes, severity (mild, mod, severe, or very severe graded 1-4), and drug toxicities. Composite score of mean frequency times mean severity. Contacted by nurses every 2-3 weeks to assess compliance, toxicities, and answer questions.	NR	NR	NR	116/116	116/116	NR	NR multiple drug exclusions including hormonal therapies	NR
Hernandez Munoz, 2003	HF diary (number and intensity)	10% (with retention of the adnexae).	NR	NR	100%	100% on tamoxifen	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Goldberg, 1994	Clonidine transdermal 0.1 mg/day, patch changed weekly	Patients were on tamoxifen for treatment of breast cancer.	No baseline differences in severity, frequency or hot flash score between C and P groups. Statistically significant decrease in median frequency ($p<0.04$), severity ($p<0.03$), and hot-flash score ($p<0.04$) between C and P after first treatment period. (These findings remained significant after crossover.)	NR	NR
Hernandez Munoz, 2003	1 tab bid ofCR BNO 1055 (C racemosa). Each tablet contained 20 mg of the herbal supplement.	All on tamoxifen; appears that control group did not have placebo	At the end of 6 months there was no significant difference in the control group for either moderate or severe HF (5-9% decline, $p=0.71$ compared to baseline). Results for intervention group are only reported in post-treatment, no comparison to pre treatment rates of symptoms	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Goldberg, 1994	NR	NR	NR	NR	NR	NR	NR
Hernandez Munoz, 2003	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Goldberg, 1994	Patient preferences for treatment option noted at the end of the study. 2-to-1 advantage for clonidine was significantly different than 50:50 odds (x2 p=0.02).	6/116 omitted from analyses (1 ineligible, 1 didn't understand study, 4 failed to submit data)	C was associated with significant increase in dry mouth (p<0.001), constipation (p<0.02), itchiness under the patch (p<0.01) and drowsiness (p<0.05) compared to the week before treatment.	21/116 omitted from efficacy analyses due lack of data or patch came off Despite unequal losses, baseline characteristics of hot flashes were similar (table 2).	Does not appear to be limited to menopausal women
Hernandez Munoz, 2003	NR	Of 150 that entered the study, 14 decided not to participate in the rest of the study.	NR	11 "minor" adverse events occurred: 7 in the usual care group and 4 in the intervetnion group." No serious events reported. No list of what the events were.	No placebo in control group The control group was allowed to start other therapies for HF after 6 months.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Jacobson, 2001	85	RCT, stratified by tamoxi-fen use	P	60 days	Women over age 18 previously treated for breast cancer, who reported experiencing daily hot flases	Inclusion: 1. Completion of primary therapy including chemo and radiation $\geq$ 2 months prior. Exclusion: 1. HRT for HF 2. Pregnancy 3. Major psychiatric illness 4. Known recurrent or metastatic breast cancer

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Jacobson, 2001	1. Menopausal symptom index 2. Changes in LH and FSH from start to end of study 3. Visual analog scale of overall health and well-being. 4. HF diary	NR	NR	NR	100%	59/85 on tamoxifen at baseline	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Jacobson, 2001	Black cohosh, 1 tablet bid with meals	Women permitted to use other nonhormonal medication while in study, but asked not to initiate new therapy for HF.	1. mean HF number at end of study (no significant difference by ANOVA): tam+tx:27.9 tam+placebo: 31.6 tx alone: 26.7 placebo alone: 29.8 2. mean HF intensity (no significant difference by ANOVA): tam+tx: 1.94 tam+placebo:2.06 tx alone: 1.97 placebo alone: 1.74	NR	Included in menopausal symptom scale, both goups improved, not significantly different from each other

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Main Outcomes (contiued)

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Jacobson, 2001	Irritability and nervousness and depression included in menopausal symptom scale, both goups improved, not significantly difference from each other	NR	1. Headaches and palpitations included in menopausal symptom scale, both goups improved, not significantly difference from each other 2. Excessive sweating improved in both groups but the treatment group reported more improvement that placebo group (p=0.04, wilcoxon test)	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Jacobson, 2001	Safety outcomes were changes in mean levels of FSH and LH: both tamoxifen groups had lower FSH than the non-tamoxifen groups but not statistically significant, and no signficant change; no significant changes in LH levels	9 participants declined further participation after baseline assessments. 16 (includes the 9) failed to complete the HF diary at the end of the study. reasons for drop outs: 1. Adverse effect 3 tx; 1 placebo 2. Forgot pills while traveling 1 tx; 1 placebo 3. unknown 5 tx, 5 placebo	4	Lack of change in LH and FSH levels reported. 3 serious AE's occurred: hysterectomy (tam+tx), breast cancer recurrence (tam+tx), appendectomy (tam+placebo) 10 minor AE's occurred: constipation (tam+tx), swolllen finger (tam+placebo), arrhythmia (tx alone), weight gain (tam+tx), endometrial hyperplasia(tam+tx), diliation and currettage(tam+tx), cramping (tx alone), indigestion(tam+tx), vaginal bleeding(tam+tx), and rash on abdomen (tam+placebo).	Randomization procedure described.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Kimmick, 2001 (abstract)	62	DBRCT Cross-over	P	6 weeks	Data from 47 women mean age 53.9 (range 36.6-77.1) 89% post-menopausal 85.5% Caucasian	Inclusion: 1. Women on tamoxifen experiencing $\geq$ 1 HF/day
Loprinzi, 1994	97	DBRCT	P	4 weeks each period, no wash out period between	97 women with history of breast cancer, 66 men with prostate cancer who had undergone androgen-deprivation therapy.	Inclusion: 1. Breast or prostate cancer with either surgical or medical orchiectomy 2. Bothersome hot flashes

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Kimmick, 2001 (abstract)	HR frequency and score (frequency x severity)	NR	NR	NR	100%	100% on tamoxifen	NR	NR	NR
Loprinzi, 1994	HF frequency	NR	NR	NR	100%	78/97 women (80%) were using tamoxifen	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Kimmick, 2001 (abstract)	Sertraline 50 mg qAM	Placebo	At 6 weeks: 36% of women on sertraline (N=25) vs 27% of women on placebo (N=22)reported a decrease in the frequency of HF by 50% (p=0.7) At 13 weeks: Women were asked which tablet/period worked best for their HF: 28% had no preference; 49% preferred sertraline; 11% preferred placebo.	NR	NR
Loprinzi, 1994	Megestrol acetate 20 mg twice daily.	Placebo	After 4 weeks (results for women only): HF frequency was 26% of baseline in megestrol group vs 73% in placebo group, p<0.001. Median HF score was 17% of baseline in megestrol acetate group vs 73% of baseline in placebo group, p<0.001. Reduction of 50% in HF frequency: 71% of megestrol group vs 24% of placebo group, p<0.001. Baseline frequency of HF was 6.1 HF/day (range 0.9-21.4) for women.	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	**Mood**	**Cognitive**	**Somatic**	**Urinary**	**Uterine Bleeding**	**Sexual Dysfunc-tion**	**Quality of Life**
Kimmick, 2001 (abstract)	NR (in process analyzed according to abstract)	NR	NR	NR	NR	NR	NR (in process analyzed according to abstract)
Loprinzi, 1994	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Kimmick, 2001 (abstract)	NR	NR	NR	NR	
Loprinzi, 1994	NR	Of 100 women enrolled in the trial, 2 were ineligible and 1 withdrew before starting any medication. Approximately 82% of women provided usable data for the analysis of efficacy.	NR	Assessed weekly for vaginal symptoms (dryness, irritation or discharge), change in appetite, fluid retnetion.vaginal bleeding reported as a side effect by 15(31%) women, who got megestrol first and had bleeding while on placebo. No suggestion that megestrol acetate was related to other vaginal symptoms, fluid retention or apetite change.	Stratified by duration of HF (< or > 9 months), type of orchiectomy, duration of androgen ablation (men), age and tamoxifen use (women).

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Loprinzi, 1997	52	DBRCT Cross-over	P	4 weeks each period with 1 week washout between	NR	Inclusion: 1. Women > 18 years with a history of breast cancer and significant vaginal complaints defined as persistent vaginal dryness and/or itching 2. Symptoms present for > 2 months. Exclusion: 1. Evidence of active vaginal infection 2. Current anti-neoplastic therapy with estrogen 3. Pregnancy or lactation 4. Previous use of Replens 5. Planned use of any vaginal preparation during study period 6. Use of any vaginal product during prior 1 week.
Loprinzi, 2000	229 (191 with data)	RCT	P	4 weeks	Breast cancer or perceived high risk of breast cancer	Inclusion: 1. > 14 bothersome hotflashes per week for $\geq$ 1 month (but no menopause criteria needed) 2. Age 18 or over 3. Breast cancer or perceived increased risk of breast cancer 4. Performance status of 0-1 on ECOG 5. Tamoxifen and raloxifene o.k. if started 4 weeks prior to study and continued for 5 weeks 6. Not on chemo, estrogens, androgens, progestins, antidepressants, clonidine, Bellergal. Exclusion: 1. Venlafaxine ever 2. Antidepressants past 2 years 3. Pregnancy, breastfeeding 4. Other hot flash treatments in past 2 weeks 5. Uncontrolled HTN.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Loprinzi, 1997	Vaginal atrophy index: summed score of vaginal elasticity, secretions, mucosal integrity and moisture collected from pelvic exam. Questionnaire grading symptoms of vaginal dryness, itching and discomfort during intercourse.	NR	NR	NR	100%	NR	NR	NR	NR
Loprinzi, 2000	Daily hot flash score (frequency x severity 1-4); hot flash frequency; Beck depression inventory; uniscale QOL instrument	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Loprinzi, 1997	Replens daily for 5 days in 1st week, then 3x/week for next 3 weeks. During washout period, placebo was given 3x/week.	Placebo consisting of hydroxymethyl-cellulose, glycerin-delta lactone, hydrogenated palm oil glyceride and water.	NR	Vaginal dryness scores improved in both groups (decreased by 64% in Replens group and 62% in placebo group after 4 wks, p=0.3). No further substantive changes in vaginal dryness in either study arm.	NR
Loprinzi, 2000	Venlafaxine 37.5mg (V 37.5) Venlafaxine 75mg (V 75) Venlafaxine 150mg (V 150)	Placebo	See table 1. (Reduction in score and frequency for all arms compared to placebo)	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Main Outcomes (contiued)

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Loprinzi, 1997	NR	NR	NR	NR	NR	Dyspareunia scores decreased in both groups after 4 weeks: decreased 60% in Replens group and 41% in placebo group, p=0.05. During cross-over period, there were no further substantial changes in either arm for dyspareunia scores compared with the end of the first 4-week period.	NR
Loprinzi, 2000	BDI reduction: P = 1.6; V 37.5 = 2.4; V 75 = 4.8; V 150 = 3.2. NS	NR	NR	NR	NR	All improved; NS between arms. See figure 5.	Tx: +3; P:-3; p=0.02

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Loprinzi, 1997	Vaginal itching: not present at baseline in the majority of women and no significant impact of either Replens or placebo on this symptom. Participants asked which lubricant worked best: of 36 responding, 41% chose Replens, 24% chose placebo and 35% had no preference (p=0.68).	Of 52 patients entering trial, 1 patient canceled before receving any therapy and 6 patients did not answer any of the weekly questionnaires.	7 of the 45 patients terminated their participation before the end of full 9-week period. Anecdotal evidence suggests that patients did not like "feeling wet" and that amount of agent and/or discomfort with applicator contirubted to their decision to quit the study.	NR	Patients stratified by 1) age, 2) whether they were receiving current chemo or hormonal therapy and 3) pt perception of vaginal symptoms (mild, moderate, severe).
Loprinzi, 2000		8 prior to study; P - 6; V 37.5 - 7; V 75 - 12; V 150 - 5	NR	Dry mouth, decreased appetite, nausea, and constipation more in tx. No difference in tiredness, dizziness, nervousness, mood changes, sweating, sleepiness or sleep trouble.	

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Loprinzi, 2002	81	RCT - cross-over	P	2 periods; 4 weeks per period	Breast cancer or perceived high risk of breast cancer	Inclusion: 1. > 14 bothersome hotflashes per week for $\geq$ 1 month (but no menopause criteria needed) 2. Breast cancer or perceived increased risk of breast cancer 3. No current evidence of malignant disease 4. Not on chemo, estrogens, androgens, progestins or coumadin 5. Tamoxifen or raloxifene ok as long as planning to continue for duration of study 6. No previous use of fluoxetine 7. No antidepressants for 2 years 8. No other treatments of hot flashes
Nikander, 2003	62	RCT cross-over	P	3 months	Women being treated for beast cancer at university hospital who volunteered for study. Mean age: 54$\pm$6, range 35-69. Age at diagnosis of breast cancer 49.9$\pm$7.8 (range 29.9-68.1).	Inclusion: 1. No residual malignant disease 2. Incapacitiating climacteric complaints 3. FSH>30 U/L Exclusion: 1. Use of sex steroids including tamoxifen 2. Use of natural products with possible estrogenic activity 3. Use of drugs possibly affecting climacteric symptoms, metabolism or absorption of drug (ie abx)

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Loprinzi, 2002	Daily hot flash score (frequency x severity 1-4); hot flash frequency; Beck depression inventory; uniscale QOL instrument	NR	NR	NR	NR	NR	NR	NR	NR
Nikander, 2003	1. Kuperman Index 2. Severity of menopausal symptoms with 10 cm long visual analogue scale. 3. Self-rating 1-5 of 5 physical and mental working capacity, and present overall work capacity (scale of 1-10) in relation to lifetime best. These all factored into Work Ability Index. 4. Depressive mood 5. Anxiety 6. Self-confidence	10 (18%)	NR	NR	100%	3/56 (5.4%) used tamoxifen ≥5 months prior	13 (23%) smoking	22/56 (39.3%) had used HRT at some point ≥5 months prior	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Loprinzi, 2002	Fluoxetine 20mg	Placebo	Not significant at end of 4-week period Cross-over analysis: median Hot Flash frequency reduction 1.5 (19%, p=0.01) and score reduction 3.1 (24%, p=0.02)	NR	Trouble sleeping : 44% Fluoxetine, 71% P, p=0.03 for 1st study period only. Not significant overall
Nikander, 2003	114 mg phytoestrogen (6 tab/day total, 3 bid)	Placebo	Kupperman Index decreased significantly in both groups compared to baseline: by 4.2±9.6 (15.5%) in phytoestrogen group and by 4.0±8.1 (14.7%) in the P group. Not significantly different between groups. HF not different when evaluated separately. Intensity of HF was significantly decreased in P group (-0.3, p=0.006) but not in phytoestrogen group.	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Main Outcomes (contiued)

Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Loprinzi, 2002	Trend for lower BDI scores with Fluoxetine (p=0.08); dichotomous analysis NS	NR	NR	NR	NR	Fluoxetine: 1 decreased, 11 increased; Placebo: 3 decreased, 9 increased.	NS (see p.1581)
Nikander, 2003	No significant decrease in anxiety among either P or phytoestrogen group.	NR	NR	NR	NR	NR	No effect on working ability or self confidence

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Loprinzi, 2002		6 prior to study; 9 had no baseline data (5 placebo, 4 tx); 5 hadno 5 week data (1 P, 4 tx); 2 had no 9 week data (1 P, 1 tx).	NR	Dry mouth (45 vs 23%, p=0.07); no difference in appetite, nausea, dizziness, constipation, nervousness, mood changes, fatigue, abnormal sweating. Sleep improved in period one on tx.	
Nikander, 2003	No change in overall severity of menopausal symptoms by VAS: 55.7±20 before (all); 46.5±26.5 after phytoestrogen; 49.3±23 after placebo (p=0.469). 25 (44.6%) preferred the phytoestrogen; 15 (26.8%) preferred placebo; 16 (28.6%) had no preference	6 people withdrew: 4 phytoestrogen group (2 stomach ache, 1 recurrent breast cancer, 1 personal); 2 in placebo group (1 lack of effect, 1 vaginal bleeding)	2 women in phytoestrogen group withdrew because of GI AE (stomach ache); 1 woman in the P group withdrew because of vaginal bleeding	Stomach ache	Serum values reported: daidzein, genistein, equol. RCT cross-over with 2 month wash-out between each 3 month treatment period

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Pandya, 2000	198	RCT	P	12 weeks (8 weeks of interven-tion and follow up 4 weeks later)	Postmenopausal women on tamoxifen for breast cancer with hot flushes. Mean age 53 in C group, 55 in P group (p=0.15) Range 35-77 Stratified by time since menopause, duration of tamoxifen therapy, and baseline frequency of hot flushes. Recruited from clinical practices of medical oncologists from participating NCI Community Clinical Oncology Programs.	Inclusion: 1. Postmenopausal women on tamoxifen for breast cancer for $\geq$ 1 month with $\geq$ 1 hot flash daily. Exclusion: 1. Premenopausal women 2. Women on chemotherapy or other endocrine therapy for breast cancer 3. Multiple other exclusions

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Pandya, 2000	Patient diary daily at baseline, and weeks 4, 8 and 12. Number, severity (mild, moderate, severe, or very severe, grade 1-4) and duration of hot flashes. Combined score (mean frequency x mean severity). Symptom checklist for 18 potential side effects (grade 0-4). Quality of life on a scale from 1 (worst possible life) to 10 (best possible life). Blood pressure.	NR	NR	NR	198/198	198/198	NR multiple drug exclusions including hormonal therapies	NR	

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Pandya, 2000	Clonidine 0.1 mg tab at bedtime	Patients were on tamoxifen for at least one month for treatment of breast cancer.	No baseline differences in severity, frequency or hot flash score between C and P groups. Statistically significant decrease in mean frequency at weeks 4 (p=0.001) and 8 (p=0.006) and hot flash score at weeks 4 (p=0.002) and 8 (p=0.006). Statistically significant difference in hot flash duration at week 12 (p=0.023). No siginifcant difference in hot flash severity at weeks 4, 8, or 12.	NR	Reported as a side effect. Increased difficulty sleeping was reported by 41% on C and 21% on P (p=0.02)

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Pandya, 2000	NR	NR	NR	NR	NR	NR	Quality of life scores improved in the C group compared to P at weeks 4 (p=0.003) and 8 (p=0.022). No difference in median score.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Pandya, 2000	Effects of clonidine by the stratification variables duration of tamoxifen use and years past menopause. States blood pressure was not adversely affected.	States patient withdrawals were due to patient preference	45/198 did not complete the full 12 weeks of the study, 31/198 did not complete the 8-week intervention. 4/198 randomized but did not provide baseline data and were considered unevaluable.	Participants were asked to complete a symptom checklist including 18 potential side effects. The only diffference was in difficulty sleeping.	Alternate analyses were done to account for patient drop outs/missing data. The results were similar except for 1) QOL at 8 weeks (p=0.082) and 2) significantly greater benefit of C for hot flash symptoms and QOL at 12 weeks.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Quella, 1998	132	Retrospective	None (open label for long term follow-up)	Contact was 3 years after end of initial study	74 men; 58 women 55 (93%) had been on megestrate continually for 3 years.	Inclusion: 1. Female breast cancer survivors and male prostate cancer survivors who underwent androgen depreivation therapy.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Quella, 1998	Telephone interview, unclear how data elicited	NR	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Quella, 1998	Megestrol acetate: doses ranged from <20mg/day to 160 mg/day.	N/A	Of 59 patients taking megestrol: 7 women were experiencing break through HF; 6 women stated that HF were infrequent and mild; 10 patients (M and W) were experiencing daily HF and 3 notes several HF/day which were occasionally severe	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Quella, 1998	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Quella, 1998	NR	NR	Reasons for discontinuation of the drug (men and women combined): no benefit: 17 vaginal spotting/bleeding/carmping: 14 taking too many other drugs: 13 HF resolved: 12 wt gain/appetite stimulation : 9 chills: 5 drug too expensive: 4 depression: 4 severe hand/wrist numbness/tingling: 3 Hand/wrist numbness/tingling was attributed to carpal tunnel, a syndrome previously associated with megestrol. Symptoms resolved within 4-6 weeks of withdrawing the drug.	Toxicity: 3 women (17%) had chillls once their HF were eliminated. 5 women reported appetite stimulation 16 men and women listed weight gain as a possible side effect (8 reported wt gain of <10 lbs; 8 reported 10-20 lb weight gain). 5 women (28%) reported abnormal vaginal bleeding 3 women (17%) complained of intermittent mild fluid retention, bloating and cramping without bleeding. 1 womean experienced an increase in blood pressure.	Retrospective data collection of pts participating in an RCT placebo controlled trial of megestrol acetate; at the end of that trial all patients were given option to take open label megestrol at the lowest dose necessary to control HF. Where given data reported for women. Other SE occurred in men (1 had headaches, 1 indigestion, 1 RLE thromboembolic event). Where data not broken down, reported here as M and W.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Quella, 2000	182	RCT, cross-over after 4 weeks	P	9 weeks	Women age 18 and older with history of breast cancer but no residual maligant disease.	Inclusion: 1. Tamoxifen or raloxifene allowed if started 4 weeks prior and planning to continue through the trial. 2. All suffering from HF $\geq$ 14 times/wk and "of such severity to warrant intervention" and HFfor $\geq$ 1 month. 3. Life expectancy $\geq$ 6 months 4. ECOG=0 or 1. Exclusion: 1. Curent treatment with antineoplasitc chemotherapies, androgens, estrogens, prgestational agesnts, or corticosteroids 2. Use of any other agent to treat hot flashes such as megestrol acetate, vitamin E and belladonna, phenobarbital and ergotamine tartrate, or other soy products.
Secreto, 2004	262	DB RCT	HH & P	3 months	Women age 49-57 years in Italy	Inclusion: 1. Postmenopausal women aged > 35 2. Last menstrual flow $\geq$ 6 months before recruitment 3. Any condition for which classic HRT is not recommended 4. Written informed consent Exclusion: 1. Breast cancer therapy (hormone or chemotherapy) or RT during the previous 3 months 2. Overt endocrinopathy (diabetes mellitus, hyperthyroidism, etc.) 3. Intolerance to soy

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Quella, 2000	1. Frequency and intensity of hot flashes 2. Toxicity: diarrhea, nausea, vomitting, gas/bloating, other 3. Compliance	NR	NR	NR	100%	68 (78%) on tamoxifen	NR	Excluded	NR
Secreto, 2004	Greene Climacteric Scale	Included	Included	NR	Included	Excluded	NR	None for 3 months prior	Mean was 23.8 - 25.0 for groups with variation of 21.5-26.8

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Quella, 2000	600 mg tablets containging 50 mg of soy isoflavones: 40-45% genistein, 40-45% diadzein, and 10-20% glycitein. Subjects instructed to take 1 tablet TID (total of 150mg isoflavones/day). Soy phytoestrogen and placebos provided by pharmavite, Mission Hills, CA.	Placebo	ANOVA for HF score and frequency produced non-significant p values for all treatment effect comparisons, regardless of period, sequence, or week of observation. Among pateints receviving placebo, 36% reported that HF frequency had been cut in half compared with only 24% of patients receiving soy (p=0.01).	NR	NR
Secreto, 2004	Group 1: midday, isoflavones 40mg; evening, isoflavones 40mg+melatonin 3 mg; Group 2: midday and evening, isoflavones 40mg; Group 3: midday, placebo; evening, melatonin 3mg	Group 4: midday and evening, placebo	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Quella, 2000	NR	NR	NR	NR	NR	NR	NR
Secreto, 2004	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Quella, 2000	No difference in percent of patients reporting daily use of medications (compliance) and percentage reporting having missed <10% of pills for soy vs. placebo.	149 (85%) had usable data at the end of 9 weeks.	None	No difference in toxicity between the two study arms: diarrhea, nausea, vomiting or bloating/gas	1. Authors do not present results separately after the 1st 4 wks, prior to cross over. They appear to have combined groups for analyses of treatment group vs placebo, which would have biased results toward positive (and this was a negative study even with combining). 2. There was no wash-out period between cross over treatments.
Secreto, 2004	Greene Climacteric Scale as a whole and subscales were nearly identical between groups at baseline. Decrease of 30% in Greene Score in placebo group; 25% in melatonin alone group; 32% in isoflavone alone group; and 34% in isoflavones and melatonin group; No statistically significant difference between groups in the total score or sub scores.	4/65 withdrew from isoflavone + melatonin group; 5/64 withdrew from isoflavone group; 12/66 withdrew from melatonin + placebo group; 9/67 withdrew from placebo group	3/65 from isoflavone and melatonin group; 2/64 from isoflavone alone group; 4/66 from melatonin group; and 3/67 from placebo group; 9 were lost to follow-up; 8 discontinued for other reasons	Not stated	Each isoflavone capsule contained 300mg of soy extract, equivalent to 40mg of isoflavones, in the following rations: daidzein 50%, glycitein 35% and genistein 15% (Soy life Nederland BV, 4283 ZG Geissen, The Netherlands

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Thompson, 2002 (abstract only)	53	DB RCT	P	16 weeks	Women with breast cancer with menopausal symptoms	Not listed

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	Measures Used	Hyster-ectomy (#/n)	Bilateral Oophorec-tomy (#/n)	Premature Ovarian Failure (#/n)	Breast Cancer (#/n)	Use of SERMS (#/n)	Behavior or Lifestyle Factors (#/n)	Recent discontin-uation of HRT (#/n)	High or Low BMI (#/n)
Thompson, 2002 (abstract only)	Measure Yourself Medical Outcome Profile (MYMOP), Hospital Anxiety and Depression score, European Organization for Research and Treatment in Cancer Quality of Life Score, Menopausal Symptom Scale	NR	NR	NR	Included	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Thompson, 2002 (abstract only)	Homeopathic intervention	Placebo	Both groups showed significant improvement over the study period by an average of 80%. No statistically significant difference betweeen groups	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Thompson, 2002 (abstract only)	NR	NR	NR	NR	NR	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Thompson, 2002 (abstract only)	NR	8/43	NR	NR	Abstract only; included as only homeopathic RCT that could be found.

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	N	Type of Trial	Compari-son	Length of Trial	Population	Inclusion/Exclusion Criteria
Van Patten, 2002	157	RCT	P	12 weeks	263 eligible women; 157 randomized; 123 completed the study (59 soy, 64 placebo). Age at study entry 55.5+6.3; P 54.9+6.5. Conducted in Canada	Inclusion: 1. Breast cancer with completion of treatment >4 months prior 2. No use of HRT for >4 months 3. Tamoxifen allowed 4. Troublesome HF: score>10/wk (frequency x intensity). 5. Other medications + CAM allowed if no change in >4 months. Exlusion: 1. Smokers 2. Use of abx 3. Diagnosis of IBD, liver impairment or recurrent breast cancer 4. Allergy to or regular consumption of soy

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

		Specific Characteristics of Population							
Study/Year	**Measures Used**	**Hyster-ectomy (#/n)**	**Bilateral Oophorec-tomy (#/n)**	**Premature Ovarian Failure (#/n)**	**Breast Cancer (#/n)**	**Use of SERMS (#/n)**	**Behavior or Lifestyle Factors (#/n)**	**Recent discontin-uation of HRT (#/n)**	**High or Low BMI (#/n)**
Van Patten, 2002	1. Frequency and intensity (0-5 scale) of HF, daily diary.	"Hyster-ectomy + ooph-orectomy" soy 23 (39%) P 28 (44%)	NR	NR	100%	Tamoxifen use: soy - 9(15%) P - 6 (9%)	NR	(No use for 4 months prior to start of study): soy 26 (44%) placebo 28 (44%)	Mean BMI: soy (n=59) 26.8+4.5 placebo (n=64) 26.6+4.2

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Treatment		Main Outcomes		
Study/Year	Main Drug type; dose; regimen	Other Drugs type; dose; regimen	Hot Flashes	Vaginal Dryness	Sleep
Van Patten, 2002	Average concentration of isoflavone in the soy veberage was 45 +13mg/250mL; isoflavones were undetectable in the rice beverage. Total isoflavones consumed by soy women: 90 mg/day.	Placebo	None of the HF reductions were significantly different between groups. 24 hour HF number and score baseline vs final 4 weeks of treatment: number: soy (7.1+ 4.3 vs 5.3 +4.1); placebo (7.4+6.4 vs 4.9+3.9). Score (intensity x frequency): soy (18.0+13.9 vs 12.6+13.4); placebo 18.9+18.9 vs 11.4+11.3). (also reported for day and night, also NS change).	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

	Main Outcomes (contiued)						
Study/Year	Mood	Cognitive	Somatic	Urinary	Uterine Bleeding	Sexual Dysfunc-tion	Quality of Life
Van Patten, 2002	NR	NR	NR	NR	Only reported as an adverse effect of treatment with soy (see AE column).	NR	NR

Appendix F. Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Study/Year	Other Outcomes	Withdrawals	Withdrawals due to AEs	Adverse Effects	Comments
Van Patten, 2002	On the study exit questionnaire, a large number of women in both soy and placebo groups perceived a marginal decrease in HF number in the day (54%soy vs 58%P) and night (48%soy vs 56%P), and in the severity of HF in the day (50%soy vs 56%P) and night (52%soy vs 55%placebo). At completion, only half of the women in the soy and placebo groups (48% and 52% respectively) could correctly identify wich beverage they were consuming.	After randomization 34 (22%) women dropped out of the study.	10 women dropped out because of intolerance to study beverage (7 from soy group; 3 from placebo). 25 dropped out because of time committment 6 dropped out for other reasons 9 women became inellgible after randomization (6 had insufficient HF, 2 had regular consumption of soy; 1 had IBD).	Frequent and severe gastrointestinal side effects in soy group: overall 28 soy women reported GI AE; 14 P women reported GI AE (list includes abdominal bloating, gas/flatulence, constipation, gastritis, diarrhea, nausea, vomiting, heartburn). This does not include the 10 women who dropped out of the study for intolerance (7 soy; 3 P). Weight gain occurred equally in both groups (5 soy vs 4 P). Vaginal spotting was reported by 4 women consuming soy and 1 consuming placebo.	No mention of intention to treat, but negative study anyway. Other CAM and Rx therapies commmon in both group: black cohosh, wild yam, red clover 3 or fewer; flaxsee and SSRI 6 women; vit E and primrose oil more common but equal in both groups. Serum values reported.

Appendix F: Evidence table 6-9. Key Question 4C therapies in women with breast cancer

Abbreviations

AE = Adverse Effect
BMI = Body mass index
C = Clonidine
CAM = Complimentary and alternative medicine
ECOG = Eastern Cooperative Oncology Group Scale
ER + = Estrogen Receptor Positive
ERT = Estrogen replacement therapy
GI = Gastrointestinal
HF = Hot flash
HH = Head to head
HRT = Hormone Replacement Therapy
HTN = Hypertension
IBD = Irritable Bowel Disorder
INT = Intervention
MVI = Multivariate
NR = Not reported
NS = Not significant
P = PlacebO
QoL = Quality of life
RAND = RAND Mental Health Inventory
RCT = Randomized Controlled Trial
SD = Standard deviation
SERMs = Selective Estrogen Receptor Modifiers
tam = Tamoxifene
tx = Treatment
UC = Usual care