Effective Health Care Program

Comparative Effectiveness Review
Number 147

Menopausal Symptoms: Comparative Effectiveness of Therapies

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Menopausal Symptoms: Comparative Effectiveness of Therapies

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This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. 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 email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Menopausal Symptoms: Comparative Effectiveness of Therapies

Structured Abstract

Objectives. To systematically review and synthesize evidence evaluating the comparative effectiveness of treatments for menopausal symptoms, along with potential long-term benefits and harms of those treatments.

Data sources. The following electronic databases were searched through January 2014: MEDLINE®, Embase®, Cochrane Controlled Trials Register, and AMED Allied and Complementary Medicine. Gray literature searches included clinicaltrials.gov, the Food and Drug Administration Web site, and relevant conference abstracts.

Review methods. Menopausal symptom outcomes included: vasomotor, quality of life, psychological, sexual function, urogenital, and sleep disturbance. Randomized controlled trials provided the evidence base for symptom relief. Standardized mean differences were calculated to allow pooling of outcomes from varied measures. Network meta-analyses were performed when possible, along with pairwise comparisons. Systematic reviews, cohort studies, and case-control studies provided evidence for the following long-term benefits and harms: breast, colon, endometrial, and ovarian cancer; coronary heart disease and venous thromboembolic events; gallbladder disease; and osteoporotic fractures.

Results. Evidence from 283 trials provided results for vasomotor symptoms (211 trials), quality of life (125 trials), psychological symptoms (108 trials), sexual function (94 trials), urogenital atrophy (71 trials), and sleep disturbance (56 trials). The most commonly studied agents were estrogens, isoflavones, and selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs). Estrogens appeared to be the most effective treatment in relieving vasomotor symptoms and were accompanied by better quality-of-life scores. SSRIs/SNRIs relieve vasomotor symptoms less effectively than estrogens but were accompanied by the largest improvement in global measures of psychological well-being. Estrogens administered vaginally diminished pain during sex and testosterone increased sexual activity. Measures of urogenital atrophy were improved with ospemifene and vaginal or oral estrogens. Estrogens also improved sleep, but the effect appeared to be modest. Over the long term, estrogen combined with progestogen has both beneficial effects (fewer osteoporotic fractures) and harmful effects (increased risk of breast cancer, gallbladder disease, venous thromboembolic events, and stroke). Estrogens given alone do not appear to increase breast cancer risk, although endometrial cancer risk is increased. There is limited evidence on the long-term effects of most nonhormone treatments. No studies were identified that examined the efficacy or safety of compounding practices for hormone therapies.

Conclusions. Women experiencing symptoms of menopause can consider a number of potential treatments of varying efficacy. From a large body of evidence, there is considerable certainty that estrogens are the most effective treatment for relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. For other common symptoms—psychological, urogenital, and sleep disturbance—although estrogens are effective,

some nonhormonal agents compare favorably. Estrogens are accompanied by potential long-term harms that require consideration. There is limited evidence on the potential consequences of long-term use of nonhormonal agents when those agents are used to treat menopausal symptoms.

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Executive Summary

Background

Menopause is defined as the permanent cessation of menstruation and ovulation due to ovarian failure. "Spontaneous" menopause occurs after 12 months of amenorrhea as ovarian hormone secretion diminishes, on average around the age of 51 years. Menopause may be induced prematurely (before age 40 years) or early (before age 45 years) through medical interventions such as surgery (e.g., bilateral oophorectomy with or without hysterectomy), chemotherapy, or radiation. In the United States, the number of women entering menopause each year is estimated to be approximately 2 million.[1]

Current terminology describing the stages of menopause was updated in 2012 at the Stages of Reproductive Aging Workshop + 10 (STRAW + 10).[2] The STRAW + 10 stages describe early and late phases of menopausal transition and early and late phases of postmenopause. Menopausal transition is defined by variability in menstrual cycle length, followed by periods of amenorrhea lasting 60 days or longer. Perimenopause is defined as the entire menopausal transition phase, extending into the first 12 months of the early postmenopause stage. Early postmenopause lasts from 5 to 8 years, from final menstrual period to stabilization of low estradiol levels.[2]

Approximately 85 percent of women report experiencing symptoms of varying type and severity during menopause.[3] Types of symptoms experienced may include[1]—

- Vasomotor symptoms: Hot flushes are recurrent, transient episodes of intense heat in the face and upper body, sometimes followed by chills. These symptoms can occur while sleeping, producing intense perspiration. Individual hot flushes may last from 1 to 5 minutes. After irregular menses, vasomotor symptoms are the second most frequently reported perimenopausal symptoms.
- Sleep disturbances: Lengthy times to fall asleep, inability to sleep through the night, or inability to resume sleeping when waked prematurely are signs of insomnia. Sleep apnea symptoms range from slight airflow reductions causing snoring to periodic cessation of breathing.
- Psychological symptoms: Depressive symptoms, anxiety, and mood disturbances may occur. Depressive symptoms can range from a depressed mood to clinical depression. A depressed mood may not require treatment, but if clinical depression is suspected, assessment and treatment are recommended. Symptoms of anxiety may include tension, nervousness, panic, and worry.
- Urogenital problems: Urinary incontinence and vaginal atrophy may occur. Vaginal atrophy involves vaginal walls that are thin, pale, dry, and sometimes inflamed. These changes cause discomfort and potential trauma during intercourse and pelvic examinations.
- Sexual function effects: Dyspareunia (pain during intercourse) and decreased libido are also reported by perimenopausal and postmenopausal women.

Longitudinal studies have shown that during early postmenopause, the prevalence of vasomotor symptoms among women ranges from 30 to 80 percent, depressed mood occurs in approximately one-third, and sleep disturbance occurs in more than 40 percent.[4-6] Vasomotor

symptoms generally begin 2 years before the final menstrual period, peak during the 1 year after the final menstrual period, and then diminish.[7] Urogenital atrophy symptoms increase during the late postmenopause stage.[2] Differences in symptoms have been found among subpopulations of women. In the Penn Ovarian Aging Trial[8] and the Study of Women's Health Across the Nation,[9] researchers report differences in prevalence and duration of vasomotor symptoms among women depending on ethnicity and body mass index (BMI).

Objectives and Key Questions

The objective of this review is to systematically review and synthesize evidence evaluating the comparative effectiveness of treatments for menopausal symptoms, along with potential long-term benefits and harms.

The Key Questions we considered are—

Key Question 1. What is the comparative effectiveness of different treatments for reducing symptoms of menopause (vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy, and sexual function) and for improving quality of life? Individual agents will be compared to the extent permitted by the evidence.

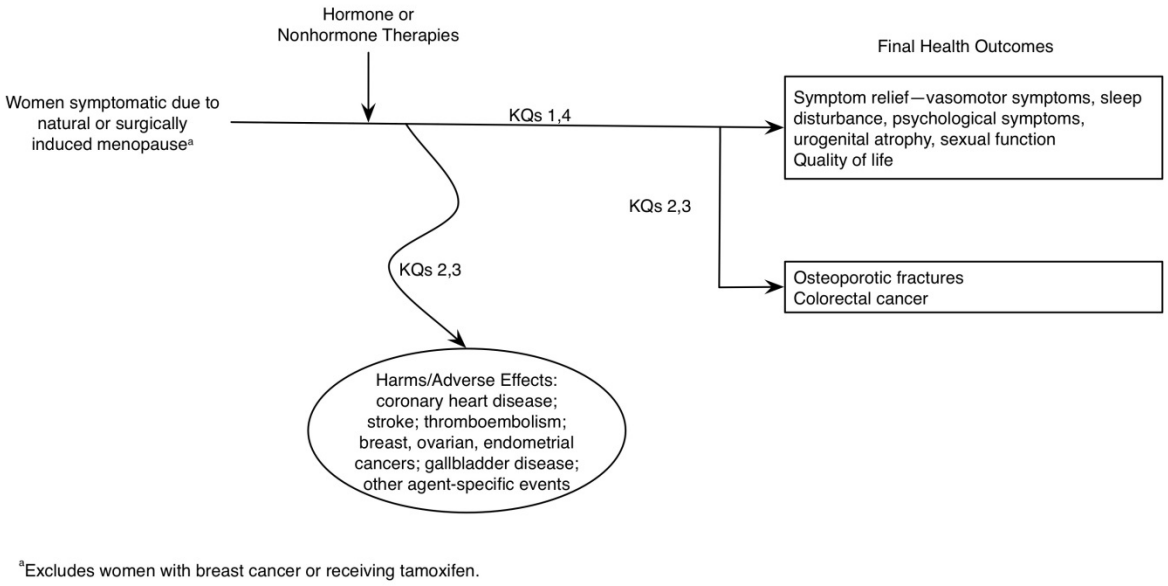
Key Question 2. What are the effects of menopausal hormone therapy preparations on coronary heart disease, stroke, or venous thromboembolism; gallbladder disease; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer? Exposure will be examined according to duration of use and initiation relative to age and onset of menopause. (For women desiring contraception, combined estrogen-progestogen and progesterone-only contraceptives are included.)

Key Question 3. What are the effects of nonhormone therapy preparations on coronary heart disease, stroke, or venous thromboembolism; gallbladder disease; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer? Exposure will be examined according to duration of use and initiation relative to age and onset of menopause. What are the significant agent-specific harms/adverse effects of nonhormone therapies?

Key Question 4. Do effectiveness and adverse effects vary among subgroups of participants defined by demographics, symptom severity, other medications, and comorbidities or according to agent, preparation, or dose?

Figure A shows the analytic framework for our review.

Figure A. Analytic framework



KQ = Key Question.

Methods

Input From Stakeholders

During topic refinement, input was sought from Key Informants representing clinicians (internal medicine, family practice, and gynecology), academicians, researchers, and patients. Key Questions were subsequently posted and public comment obtained. A Technical Expert Panel was assembled, including content and clinical experts. Comments were reviewed and appropriate changes to Key Questions made.

Data Sources and Selection

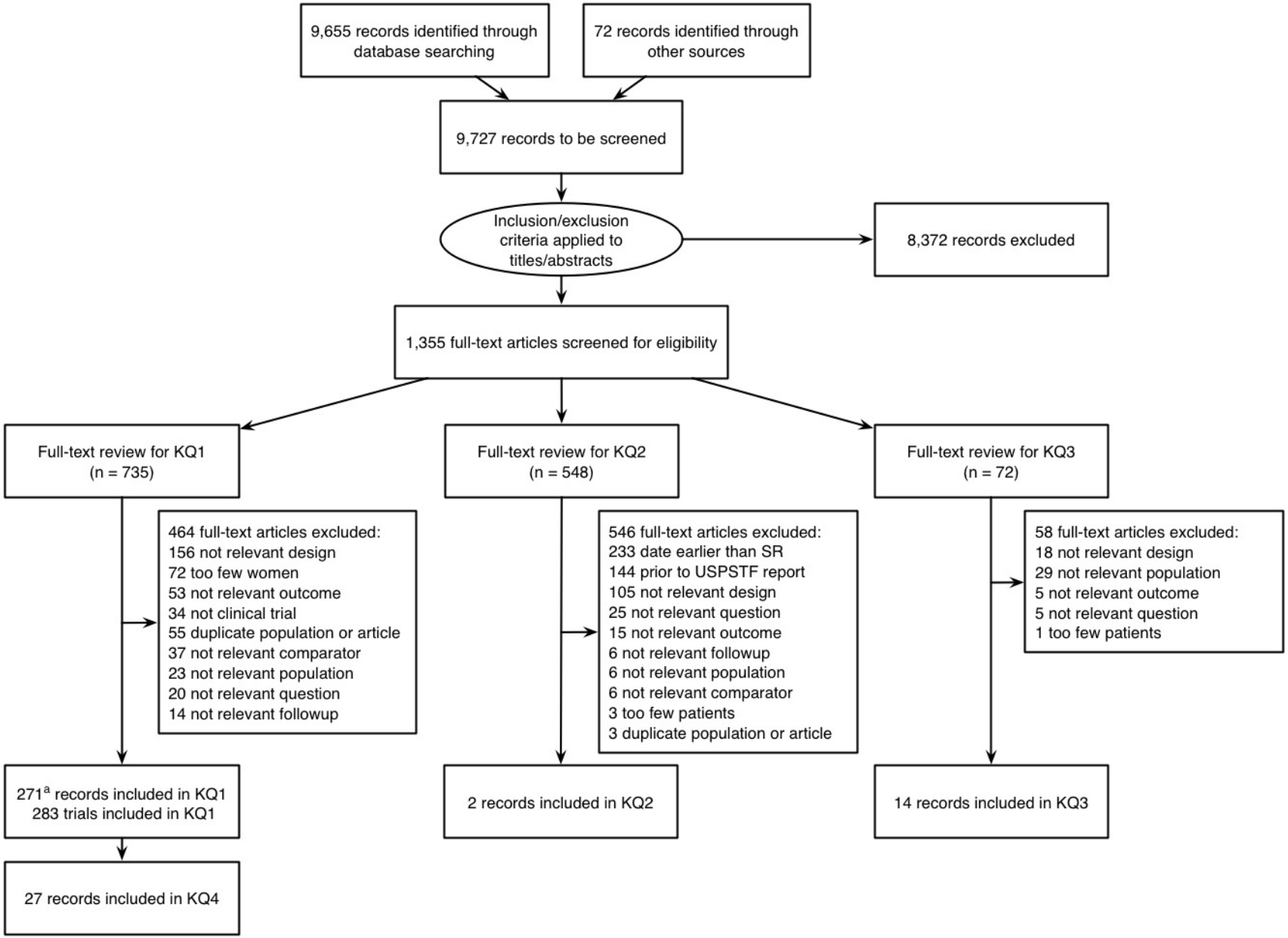
The final literature search, including articles through January 2014, was run on MEDLINE®, Embase®, Cochrane Controlled Trials Register, and AMED Allied and Complementary Medicine. The reference lists for systematic reviews and meta-analyses were also screened to identify additional references. The gray literature search included extensive reviews of clinicaltrials.gov, the U.S. Food and Drug Administration (FDA) Web site, and relevant conference abstracts. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (Figure B) depicts the flow of search, title/abstract screening, full-text screening, and study selection.

For Key Question 1 (symptom relief from any therapy), we included randomized controlled trials (RCTs) with 25 or more participants per arm and a followup of 4 weeks or longer for centrally acting agents and 12 weeks for all other therapies. Trials enrolling women with preexisting conditions (e.g., heart disease, lupus, fibromyalgia, breast cancer) were excluded. For

Key Question 2 (long-term effects of hormone therapies), systematic reviews and meta-analyses were included. Studies with intermediate outcomes and studies with both pre- and postmenopausal women combined were excluded. Key Question 3 was a two-part question examining adverse events and long-term effects of nonhormone therapies. For the adverse events question, trials included in Key Question 1 that also reported adverse events were included. For the long-term effects question, RCTs and observational studies were included. Exclusions for Key Question 3 included dietary population studies, studies with intermediate outcomes, and studies with both pre- and postmenopausal women combined. For Key Question 4, subgroup analyses of symptom relief from any therapy, trials from Key Question 1 that reported subgroup analyses were included.

A total of 8,372 records were excluded in the first round of screening because, from the title and abstract, the screeners could discern that the articles did not meet one or more of the inclusion criteria relating to study design, outcome, population, or comparator.

Figure B. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram



KQ = Key Question; SR = systematic review; USPSTF = U.S. Preventive Services Task Force.
[a]12 records presented results from 2 distinct patient populations and were divided into 2 trials each.

Data Abstraction and Quality Assessment

Data Abstraction

Key Question 1 and Key Question 4

Data were abstracted into collection forms created in DistillerSR. Two training sets of three articles each were abstracted by all team members. Results of each training set were reviewed to discuss any discrepancies in abstraction. Final data abstraction was performed by one team member and verified by a different team member, with any identified inconsistencies resolved by consensus. The following data were abstracted:

- Trial characteristics: Author, year, country, number of trial sites, trial design, total number randomized, length of followup, intervention, uterine status, disclosures and conflicts of interest, funding, primary and secondary outcomes
- Trial arm characteristics: Participant information such as number of participants, age, ethnicity, BMI, time since menopause, tobacco use; treatment specifics such as type of treatment, dosage, dosage category, and route of administration
- Outcomes: Scale; results from baseline, 12-week, and final assessments; mean scores, mean changes, percent reductions, standard deviations, 95% confidence intervals, pre/post intervention comparisons, and between-group comparisons

When only graphical outcomes were presented, figures were digitized. For Key Question 1, standardized mean differences were calculated from reported estimates of treatment effects, standard deviations, and p-values.

Key Question 2

Data abstracted from the systematic reviews and meta-analyses include the following: included trials, treatment type, treatment dose, length of followup, and results.

Key Question 3

Summary tables of long-term effects of nonhormone therapies contained the following information: condition, treatment, study design, study descriptions, and results.

Agent-specific adverse events for nonhormone therapies were categorized using a system recommended by the International Federation of Pharmaceutical Manufacturers and Associations.[10] The following data were abstracted for each category: author, year, country, treatment, dose, trial size, total adverse events, and percentage of events.

Quality Assessment

In adherence with the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide),[11] the general approach to grading trials was performed by applying the criteria of the U.S. Preventive Services Task Force (USPSTF).[12] Discordant assessments were resolved with input from a third reviewer.

Study quality of RCTs was assessed by assembly of comparable groups, blinding of researchers and subjects, concealment of group assignment, maintenance of comparable groups, differential loss to followup, equal and reliable measurements, clearly defined interventions, important outcomes considered and defined, and intention-to-treat analysis.

Study quality of cohort studies was assessed by assembly of comparable groups, maintenance of comparable groups, differential loss to followup, equal and reliable measurements, important outcomes considered and defined, and statistical adjustment for potential confounders.

Study quality of case-control studies was assessed by accurate ascertainment of cases, nonbiased selection of cases and controls, response rate, equal application of diagnostic tests, accurate and equal measure of exposure, and attention to potential confounders.

Data Synthesis and Analysis

For Key Question 1, trials employed a variety of outcome instruments. Standardized mean differences were calculated and pooled according to the Methods Guide.[11,13] Calculating the standardized mean difference (SMD), which is (effect treatment – effect comparator)/standard deviation, allows comparison of results across trials using different measures. Clinical heterogeneity and appropriateness for pooling were judged by the review team on the basis of study characteristics together with clinical context. Because the goal of any pooling is to estimate unconditional effects,[14] random-effects models were used. The magnitude of statistical heterogeneity was examined by using tau^2 owing to limitations of the I^2 metric and because between-trial variances are more intuitively interpreted on the effect-estimate scale.[15] Evidence of possible publication bias were explored using funnel plots and Egger test when results from at least 10 studies were pooled.

For vasomotor symptoms and quality-of-life outcomes, network meta-analyses formed the primary analyses, including the most relevant comparisons with sufficient data. Network meta-analysis formally allows quantitative indirect and mixed-treatment comparisons. The random-effects network meta-analysis was performed by pooling standardized mean differences in a Bayesian model described by Chaimani (www.mtm.uoi.gr/). Models were fitted in OpenBUGS using noninformative priors and convergence assessed using the Brooks-Gelman-Rubin plot and statistic, autocorrelation, and history plots. A burn-in of 20,000 samples was discarded and the subsequent 40,000 analyzed. Rankings were estimated for the probability a treatment was most effective, next most effective, and so on. Effect estimates and accompanying 95% credible intervals were obtained from the samples. To evaluate consistency, we compared available pairwise estimates with the network results[16] and explored them graphically (www.mtm.uoi.gr). We examined pairwise comparisons individually in random-effects models and graphically using forest plots.

Evidence for the remaining Key Questions consisted of systematic reviews, observational studies, and a few RCTs. Quantitative analyses were not possible, and therefore a qualitative discussion of the evidence was conducted.

Strength of the Body of Evidence

Strength-of-evidence (SOE) assessments were based on the Evidence-based Practice Center approach,[11] which is conceptually similar to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[17] Two reviewers graded the strength of evidence, resolving disagreements by consensus.

We adopted a point-based approach to SOE ratings. Each rating started at high (3 points) and was downgraded by 1 point each for high risk of bias, inconsistent or unknown consistency, imprecise or unknown precision, indirect body of evidence, and suspected reporting bias. Domain ratings were entered into a spreadsheet that provided a summary SOE. If the summary SOE remained 3 with no downgrades, it was rated high; if the summary SOE equaled 2, it was

rated moderate; if the summary SOE equaled 1, it was rated low; if the summary SOE was 0 or lower, it was rated insufficient. Following Agency for Healthcare Research and Quality guidance for assessing evidence on equivalence and noninferiority, studies can be appropriately considered individually in the presence of clinical heterogeneity; as stated by Treadwell and colleagues, "the lack of meta-analysis does not necessarily preclude a conclusion of EQ-NI [Equivalence-noninferiority], just as it does not preclude an evaluation of the strength of evidence in relation to a particular outcome."[18]

Results

Results are presented below for symptom relief (Key Question 1), other benefits and harms (Key Questions 2 and 3), and symptom relief among subgroups (Key Question 4).

Symptom Relief

Summary results are presented by outcome (vasomotor symptoms, quality of life, psychological symptoms, sexual function, urogenital atrophy, and sleep disturbances), followed by a brief discussion of compounded hormone therapies and limitations of the evidence base for symptom relief. Investigators used many different measurement rating scales to evaluate treatment effects. Pooling across scales can be accomplished only by using SMDs. Although they enable pooling, SMDs pose challenges for clinical interpretation. To place their magnitudes into context, with control-group event rates of 20 to 60 percent, SMDs can be expressed as approximate odds ratios (ORs). For example, SMDs and corresponding ORs (in parentheses) are as follows: SMD, -0.2 (OR, 0.7); -0.3 (0.6); -0.4 (0.5); -0.5 (0.4); 0.3 (2); 0.6 (3); and 0.75 (4). Although the ORs exceed relative risks when placebo group event rates exceed 10 percent, they provide a rough guide to the relative effect. For example, the placebo response rate of women with vasomotor symptoms can vary between approximately 20 and 40 percent.

For analytical purposes, estrogen doses were classified as low/ultralow, standard, and high. For oral treatment, which was the most common route of administration, the dosing categories were based on the 2009 Cochrane Review on hormone replacement therapy and endometrial hyperplasia.[19] For example, dose categories for oral conjugated equine estrogens were ultralow (0.15 to 0.3 mg), low (0.4 mg), standard (0.625 mg), and high (1.25 mg). For other routes of administration, such as transdermal and spray, dosing categorizations were established in consultation with the clinical content expert.

Vasomotor Symptoms

A large body of evidence was identified comparing the efficacy of agents versus placebo and other active treatments for the relief of vasomotor symptoms (Table A). One quarter of trials were rated good or fair quality and the remainder poor. Trials were most numerous for estrogens, isoflavones, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, black cohosh, and ginseng. Estrogens of any dose appeared more effective than other comparators, without apparent meaningful differences according to dose or route of administration. Small differences in effect magnitudes among SSRIs/SNRIs, isoflavones, gabapentin, black cohosh, and ginseng were apparent in network meta-analysis. Mean rankings of treatment effectiveness (1 being best, 9 worst; placebo ranked 8.9) were as follows: high-dose estrogens (1.9), standard-dose estrogens (1.3), low-dose estrogens (2.9), SSRI/SNRI (4.9), gabapentin (5.6), isoflavones (5.9), black cohosh (6.7), and ginseng (7.0). A host of other agents have been studied, but evidence is limited to single trials.

The efficacy of estrogens in treating vasomotor symptoms is well established. The comparative effectiveness of other agents relative to estrogens has been less clear. Albeit limited by the trial quality, the findings show that other agents can ameliorate vasomotor symptoms, but none have estrogen's effectiveness.

Table A. Magnitude and strength of evidence of treatments for vasomotor symptoms: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
9	Estrogen (high) vs. placebo	-0.50 (-0.61 to -0.39)	High
39	Estrogen (standard) vs. placebo	-0.64 (-0.74 to -0.53)	High
53	Estrogen (low/ultralow) vs. placebo	-0.55 (-0.61 to -0.48)	High
13	SSRI/SNRI vs. placebo	-0.35 (-0.46 to -0.24)	High
5	Gabapentin vs. placebo	-0.28 (-0.38 to -0.19)	Moderate
35	Isoflavones vs. placebo	-0.31 (-0.41 to -0.22)	Low
4	Black cohosh vs. placebo	-0.31 (-0.46 to -0.15)	Low
3	Ginseng vs. placebo	-0.17 (-0.43 to 0.09)	Low

CI = confidence interval; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Quality of Life

Trials evaluating numerous agents—estrogens, isoflavones, SSRIs/SNRIs, ginseng, black cohosh, and dehydroepiandrosterone (DHEA)—reported some quality-of-life metric (Table B). Less than a third of trials (27.2%) were rated good or fair quality. Compared with placebo, improved quality-of-life scores accompanied estrogens, with SMDs exceeding 0.35 with high SOE; effect sizes for all other agents were lesser in magnitude or low SOE. Similarly, estrogens ranked highest in the network comparison. For estrogens, there were no apparent meaningful differences in effect according to dose or route of administration. Quality-of-life scores were reported from trials of many nonprescription agents, but results from single trials do not allow conclusions concerning effects.

We found improved global quality-of-life scores in women taking estrogens. Two of the larger trials, Women's International Study of long Duration Oestrogen after the Menopause (WISDOM)[20] and Women's Health Initiative (WHI)[21,22] reported no effect of estrogens on quality of life, a finding potentially attributable to older age and less symptom severity of enrolled women in these trials or the lack of employment of menopause-specific instruments. For the larger body of comparisons in women receiving estrogens, despite between-trial variability, results were more consistent. The general pattern of comparative efficacy seen with quality-of-life scores paralleled results for vasomotor and other symptoms.

Table B. Magnitude and strength of evidence of treatments for quality of life: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
5	Estrogen (high) vs. placebo	0.76 (0.48 to 1.03)	High
26	Estrogen (standard) vs. placebo	0.55 (0.41 to 0.69)	High
17	Estrogen (low/ultralow) vs. placebo	0.36 (0.27 to 0.45)	High
6	SSRI/SNRI vs. placebo	0.28 (0.17 to 0.39)	High
24	Isoflavones vs. placebo	0.27 (0.17 to 0.37)	Low
4	Black cohosh vs. placebo	0.26 (-0.15 to 0.66)	Insufficient
3	Ginseng vs. placebo	0.19 (0.01 to 0.36)	Low

CI = confidence interval; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Psychological Symptoms

Just over one-third of trials examining symptom treatment reported at least one psychological outcome—depressive symptoms, anxiety, or global psychological well-being. Of these trials, 28.8 percent were rated good or fair quality. Approximately half specified some psychological symptom as a primary outcome. Generally, the samples were not selected to represent populations with clinical depression or anxiety. Compared with placebo, SMDs were in general not large (i.e., SMD between -0.5 and 0) for any of the agents studied for any psychological domain (Table C). The SOE was high that SSRIs/SNRIs and estrogens can effectively alleviate psychological symptoms in all domains.

An increased risk for depressive symptoms during the menopausal transition in the absence of prior depressive illness has been described[23] and may be associated with vasomotor symptoms.[24] The effects assessed here may provide guidance when menopausal women are experiencing psychological symptoms.

Table C. Magnitude and strength of evidence of treatments for psychological symptoms: standardized mean differences from pairwise comparisons

Domain	Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
Global	6	SSRI/SNRI vs. placebo	-0.42 (-0.60 to -0.24)	High
Depressive symptoms	5	SSRI/SNRI vs. placebo	-0.43 (-0.60 to -0.26)	High
Anxiety symptoms	3	SNRI vs. placebo	-0.31 (-0.50 to -0.12)	High
Global	14	Estrogen vs. placebo	-0.26 (-0.40 to -0.13)	High
Depressive symptoms	18	Estrogen vs. placebo	-0.36 (-0.53 to -0.20)	High
Anxiety symptoms	13	Estrogen vs. placebo	-0.34 (-0.50 to -0.18)	High
Global	2	Gabapentin vs. placebo	-0.23 (-0.48 to 0.02)	Insufficient
Global	7	Isoflavones vs. placebo	-0.11 (-0.22 to 0.01)	Low
Depressive symptoms	9	Isoflavones vs. placebo	-0.29 (-0.49 to -0.09)	Low
Anxiety symptoms	7	Isoflavones vs. placebo	-0.30 (-0.46 to -0.14)	Moderate

CI = confidence interval; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Sexual Function

Some measure of sexual function was reported in approximately one-third of trials; 41.4 percent of those trials specified the outcome as primary. Of these trials, 21 percent were rated good or fair quality. Outcomes were reported in four domains: pain (dyspareunia), a global metric, activity, and interest. Vaginal estrogens decreased pain most convincingly (high SOE), and lower pain scores were also reported with oral estrogens (moderate SOE) (Table D). There was improvement in global measures with all estrogens (high SOE). Estrogens appeared to enhance measures of interest, while SSRIs/SNRIs showed only modest improvement. Sexually satisfying episodes were more frequent with testosterone (7 out of the 8 trials administered testosterone through a patch) compared with placebo—slightly more than one extra episode reported every 4 weeks (moderate SOE). Overall, these results are generally consistent with evidence-informed expert clinical opinion.[1]

The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study[25] estimated that approximately 15 percent of women age 45 to 64 years experienced some form of sexual distress. A cohort study, Study of Women's Health Across the Nation (SWAN),[26] reported that during the menopausal transition, there are significant decreases in sexual interest, frequency, and arousal along with increased pain during sex. One quantitative review on sexual outcomes during menopause included literature published between 1972 and 1992.[27] In this review by Myers, the effect of estrogen therapy on all four sexual function domains combined (108 studies) yielded an SMD of -0.67—somewhat larger in magnitude than that obtained in this review.

Table D. Magnitude and strength of evidence of treatments for sexual function: standardized mean differences from pairwise comparisons

Domain and Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
Pain (lower is better)			
10	Vaginal estrogens vs. placebo	-0.54 (-0.73 to -0.34)	High
4	Oral estrogens vs. placebo	-0.22 (-0.35 to -0.09)	Moderate
	Global (higher is better)		
15	All estrogens vs. placebo	0.27 (0.19 to 0.35)	High
2	SSRI/SNRI vs. placebo	0.27 (0.01 to 0.52)	Insufficient
4	Isoflavones vs. placebo	0.24 (-0.12 to 0.61)	Low
	Interest (higher is better)		
7	All estrogens vs. placebo	0.18 (0.10 to 0.26)	Moderate
2	SNRI vs. placebo	0.16 (-0.07 to 0.39)	Insufficient
5	Isoflavones vs. placebo	0.26 (-0.001 to 0.52)	Insufficient
Pain, interest, global			
10	Estrogen route a vs. route b	Not estimated	Moderate
Activity (higher is better)		**SSE/4 weeks (95% CI)**	
8	Testosterone (7 patch, 1 oral), all trials	1.17 (0.88 to 1.46)[a]	Moderate

CI = confidence interval; SMD = standardized mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSE = satisfying sexual episode; SSRI = selective serotonin reuptake inhibitor.
[a] Number of satisfying sexual episodes per four weeks

Urogenital Atrophy

One-quarter of trials reported urogenital atrophy outcomes—a primary outcome in 56.3 percent. A minority of the trials (20%) were assessed as good or fair quality. Ospemifene, an estrogen agonist/antagonist, was approved by FDA in February 2013 to treat moderate to severe dyspareunia in postmenopausal women. Evidence from three clinical trials showed that ospemifene improved symptoms of vulvar and vaginal atrophy. Although multiple scales were employed and heterogeneity noted in the pooled estimate for vaginal route of administration, the SOE was high that either oral or vaginal estrogens improve symptoms (Table E). The SOE was low for isoflavones.

The conclusions here are similar to those provided to clinicians[1] when considering treatment of symptoms that may be experienced by as many as 40 percent of postmenopausal women.[28] A 2006 Cochrane review including 19 trials concluded that vaginal or oral estrogens were similarly effective for treating vaginal atrophy symptoms.[29] These results, albeit indirectly based on placebo comparisons, indicate a greater magnitude of effect for vaginal compared with oral administration.

Table E. Magnitude and strength of evidence of treatments for urogenital atrophy: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
3	Ospemifene vs. placebo	-0.75 (-1.05 to -0.45)	High
12	Vaginal estrogen vs. placebo	-0.44 (-0.65 to -0.23)	High
14	Nonvaginal estrogen vs. placebo	-0.35 (-0.44 to -0.26)	High
5	Isoflavones vs. placebo	-0.48 (-0.77 to -0.18)	Low

CI = confidence interval; SMD = standardized mean difference.

Sleep

Many trials ascertained self-reported sleep outcomes, but a single trial examined a drug approved by FDA for use in insomnia (eszopiclone). Compared with placebo, the SMD for improved sleep measures was approximately threefold greater with eszopiclone than with estrogens or any other agent. This suggests that modestly improved sleep accompanies other agents, including estrogens, used to treat menopausal symptoms (Table F). Of the trials reporting sleep outcomes, 11 percent were rated good or fair quality.

Although sleep disturbances during menopause are common,[30] how often they are secondary to menopausal symptoms is not well defined. Sedative hypnotic agents are not generally used to treat menopausal symptoms and so were not represented in the trials identified. Reported improvement in sleep evident with other agents such as estrogens is possibly due to treatment of vasomotor symptoms but requires evidence not considered here.

Table F. Magnitude and strength of evidence of treatments for sleep: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Effect Size (SMD) (95% CI)	Strength of Evidence
1	Eszopiclone vs. placebo	1.08 (0.53 to 1.62)	Not rated[a]
24	Estrogen vs. placebo	0.32 (0.24 to 0.46)	High
2	SSRI vs. placebo	0.46 (0.24 to 0.69)	Low
2	Gabapentin vs. placebo	0.33 (0.18 to 0.49)	Low
6	Isoflavones vs. placebo	0.37 (0.10 to 0.64)	Low
2	Ginseng vs. placebo	0.13 (-0.05 to 0.32)	Insufficient

[a]Eszopiclone, an oral sedative hypnotic used to treat insomnia, was included as a referent. With a single trial comparing eszopiclone with placebo, a rating could not be made.
CI = confidence interval; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitor.

Compounded Hormone Therapies

Compounded hormone therapies are commonly prescribed, often in combination with some testing for hormone levels, with effectively no direct evidence base. We identified a single RCT examining pharmacokinetics in 40 women studied for 16 days.[31] No studies were identified examining the safety of the compounding practices for hormone therapies.

Limitations of the Evidence on Symptom Relief

The body of evidence synthesized for Key Question 1 was large, with many trials rated poor quality. However, the challenges of synthesizing this evidence extend far beyond trial quality to limitations incompletely incorporated in SOE assessments. These include—

- Use of different outcome scales or metrics
- Necessity of calculating SMDs and inherent difficulties estimating from publications
- Potential differences in populations represented by trial samples
- Potential for selective outcome reporting

Interpreting results when presented with continuous measures and multiple scales requiring the use of SMDs is challenging. It is difficult to infer proportions of women achieving minimal clinically important improvements.[32,33] Calculating SMDs is also not without challenges. There were a number of ways to obtain effect sizes from the continuous measures reported. Unbiased ANCOVA (analysis of covariance) effect estimates[13,34] were not typically reported, requiring the use of change score or sometimes end-of-followup comparisons.

A separate issue is that, although trial populations included women experiencing menopause, there were some differences in mean age, length of followup, and symptom severity. While the initial intent was to examine subgroups according to characteristics such as the presence of a uterus, lack of reporting did not allow us to do so. Results, then, apply to average women across all trials.

It is also difficult to evaluate potential selective outcome reporting from the included trials. Vasomotor symptoms were reported in about three-quarters of trials, but all other outcomes were reported in less than half. While some trials, such as those of sexual function or vaginal atrophy, were clearly not designed to primarily assess all outcomes, insignificant results may have gone unreported. For some of the outcomes reported, the outcome was stated as primary in only half of the studies. Results do not allow assessment of whether effects on different outcomes are independent.

We did not include studies examining effects among breast cancer survivors—women frequently affected by troublesome symptoms, including hot flushes. Although effects of nonhormonal agents on hot flushes may be similar regardless of breast cancer history, cancer survivors constitute a different patient population. Accordingly, these results are not intended to apply to those women. Further, the results are not intended to apply to women experiencing menopause at an early age due to ovarian insufficiency.

Other Benefits and Harms

Summary results are presented first for hormone therapies, then for nonhormone therapy preparations, followed by a discussion of limitations of the evidence base for other benefits and harms.

Menopausal Hormone Therapy Preparations

Evidence for this Key Question included the recent report for the USPSTF by Nelson and colleagues[35] and results from the Danish Osteoporosis Prevention Study (DOPS), which were published after the report by Nelson and colleagues. A majority of evidence in that report was derived from WHI trials, representing an older population without severe menopausal symptoms, but one that overlaps with the population for this review. Therefore, findings from large observational studies with younger populations were incorporated to inform the discussion on applicability. The picture of long-term effects emerges with some clarity, as summarized in Table G.

The USPSTF review reported differences in event rates with estrogen/progestin or estrogen compared with placebo. However, extrapolating absolute rates from the WHI samples to the target population of this review is problematic. In broad absolute terms, gallbladder disease is the most frequent occurrence, with thromboembolic events, stroke, and breast cancer less frequent.

Table G. Summary of long-term effects of menopausal hormone therapy preparations

Outcome	Risk	Treatment vs. Placebo	Strength of Evidence	Comment
Breast cancer	↑	Estrogen/progestin	High	
	↓	Estrogen	Low	Inconsistent
Gallbladder disease[a]	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	↑	Estrogen	Moderate	Consistency unknown with 1 trial
Venous thromboembolic events[b]	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	↑	Estrogen	High	
Stroke	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	↑	Estrogen	High	
Ovarian cancer	↑	Estrogen/progestin	Low	Consistency unknown with 1 trial; imprecise with few cases
Colorectal cancer	↓	Estrogen/progestin	Low	Consistency unknown with 1 trial; imprecise with wide confidence interval
	—	Estrogen	Moderate	Consistency unknown with 1 trial
Coronary heart disease	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	—	Estrogen	Moderate	Consistency unknown with 1 trial
Endometrial cancer	—	Estrogen/progestin	Moderate	Imprecise
Osteoporotic fractures	↓	Estrogen/progestin	Moderate	Inconsistency between 2 trials
	↓	Estrogen	Moderate	Consistency unknown with 1 trial

Risk: ↑ increased, ↓ decreased, — no change.

[a]Risk may be lower with transdermal estrogen administration.
[b]Risk may not be increased with transdermal estrogen administration.

Nonhormone Therapy Preparations

The evidence base informing other potential benefits and harms of nonhormone therapies in women treated for menopausal symptoms is limited but does not suggest that harmful long-term effects are likely for those agents studied (Table H). We identified large trials examining vitamin E, small trials of isoflavones, and observational studies evaluating antidepressants. Some studies of the long-term use of antidepressants did not distinguish risks for the different classes of agents used to treat symptoms and therefore did not meet our inclusion criteria. Although no salient long term benefits were identified, neither were safety signals apparent. However, given the large numbers of women potentially taking these agents, some caution is advised, particularly for nonprescription agents. For example, the possibility of increased mortality with high-dose vitamin E has been raised.[36] Additionally, case reports of hepatotoxicity with black cohosh have been published.[37] This association has been debated,[38] but surveillance for adverse effects of nonprescription agents is generally inadequate. Safety data are also needed for the broad array of herbs and botanicals used to treat menopausal symptoms.

Table H. Summary of long-term effects of nonhormone therapy preparations

Outcome	Risk	Treatment vs. Placebo	Strength of Evidence
Breast cancer	—	Vitamin E	High
Breast cancer		SSRI	Insufficient
Colorectal cancer	—	Vitamin E	High
Cardiovascular events	—	Vitamin E	High
Cardiovascular death	↓	Vitamin E	Low
Osteoporotic fractures	↑	SSRI	Low
Osteoporotic fractures		Isoflavones	Insufficient
Ovarian cancer		Vitamin E	Insufficient

Risk: ↑ increased, ↓ decreased, — no change. SSRI = selective serotonin reuptake inhibitor.

Limitations of the Evidence Base on Other Benefits and Harms

One limitation of the evidence base concerning long-term outcomes of hormone therapies derives from the necessity to rely on results of RCTs. There are well-described discrepant conclusions between observational studies and RCTs concerning long-term outcomes accompanying hormone therapies.[39] The discrepancies have been largely attributed to selection bias and time-varying confounding.[40-42] Although the association with cardiovascular outcomes has been most scrutinized, difficulties assessing causal effects of menopausal hormone therapy from observational data appear to extend to other outcomes, including hip fractures[40] and colorectal cancer.[42] As noted throughout, trials have been conducted in a target population overlapping with the one for this review, creating some challenges for assessing applicability.

There are several limitations to the evidence base of nonhormone therapies to consider. Many studies included women of all ages and therefore were excluded unless subgroup analyses on older women or menopausal women were specified. Much of the research available on the long-term effects of isoflavones and vitamin E consisted of population-based dietary studies and therefore did not meet inclusion criteria. Intermediate outcomes were reported in many of the studies: for example, bone density rather than osteoporotic fractures, and cholesterol levels rather than cardiovascular events. Finally, in studies that included all women rather than focusing on menopausal women, it was difficult to discern if exposure (e.g., to SSRIs/SNRIs or isoflavones) occurred during menopausal years.

Symptom Relief in Subgroups

A small subset of trials identified for Key Question 1 reported subgroup analyses on symptom relief: 10 for hormone therapies, 2 for nonhormone prescription therapies, and 4 for nonprescription therapies. No subgroup analyses could be pooled, as no two trials had the same comparators, definitions of subgroups, and outcomes. The sparse evidence did not allow rating of SOE.

Discussion

This section addresses research gaps, implications for clinical policy and decisionmaking, limitations of the Comparative Effectiveness Review process, and conclusions.

Research Gaps

The principal gaps in the evidence on symptom relief include lack of common validated instruments and assessment of meaningful clinical improvement; safety data on nonprescription agents; lack of evidence on compounded hormone therapies; and potential for predicting treatment response for nonhormonal agents:

- The trials comprising the body of evidence included in this review had in common the evaluation of outcomes on continuous scales using multiple instruments. A standard set of common data elements using validated instruments would facilitate evidence synthesis and interpreting results across trials. In place of, or in addition to, summary continuous effect measures, reporting differences in proportions of women achieving defined clinically meaningful improvements would be more informative for decisionmaking. Reporting only summaries of continuous effect measures challenges interpretation for patients and providers.
- A large number of nonprescription agents were studied in individual trials. The Dietary Supplement Health and Education Act requires manufacturers of these agents to determine their products' safety and efficacy, but the manufacturers are not required to submit the safety or efficacy data to FDA. As women may elect to use these agents, the data need to become available.
- Millions of women use compounded hormone treatments. Yet there is a stark absence of evidence concerning compounded hormone therapies and the methods used to determine the personalized dosages. Although the gap is most concerning regarding safety, efficacy issues are important as well.
- For nonhormonal interventions for which there is moderate evidence of efficacy, identifying predictors of response would likely be helpful.

Many important previous gaps in the evidence concerning long-term effects of hormone therapies have been filled. For some nonhormone therapies, with reasonable certainty (i.e., moderate or greater SOE), significant safety issues have not been apparent; the same cannot be said for the entirety of the nonprescription agents.

Finally, estrogen therapy has efficacy relieving many symptoms but is accompanied by other potentially important harms (varying according to whether combined with progestogen). Given the number of outcomes to consider with different exposure effects (e.g., duration of use), the overall risk-benefit calculus is not simple. Juxtaposing evidence concerning symptom relief (as obtained here) with models for the long-term harms and potential benefits[43] according to patient characteristics (e.g., lower risk of hip fracture in blacks) could facilitate informed decisions by women and health care providers.

Implications for Clinical and Policy Decisionmaking

The implications of this review for clinical decisionmaking follow from better defining evidence supporting the multiple treatment options for different yet overlapping menopausal symptoms, each treatment option having different potential harms. The results provide a guide to comparative efficacy alongside potential long-term harms and benefits; all are weighed in clinical decisions. For vasomotor symptoms and quality of life, the review provides clinicians with efficacy comparison for the most commonly used treatments. Although evidence concerning potential long-term benefits is included as they are part of the decisionmaking process, this review did not specifically address use of therapies for those purposes.

Limitations of the Comparative Effectiveness Review Process

This review was a large undertaking with many complexities. These included the variable manner in which trials reported results, multiple trial arms, and multiple treatments, along with the goal of not excluding results for any a priori potentially arbitrary reason. Obtaining standardized effects can be challenging.[44] Furthermore, given multiple trial arms and multiple outcomes; the number of calculations required was substantial. Confidence intervals and SOE ratings do not incorporate this analytical uncertainty. Pooled estimates should be interpreted with this understanding.

Analyses of the multiple treatments required imposing some classification scheme that has limitations. For example, the estrogen dose categorization scheme did not consider progestogen or distinguish between combined and sequential progestogen administration. Progestogen use was problematic to distinguish because trials may have not given the agent to women without a uterus yet reported an effect for the entire sample.

Finally, interpreting network and pairwise meta-analyses deserves comment. In the pairwise meta-analyses, only direct randomized comparisons are included; the network analyses incorporate both direct and indirect evidence. Underlying the network of comparisons is assumed similarity of study characteristics and patients (transitivity) as well consistency of effects throughout the network. All enrolled women were menopausal or perimenopausal, but there were some differences in studies and samples as noted in the review. However, across all studies the assumption was likely satisfied. The closeness of most network and pairwise estimates shows that inconsistencies are likely small.

Conclusions

Women experiencing symptoms of menopause can consider a number of potential treatments of varying efficacy. From a large body of evidence, there is considerable certainty that estrogens are the most effective treatment for relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. For other common symptoms—psychological, urogenital, and sleep disturbance—although estrogens are effective, some nonhormonal agents compare favorably. Estrogens are accompanied by potential long-term harms that require consideration. There is limited evidence on the potential consequences of long-term use of nonhormonal agents when those agents are used to treat menopausal symptoms.

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Introduction

Background

Menopause is defined as the permanent cessation of menstruation and ovulation due to ovarian failure. After 12 months of amenorrhea without pathological etiology, menopause is considered "natural" or "spontaneous." Menopause can also be induced prematurely (before age 40 years) or early (before age 45 years), through medical interventions such as surgery (e.g., bilateral oophorectomy with or without hysterectomy), chemotherapy, or radiation. It occurs naturally between the ages of 42 and 58 years[1-3] and is a consequence of reproductive senescence. The average age at onset appears fixed, as it has been unchanged since ancient Greece.[4] In the United States, the number of women entering menopause (approximately 2 million per year[5]) will remain generally stable or even decline as baby boomers age. But given the continued improvement in life expectancy at age 50, the number of menopausal years will increase both for individual women and the population as a whole.

Current terminology describing the stages of menopause were updated in 2012 at the Stages of Reproductive Aging Workshop + 10 (STRAW + 10).[6] The STRAW + 10 stages describe early and late phases of menopausal transition and early and late phases of postmenopause. Menopausal transition is defined by variability in menstrual cycle length, followed by periods of amenorrhea lasting 60 days or longer. Early postmenopause lasts 5 to 8 years, from final menstrual period to stabilization of low estradiol levels. Perimenopause is defined as the entire menopausal transition phase, extending into the first 12 months of the early postmenopause stage.[6]

During menopause, approximately 85 percent of women report experiencing symptoms of varying type and severity.[7] Types of symptoms experienced include the following.[5]

- Vasomotor symptoms are recurrent, transient episodes of flushing, with intense heat on the face and upper body, sometimes followed by chills. These symptoms can occur while sleeping and can produce intense perspiration (night sweats). Individual hot flushes may last from one to five minutes. After irregular menses, vasomotor symptoms are the second most frequently reported perimenopausal symptom.
- Increases in sleep disturbances such as insomnia and sleep apnea/hypopnea may occur. Insomnia includes lengthy times to fall asleep, inability to sleep through the night, or inability to resume sleeping when woken prematurely. Sleep apnea symptoms range from slight airflow reductions that cause snoring, to periodic cessation of breathing (apnea).
- Psychological symptoms such as depressive symptoms, anxiety, and mood disturbances may also occur in perimenopausal and postmenopausal women. The term "depression" may include a depressed mood or an intense adjustment reaction to a life event that may not require treatment. The term may also include clinical depression. If clinical depression is suspected, assessment and treatment are recommended. Symptoms of anxiety may include tension, nervousness, panic, and worry.
- Urogenital problems such as urinary incontinence and vaginal atrophy may occur. Vaginal atrophy describes vaginal walls that are thin, pale, dry, and sometimes inflamed. These changes cause discomfort and potential trauma during intercourse and during pelvic examinations.

- Sexual function effects such as dyspareunia (pain during intercourse) and decreased libido are also reported by perimenopausal and postmenopausal women.

Longitudinal studies have shown that during the early postmenopausal period the prevalence of vasomotor symptoms among women ranges from 30 to 80 percent, depressed mood occurs in approximately one-third, and sleep disturbance in more than 40 percent; diminished sexual function and vaginal dryness are also common.[8-10] A natural history of symptoms has been described, including the presence, severity, and time since menopause. For example, vasomotor symptoms generally begin 2 years before last menstrual period, peak during the 12 months following last menstrual period, and then diminish over the next 10 years.[6, 11] Urogenital atrophy symptoms increase during the late postmenopause stage.[6] However, differences in symptoms have been found among different subpopulations of women. In the Penn Ovarian Aging Trial, moderate to severe vasomotor symptoms lasted a median of 10.2 years; black women experienced a longer median duration of vasomotor symptoms, while women with a high body mass index tended to have shorter symptom duration.[12] In the Study of Women's Health Across the Nation, the prevalence of vasomotor symptoms was greater among black and Hispanic women and women with a higher body mass index.[13]

Menopausal Treatment Strategies

Overview

Estrogens have been a mainstay for treating menopausal symptoms, but are surrounded by controversy. Estrogens were approved by the U.S. Food and Drug Administration (FDA) in 1942 for treating menopausal symptoms, and by 1947, the *Physician's Desk Reference* listed more than 50 estrogen preparations approved for treating menopausal symptoms. In 1995, an estimated 37 percent of women aged 50 years or older in the United States reported using menopausal hormone therapy (estrogen with or without progestogen),[14] owing in part to the results of observational studies interpreted to support a protective effect for cardiovascular disease. The clinical landscape shifted abruptly in 2002 with the first results from the Women's Health Initiative (WHI), a randomized comparison of estrogen/progestin versus placebo. Not only was cardiovascular risk increased, but overall harms from the treatment exceeded benefits.[15] Although subsequent evaluation of the body of evidence has indicated that interpretations of the results are more complex,[16] particularly for the target population included in this review, the consequences for menopausal hormone therapy use in the United States remain uncertain.[17]

In addition to decreasing estrogen production in menopausal women, the decrease of androgen production is of concern. Androgens affect sexual interest, muscle mass and strength, body mass index, and adipose tissue distribution. Androgens may also affect energy and psychological health. Two major androgens in women are testosterone and dehydroepiandrosterone (DHEA). In women with naturally occurring menopause, there is not a sudden decrease in androgen production, but in women with surgical menopause, testosterone levels decrease by about 50 percent.[5] A Cochrane review has reported sufficient evidence to suggest that supplementing estrogen therapy or estrogen/progestogen therapy with testosterone has a beneficial effect on menopausal women experiencing sexual dysfunction.[18] DHEA is available without prescription as a dietary supplement, and is, therefore, under limited regulation. The efficacy of DHEA supplements for the treatment of menopausal symptoms has not been established.

Generally prepared for the individual patient, compounding of menopausal hormone therapy combines several hormones and employs nonstandard routes of administration.[19] Compounded hormones are claimed to be biochemically similar or identical to endogenous hormones. Compounded preparations typically contain estriol and can have variable potency.[20] Growing interest in compounded hormones is undisputed; evidence from surveys of pharmacists, practitioners, and women suggests a growing market for and belief in their effectiveness.[21, 22] In 2003, approximately 30 million prescriptions for compounded products were filled.[23] The products are heavily marketed, currently a $1 billion industry and growing.[24]

While menopausal hormone therapy can relieve symptoms, concerns about potential risks (especially cardiovascular disease and uterine and breast cancer) provide reason to consider other agents. Both nonhormone prescription medications and nonprescription agents including complementary and alternative medicine (CAM) therapies have been studied in comparison with menopausal hormone therapy or placebo. These studies focus primarily on the relief of vasomotor symptoms.[25] Nonhormone prescription therapies include selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI), eszopiclone, clonidine, methyldopa, gabapentin; biologic CAM therapies include isoflavones, red clover (Trifolium pratense), black cohosh (Cimicifuga racemosa), St. John's wort (Hypericum perforatum), ginseng, flax seed, vitamin E, dong quai (Angelica sinensis), and DHEA. Postulated mechanisms for SSRIs and SNRIs include central effects on serotonin, dopamine, or norepinephrine,[26] while the potential benefit of isoflavones is thought to be mediated through their affinity for estrogen receptors. In the Study of Women's Health Across the Nation, depending on ethnicity, 20 to 70 percent of participants reported using some form of CAM therapy during the menopausal transition phase.[27]

Guidelines and Society Statements

The principal uncertainty for nonhormone therapies is effectiveness, whereas for hormone therapies it is the balance of benefits and harms. In May 2012, the U.S. Preventive Services Task Force (USPSTF) issued an update to their 2005 guideline titled *Hormone Replacement Therapy for the Prevention of Chronic Conditions in Postmenopausal Women*, in which the use of hormones for the prevention of chronic conditions was not recommended. This updated systematic review included research published through November 2011, but the report did not consider treatment of menopausal symptoms.[28]

The 2010 North American Menopause Society (NAMS) position statement on menopausal hormone therapy concluded, "Recent data support the initiation of [menopausal hormone therapy] around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal [hormone therapy] is favorable for women who initiate [hormone therapy] close to menopause but decreases in older women and with [greater] time-since-menopause in previously untreated women."[29]

The 2007 International Menopause Society (IMS) recommendations state, "The safety of [menopausal hormone therapy] largely depends on age. Women younger than 60 years old should not be concerned about the safety profile of [menopausal hormone therapy]. New data and reanalyses of older studies by women's age show that, for most women, the potential benefits of menopausal hormone therapy given for a clear indication are many and the risks are few when initiated within a few years of menopause."[30] Neither the NAMS position statement nor the IMS recommendations were accompanied by systematic reviews, yet both express

considerable certainty and are somewhat at odds with trends in menopausal hormone therapy use.[17]

The Endocrine Society recently performed an extensive review of evidence surrounding postmenopausal hormone therapy, published as a scientific statement.[31] Efforts to systematically review and synthesize the literature were described, although methods used in the review (e.g., search strategies and the process for rating evidence) were not detailed. Reviewers graded the quality of the evidence supporting use of menopausal hormone therapy as "high" for ameliorating vasomotor symptoms and vaginal atrophy, preventing bone loss, decreasing colon cancer risk, and increasing the risk of venous thromboembolism and gallbladder disease.

Position statements on compounded therapies have also been issued. The NAMS does not generally recommend compounded combined hormone therapy and suggests that compounded hormone products include a patient package insert identical to that required for products that have government approval. The NAMS states that "in the absence of efficacy and safety data for bioidentical [compounded] hormone therapy, the generalized benefit-risk ratio data of commercially available hormone therapy products should apply equally to bioidentical [compounded] hormone therapy."[19] Similar views are held by American College of Obstetricians and Gynecologists (ACOG), The Endocrine Society, and the American Association of Clinical Endocrinologists (AACE). ACOG states that in addition to having the same safety issues as those associated with FDA-approved menopausal hormone therapy, compounded hormones may have additional risks intrinsic to compounding.[32] The FDA maintains that while pharmacists engaging in traditional compounding provide a valuable service, anyone receiving compounded hormones should discuss options with their health-care provider to determine if compounded drugs are the best option for their medical needs.[33]

Challenges in Synthesizing the Evidence

From the perspectives of systematic review and evidence synthesis, there are a number of challenges in comparing different hormone therapies and comparing those therapies to alternatives:

- Population: Trial populations vary by factors such as age, ethnicity, time since menopause, length of time on hormone replacement therapy, BMI, and uterine status. For example, in a single trial, women with and without a uterus may be offered different treatment regimens.
- Intervention: The array of hormone and nonhormone therapies is broad and includes a number of biologic CAM and prescription agents, making synthesis difficult. Hormone therapies vary by preparation, type, and administration route. Compounded hormones are not standardized.
- Outcomes: There are numerous categories of menopausal outcomes: psychological, vasomotor, sexual function, sleep disturbances, and overall quality of life. Each of these categories can be measured by a variety of standardized scales, making synthesis challenging. Also, these outcomes are self-reported, and individuals assess levels of importance and severity of symptoms differently.
- Timing: Some harms are not immediately evident (e.g., breast cancer), and some benefits are not immediately evident (e.g., prevention of osteoporosis and fractures). Long followup times are necessary to adequately determine benefits and harms from these therapies.

Two large-hormone replacement therapy trials exemplify the complexities described above when collecting evidence for a systematic review on this topic. The WHI, which is a primary evidence base for harms from hormone replacement therapy, had a treatment population that overlaps but differs from the target population in this review. The WHI hormone trials excluded women with severe menopausal symptoms and enrolled primarily women older than those recently menopausal. These population characteristics of the WHI trials are relevant when attempting to interpret the results. A more recent report from the WHI observational trial[34] found women experiencing early vasomotor symptoms were at the lowest risk of cardiovascular disease and cardiovascular events. Another large trial with combined menopausal hormone therapy,[35] the Women's International Trial of Long Duration Oestrogen after Menopause [WISDOM], was prematurely closed because of the findings of the WHI trial, resulting in a trial with only one year of followup.

Objectives

For an individual menopausal woman considering hormonal or nonhormonal therapies, the questions of interest are: Given the presence of menopausal symptoms, what is the balance of benefits and harms of these therapies? Does the timing and duration of these therapies affect the balance? Accordingly, the objectives of this review include: systematically reviewing and synthesizing evidence evaluating the comparative effectiveness of treatments for menopausal symptoms, potential benefits other than symptom relief, and potential harms.

Population(s), Interventions, Comparators, Outcomes, Timing, and Setting

Population(s)

Women experiencing symptoms accompanying natural menopause (during perimenopausal or postmenopausal periods) or surgically induced menopause (during the postmenopausal period).

Interventions

Three categories of interventions are included in the report: hormone therapies, nonhormone prescription therapies, and nonprescription therapies:

- Hormone therapies including estrogen therapy and estrogen/progestogen (or estrogen/androgen) therapy administered by oral, transdermal, nasal, or vaginal route; combined estrogen-progestogen and progesterone-only contraceptives; compounded menopausal hormone therapy, often referred to as "bioidentical hormones"
- Nonhormone prescription therapies including SSRI/SNRIs, eszopiclone, clonidine, methyldopa, and gabapentin
- Nonprescription therapies including isoflavones, red clover, black cohosh, St. John's wort, ginseng, flax seed, vitamin E, dong quai, and DHEA

Comparators

Placebo or direct comparison between therapies, such as varying hormone dose and formulation.

Outcomes

- For Key Question 1 (KQ1) and Key Question 4 (KQ4):
- Final outcomes are menopausal symptom-related:
    - Vasomotor symptoms
    - Sleep disturbance
    - Psychological symptoms
    - Urogenital atrophy
    - Sexual function
    - Quality of life
- For Key Question 2 (KQ2) and Key Question 3 (KQ3):
- Final outcomes are other benefits and harms:
    - Coronary heart disease
    - Stroke
    - Venous thromboembolism
    - Breast cancer
    - Endometrial cancer
    - Ovarian cancer
    - Colorectal cancer
    - Gallbladder disease
    - Osteoporotic fractures
    - Agent-specific adverse events

Timing

For KQ1 and KQ4, at least 12 weeks of followup for adequate assessment of hormone and nonprescription treatment effects is required for inclusion. For centrally acting agents (SSRI, SNRI, and gabapentin) minimum trial duration will be 4 weeks. This is based on evidence that efficacy in treating vasomotor symptoms with these agents is demonstrable by 4 to 8 weeks—and translates into similar efficacy at 12 weeks.[36] For KQ2 and KQ3, longitudinal studies on colorectal cancer, breast cancer, and ovarian cancer require a followup of 5 years or greater for inclusion. Longitudinal studies on coronary heart disease, stroke, venous thromboembolism, endometrial cancer, gallbladder disease, and osteoporotic fractures require a followup of one year or greater for inclusion.

Setting

Primary care and community settings

Key Questions

Key Question 1. What is the comparative effectiveness of different treatments for reducing symptoms of menopause (vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy, and sexual function) and for improving quality of life? Individual agents will be compared to the extent permitted by the evidence.

Treatments of interest include:

- Hormone therapies
    - Oral estrogen alone or combined with progestogen (or androgen)
    - Transdermal estrogen or combined with progestogen
    - Vaginal estrogen
    - Combined estrogen-progestogen and progesterone-only contraceptives (for women desiring contraception)
    - Compounded menopausal hormone therapy

Evidence evaluating hormone therapies will be considered separately for women with and without a uterus. Women with breast cancer will be excluded.

- Nonhormone therapies
    - Prescription
        - SSRI/SNRIs
        - Eszopiclone
        - Clonidine
        - Methyldopa
        - Gabapentin
    - Nonprescription, complementary and alternative therapies
        - Isoflavones, including red clover (*Trifolium pratense*)
        - Black cohosh (*Cimicifuga racemosa*)
        - St. John's wort (*Hypericum perforatum*)
        - Ginseng
        - Flax seed
        - Vitamin E
        - Dong quai (*Angelica sinensis*)
        - Dehydroepiandrosterone

Key Question 2. What are the effects of menopausal hormone therapy preparations on coronary heart disease, stroke, or venous thromboembolism; gallbladder disease; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancers? Exposure will be examined according to duration of use and initiation relative to age and onset of menopause. (For women desiring contraception, combined estrogen-progestogen and progesterone-only contraceptives are included.)

Key Question 3. What are the effects of nonhormone therapy preparations on coronary heart disease, stroke, or venous thromboembolism;

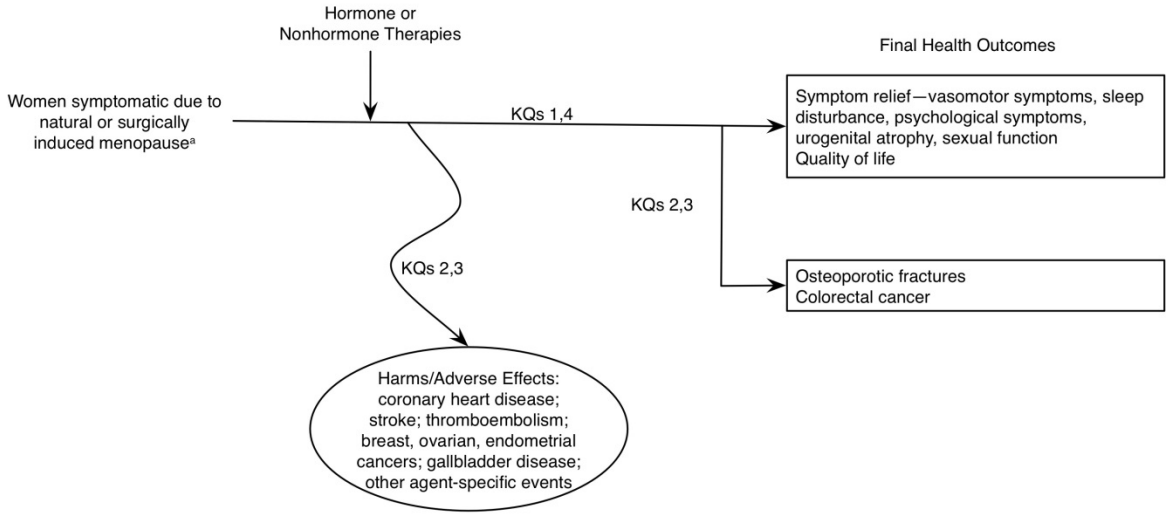
gallbladder disease; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer? Exposure will be examined according to duration of use and initiation relative to age and onset of menopause. What are the significant agent-specific harms/adverse effects of nonhormone therapies?

Key Question 4. Does effectiveness and adverse effects vary among subgroups of participants defined by demographics, symptom severity, other medications, and comorbidities or according to agent, preparation, or dose?

Analytic Framework

Figure 1 depicts the potential impact of both hormonal and nonhormonal treatments among women with menopausal symptoms. KQ1 and KQ4 illustrate how hormone and nonhormone therapies for menopausal symptoms may improve quality of life as well as reduce the occurrence or severity of the following symptoms: vasomotor symptoms, sleep disturbance, sexual function, urogenital atrophy, quality of life, and psychological symptoms. Other benefits of these treatments may include the prevention of osteoporotic fractures and colorectal cancer, as represented by the straight line of KQ2 and KQ3. The curved line of KQ2 and KQ3 represent potential consequential adverse effects among women using hormone and nonhormone therapies. These adverse effects include coronary heart disease, stroke, venous thromboembolism, breast cancer, endometrial cancer, ovarian cancer, and gallbladder disease.

Figure 1. Analytic framework



[a]Excludes women with breast cancer or receiving tamoxifen.

Methods

This comparative effectiveness review (CER) followed the methods suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[37] Methods were applied as appropriate for the evidence available for each Key Question. For KQ1 and KQ4, evidence included only randomized, controlled trials (RCTs). For KQ2, systematic reviews of randomized controlled trials were supplemented by observational studies when appropriate to assess applicability. Evidence sought for KQ3 included systematic reviews, meta-analyses, randomized controlled trials, and observational studies. The topic refinement process, literature search strategies, inclusion/exclusion criteria, data extraction and management procedures, evidence syntheses, and quality assessment methods are described below, specific to each Key Question.

Topic Refinement and Review Protocol

The topic for this report was nominated in a public process. Input was sought from Key Informants representing clinicians (internal medicine, family practice, and gynecology), academicians, and patients during topic refinement. Key Questions were subsequently posted and public comment obtained. A Technical Expert Panel (TEP) was assembled including content and clinical experts. Public comments were reviewed along with input from Key Informants and the TEP to assure that the questions were specific and explicit concerning the evidence reviewed. The Key Questions were finalized by the EPC after review of the comments (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1022).

A review protocol was drafted by the EPC in consultation with the TEP and also posted for public comment. Comments were reviewed by the EPC, discussed with the TEP, and appropriate changes made to the protocol. The protocol was amended during the course of the review in two main respects. First, for KQ1 vasomotor symptom and quality-of-life outcomes, for the most common treatments a network meta-analysis was judged appropriate. Second, the USPSTF report[28] was released addressing KQ2 in its entirety, save issues of applicability. With the release of that report and the discrepant conclusions concerning associations observed from observational studies and randomized, controlled trials, evidence for effects was limited to randomized comparisons.

Literature Search Strategy

Search strategies were developed (see Appendix A) by an expert librarian in collaboration with the trial team. No date limitations were applied. Only English-language articles were included.

The literature search was run on MEDLINE®, EMBASE®, Cochrane Controlled Trials Register, and AMED Allied and Complementary Medicine. The search included articles through January 2014. Duplicate records were deleted. The reference lists for systematic reviews and meta-analyses were screened to identify additional references which may not have been included in the original search. The search strings are provided in Appendix A. A single search strategy was used for all Key Questions, but different inclusion/exclusion criteria were used for the different Key Questions, details of which are outlined in the Inclusion and Exclusion Criteria section below.

Gray Literature Search Strategy

Searches were performed in clinicaltrials.gov, the FDA Web site, and relevant conference abstracts (conferences identified by TEP members). Attempts to locate related publications were made and trial authors were contacted for unpublished results if two senior team members concurred that the evidence could impact results meaningfully (i.e., potentially alter the strength of evidence). A text search for the following words was used to identify relevant conference abstracts: random, meta, systematic, testosterone, sertraline, citalo, fluoxetine, paroxetine, vilazodone, venlafax, eszopiclone, gaba, clonidine, methyl, myocardial, stroke, thromboembol, breast ca, endometrial ca, ovarian ca, colorectal ca, gallbladder disease, fracture.

References identified in the gray literature search were then screened using the same inclusion criteria as the original literature search and were incorporated into the review process when appropriate. Potentially unpublished evidence was also requested by the Scientific Resource Center from manufacturers.

Additional strategies were conducted to identify relevant literature on compounded—often referred to as "bioidentical" hormone therapies. Based on the absence of clinical trials for compounded menopausal hormone therapy, specific position statements containing keywords: "compounded or bioidentical hormones" were identified, reviewed, and selected from the following professional societies:

North American Menopause Society[19]

American College of Obstetricians and Gynecologists[32]

The Endocrine Society[38]

American Association of Clinical Endocrinologists[39]

Special committee reports from the United States Senate[40] and U.S. FDA[33] were also identified for review. Finally, we reviewed an influential lay-press publication on compounded "bioidentical" hormones to provide further perspective regarding the controversial topic of compounded menopausal hormone therapy.[41]

Inclusion and Exclusion Criteria

Population(s), Interventions, Comparators, Outcomes

- **Population(s)**

Women experiencing symptoms accompanying natural menopause (during perimenopausal or postmenopausal periods) or surgically induced menopause (during the postmenopausal period). **Exclusions:** KQ1—women with breast cancer; trial populations that consisted of only participants with preexisting conditions such as fibromyalgia, rheumatoid arthritis, or cardiovascular disease; KQ2 and 3—dietary population studies and studies including both pre- and postmenopausal women.

- **Interventions**

Menopausal hormone therapy including estrogen therapy and estrogen-progestogen (or estrogen-androgen) therapy administered by oral, transdermal, or vaginal route; combined estrogen-progestogen and progesterone-only contraceptives; compounded menopausal hormone therapy, often referred to as "bioidentical hormones" (Key Questions [KQs] 1 and 2).
Exclusions: Women receiving tamoxifen, either alone or in combination with other treatments.

Nonhormone therapies are listed under KQ1.

- **Comparators**
  Placebo or direct comparison between therapies, including hormone dose and formulation.
- **Outcomes**
  - No intermediate outcomes are included.
  - Final outcomes - menopausal symptom-related:
    - Vasomotor symptoms
    - Sleep disturbance
    - Psychological symptoms
    - Urogenital atrophy
    - Sexual function
    - Quality of life
  - Final outcomes - other benefits and harms:
    - Coronary heart disease
    - Stroke
    - Venous Thromboembolism
    - Breast cancer
    - Endometrial cancer
    - Ovarian cancer
    - Colorectal cancer
    - Gallbladder disease
    - Osteoporotic fractures
    - Agent-specific adverse events

- **Timing**

For hormone and nonhormone therapies, exposure to treatment will be at least 12 weeks from the baseline assessment. For centrally acting agents such as SSRIs, SNRIs, and gabapentin, trial duration will be at least four weeks from baseline assessment.

- **Setting**
  Primary care and community (biologic complementary and alternative therapies).

Study Designs—Inclusion and Exclusion Criteria

Key Question 1—Symptom Relief

We included RCTs with placebo or an active comparator. Anticipating sufficient RCTs for this Key Question, nonrandomized studies were not included. RCTs should have at least 25 women randomized per arm who are studied for at least 12 weeks for hormone and nonhormone therapies, 4 weeks for centrally acting agents (SNRIs, SSRIs, gabapentin); these conditions are minimums consistent with trials used to define efficacy for vasomotor symptoms. Other meta-analyses and systematic reviews will not be included. Table 1 summarizes the inclusion and exclusion criteria.

Table 1. All therapies: inclusion/exclusion criteria for the relief of vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy, sexual function, and quality of life

Trial Design	Criteria
RCTs with placebo comparator or active comparator	Include[a]
Meta-analyses and systematic reviews	Exclude[b]
Observational studies	Exclude
Single arm/case series	Exclude
Case reports	Exclude
Minimum duration[c]	≥12 weeks
Sample size	≥25 participants randomized per arm

[a] Women with breast cancer excluded.
[b] Bibliographies of meta-analyses and systematic reviews will be reviewed for any trials not identified in the literature search.
[c] Minimum duration for centrally acting agents such as SSRI, SNRI, and gabapentin, is 4 weeks. This is based on evidence that efficacy in treating vasomotor symptoms with these agents is demonstrable by 4 to 8 weeks.[36, 42]
RCTs: randomized controlled trials

Several of the nonhormone therapies are consumed as part of a regular diet (soy, vitamin E, ginseng, for example) and are therefore often part of large population-based food consumption observational studies. For the purposes of this report, those studies were not included. Only studies in which the nonhormone therapies are treatments were included.

Therapies were required to be administered during the perimenopausal or menopausal years for study inclusion. If therapies were used only during the premenopausal years, those studies were excluded. If we were unable to determine if the nonhormone therapies were administered during the perimenopausal or menopausal years, for example, studies reporting "ever" use, those studies were excluded.

Key Question 2—Other Benefits/Harms of Hormones

The associations of hormone therapies with the other benefits and harms considered here has been the subject of controversy, considerable research, and a motivation for conducting the WHI trials. Discrepant conclusions concerning these associations have been observed from observational studies and randomized controlled trials.[43] The discrepancies have been attributed to two primary reasons—selection bias and time-varying confounding.[44-46] While the association with cardiovascular outcomes has been most scrutinized, difficulties assessing causal effects of menopausal hormone therapy on the KQ2 outcomes from observational data appear to extend to other outcomes as well, including hip fractures[44] and colorectal cancer.[46] Relying on observational data employing standard analyses to examine these outcomes is problematic.[45] Accordingly, study selection to evaluate treatment effects (i.e., those causal) for KQ2 will be limited to systematic reviews of RCTs.

Systematic reviews examining relevant outcomes (coronary heart disease, stroke, or venous thromboembolism; gallbladder disease; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer) will be considered if meeting the following criteria derived from the AMSTAR tool and AHRQ guidance: 1) at least two electronic sources were searched; key words and/or MeSH® terms stated; 2) study inclusion/exclusion criteria reported; 3) study quality (potential bias) of included trials assessed and documented. However, during the course of this review, Nelson et al. completed a review for the USPSTF on the effects of menopausal hormone therapy for chronic disease prevention[28] which met all criteria and addressed outcomes included in KQ2. Accordingly, it was used as the primary basis for KQ2.

It is important to note that the approach adopted was not to appraise conclusions of the identified review, but to use the review to identify relevant trials meeting our inclusion criteria and appraise and synthesize evidence from them, including assigning a strength of evidence rating.

Given the natural history of osteoporosis, as well as breast, ovarian, and colorectal cancer, minimum trial duration of 5 years was specified as an inclusion criterion for longitudinal studies investigating those outcomes. A minimum sample size of 250 women per trial was imposed to allow valid assessment of event rates. Outcomes were identified in consultation with the TEP to capture those most consequential. They were not intended to be an exhaustive list.

We anticipated evidence for KQ2 to ultimately derive in whole or in part from the WHI trials. These trials enrolled an older sample overlapping the target population of this review.[47] Owing to this difference, applicability of evidence requires scrutiny. This step is in addition to those outlined in AHRQ guidance[37] (which notes "the exact process needs to be flexible and will likely evolve") and adopted by the review team owing to the controversy surrounding applicability of WHI results to the review target population. To assess applicability for KQ2 we examined our search to identify trials and observational studies enrolling peri- and recently menopausal women and consulted a clinical content expert. Informative studies were selected based on recommendations from the content expert in consultation with the review team. Results from these studies were included in the applicability discussion.

Key Question 3—Other Benefits/Harms of Nonhormones

For nonhormone prescription treatments, we limited our review to studies using the drugs to treat menopausal symptoms (and not for other indications for which the interventions may be commonly used) to increase the applicability of the review to the population of women with menopausal symptoms. An evaluation of all safety data on the nonhormonal agents was beyond the scope of the review.

For nonhormone nonprescription treatments, any study design identifying agent-specific harms was included. Due to scope issues, we limited the list of included agents as prioritized in consultation with the TEP. The list is not exhaustive—see KQ1 for included agents.

The evidence base for agent-specific adverse events for nonhormone therapies consisted of articles included in KQ1 that also reported adverse events, as well as meta-analyses, systematic reviews, and observational studies. Reference lists in the systematic reviews and meta-analyses were reviewed, to identify RCTs and observational studies meeting inclusion criteria (Table 2 and Table 3).

Table 2. Inclusion/exclusion criteria for agent-specific adverse events of nonhormone therapies

Trial Design	Prescription Therapies	Nonprescription Therapies
RCTs with placebo comparator or with active comparator	Include	Include
Meta-analyses and systematic reviews	Include	Include
Observational studies	Include	Include
Single arm and case series	Exclude	Include
Case reports	Exclude	Include
Minimum duration	≥12 weeks	None
Sample size	≥25 participants randomized per arm	None

RCTs: randomized controlled trials

Table 3. Inclusion/exclusion criteria for long-term effects (coronary heart disease, stroke, or venous thromboembolism; gallbladder disease; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer) of nonhormone therapies

Trial Design	Prescription Therapies	Nonprescription Therapies
RCTs with placebo comparator or with active comparator	Include	Include
Meta-analyses and systematic reviews	Include	Include
Observational studies	Include	Include
Single arm and case series	Exclude	Exclude
Case reports	Exclude	Exclude
Minimum duration	5 years[a] 1 year[b]	5 years[a] 1 year[b]
Sample size	>250	>250

[a] Longitudinal studies of colorectal, breast, or ovarian cancers; and fracture outcomes (does not apply to case-control studies).
[b] All other outcomes (does not apply to case-control studies).
RCTs: randomized controlled trials

Key Question 4—Subgroups

Subgroups (age, BMI, prior use of therapies, vasomotor severity of symptoms, time since menopause, uterine status, therapy schedule, comorbidities [smoking, anxiety, premenstrual syndrome or postnatal depression]) were selected from included trials in KQ1. Women with breast cancer were excluded.

Key Question 1 and Key Question 4 Duplicate Populations

Duplicate populations already described in an included article not reporting additional outcomes of interest (KQ1 and KQ4) were excluded.

Study Selection Process

Articles from the literature search were transferred into EndNote® (Thomson Reuters, New York, NY) and then into DistillerSR (Evidence Partners Inc., Manotick, ON, Canada) for trial selection. A pilot training set of 50 titles was screened by two team members. Titles alone did not provide sufficient screening information and the review proceeded with title/abstract screening. A set of 50 titles/abstracts was used to train the team members. In the title/abstract

screening phase, all references underwent dual review for inclusion in the full-text review. Disagreements were resolved by an independent team member.

Citations marked for inclusion during the title/abstract screening phase were retrieved for full text review. A dual screening process was conducted to determine inclusion/exclusion status from the full text. Disagreements between reviewers were resolved by an independent team member. Articles were excluded if they did not meet the criteria specific for each Key Question for appropriate trial design, minimum number of participants, and minimum length of followup. Reasons for exclusion were recorded in the DistillerSR database (Appendix B).

Data Extraction and Management

Key Question 1 and Key Question 4

Data elements were defined in a data dictionary and abstracted into tables created in DistillerSR (Appendix C). Two training sets of three articles each were abstracted by all team members. Meetings were held after each training set of articles was abstracted, to discuss potential abstraction discrepancies. The data dictionary and abstraction forms were modified based on input from team members. After finalizing the data dictionary, abstraction forms, and abstraction instructions, data abstraction was conducted. Abstraction was performed by one team member, and verified by a second team member. Inconsistencies identified were resolved by consensus with publication review. For crossover trials only the first phase was included.

Included in abstracted data were the following (see data dictionary Appendix C) for complete listing):

- Trial Characteristics: author, year, country, number of trial sites, trial design, total number randomized, intervention, surgical or natural menopause, disclosures and conflicts of interest, funding, primary and secondary outcomes, and if required for inclusion into trial frequency or intensity of climacteric symptoms
- Trial Arm Characteristics: number of participants, age, ethnicity, BMI, time since menopause, tobacco use, and treatment specifics such as type of treatment, dosage, and route of administration
- Outcomes: scale or measurement; results from baseline, 12-weeks, and final assessments; depending on how the results were reported, mean scores, mean changes, percent reductions, standard deviations, 95% confidence intervals, preintervention/postintervention comparisons, and between group comparisons.
- Many trials included in KQ1 reported outcomes using more than one scale or metric for each domain (with up to 6 arms per trial). For example, psychological symptoms reported may have included depressive symptoms, anxiety, and a global measure of psychological well-being; vasomotor symptoms may have been reported as frequency, severity, and with a menopausal symptom instrument. Selecting outcome metrics to abstract a priori could potentially introduce bias if one was chosen not uniformly or most frequently reported. In addition, data reported with one metric/scale for the same outcome might not provide sufficient quantitative data to estimate an effect while another did. Therefore, we abstracted (digitizing figures when necessary) up to 3 metrics/scales per KQ1 outcome from each trial.

Treatment dosages were recorded for all agents. For analytical purposes, estrogen doses were classified: ultralow, low, standard, and high. With oral treatments, the dosing category

definitions were based on those used in the 2009 Cochrane review on hormone replacement therapy and endometrial hyperplasia.[48] For example, dose categories for oral conjugated equine estrogens were: ultralow (0.15 to 0.3 mg); low (0.4 mg); standard (0.625 mg); and high (1.25 mg). For other routes of administration, such as transdermal and spray, dosing categorizations were established in consultation (i.e., primarily) with the clinical content expert. For a complete list of estrogen dose categories, by type of estrogen and route of administration, refer to Appendix D.

When only graphical outcomes were presented, figures were digitized. Data were exported to and analyzed with R.[49] Data were abstracted into separate datasets. For KQ1 we three study level data sets: study characteristics, study quality ratings, and a data set including characteristics for each study arm; and six datasets or one for each outcome. With few exceptions, trial-level and summary evidence tables were created by manipulating, analyzing, and formatting data in R, then exporting to Microsoft Excel®. Inaccuracies produced in this manner are then due to either abstraction or coding.

Key Question 2

Data from trials identified through the Nelson report for the USPSTF [28] were abstracted, including treatment type, treatment dose, length of followup, and results.

Key Question 3

With a limited literature base for the effect of nonhormone therapies on long-term conditions, quantitative synthesis was not possible. Descriptive summaries of the available evidence were generated. Summary tables were created and contained the following information: condition, treatment, trial design, trial descriptions, and results.

Adverse events reported for nonhormone therapies included a wide variety of symptoms. Events were categorized according to the International Federation of Pharmaceutical Manufacturers and Associations[50] recommended scheme: blood and lymphatic system; cardiac; congenital, familial, and genetic disorders; ear and labyrinth disorders; eye; endocrine disorders; gastrointestinal; general disorders and administration site conditions; hepatobiliary disorders; immune system disorders; infections and infestations; investigations; injury, poisoning, and procedural complications; metabolism/nutritional; musculoskeletal; neoplasms benign, malignant, and unspecified (including cysts and polyps); nervous system; psychiatric disorders; renal/urinary; respiratory, thoracic, and mediastinal disorders; skin and subcutaneous tissue; and vascular.

Data were abstracted into adverse events tables including: author, year, country, treatment, dose, trial population size, total adverse events, and percentage of events for each category.

Evidence Tables

The body of evidence for KQ1 (and contributing to KQ4) was large, including multiple comparators and trials reporting multiple outcomes. Following exploratory and descriptive analyses, we organized seven sets of evidence tables according to nine generally exclusive categories of comparators: (1) hormone versus placebo; (2) SSRI/SNRI versus placebo; (3) other prescription agents versus placebo; (4) nonprescription agents versus placebo; (5) hormone, nonprescription, placebo comparisons; (6) hormone versus hormone; (7) nonprescription versus hormone; (8) nonprescription versus nonprescription; and (9) SSRI/SNRI versus nonprescription.

The evidence tables generated included: (1) descriptive trial data; (2) patient age, body mass index, smoking history; (3) ethnicity/race; (4) uterine status, mean at menopause, years since menopause, prior menopausal hormone therapy; (5) outcomes reported; (6) treatment specifics including category, dose, route, generic and trade name, and estrogen dose if estrogen given (for each treatment arm); and (7) study quality elements and overall ratings. Only for the treatment specifics were trial arms specified which ranged from two to six (the single seven-arm trial footnoted). For each of the 63 tables, studies were ordered chronologically. These tables appear in Appendix E.

Quality Assessment of Individual Studies

In adherence with the EPC Program "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (hereafter Methods Guide),[37] quality (bias) assessment was performed by applying the criteria of the USPSTF.[51] An assessment was performed by two independent reviewers. Studies were given ratings of good, fair, and poor.[51] Discordant quality assessments were resolved with input from a third reviewer. We were typically unable to assess study quality for trials available only as abstracts or gray sources, such as posted results on clinicaltrials.gov, owing to insufficient trial detail. A modified version of AMSTAR, a validated tool, was used for quality assessment of meta-analyses and systematic reviews.[52]

When interpreting study quality ratings, it is important to note the study design along with the rating. Features such as randomization and control arms in RCTs inherently reduce risk of bias, while observational studies generally have more sources of bias.[53] A "fair" rating for an RCT is not equivalent to a "fair" rating for an observational study. We therefore added the qualifier "observational study" next to the good, fair, and poor ratings in the quality assessment tables for the cohort and case control studies.

Even with appropriate analysis, the ability of observational studies to identify unconfounded associations and causal effects[54] or ascertain harms[55] can be highly variable. Moreover, all observational data are considered lesser (low) strength of evidence.[56] The perspective here is that a qualitative appraisal of observational studies that scrutinizes both the design and analytic approaches used to evaluate any causal effects is informative alongside a more quantitative one (i.e., checklist).

Randomized Controlled Trials

The following criteria were used to assess the study quality of RCTs: assembly of comparable groups; blinding of researchers and subjects; adequate concealment of group assignment; maintenance of comparable groups; differential loss to followup; equal and reliable measurements; clearly defined interventions; important outcomes considered and defined; and intention-to-treat analysis.

Based on these criteria, ratings for RCTs were defined as:

Good: Meets all criteria; comparable groups are assembled and maintained throughout study (followup at least 80 percent); reliable and valid measurement instruments used and applied equally between groups; interventions clearly defined; important outcomes defined; and intention-to-treat analysis performed.

Fair: Generally comparable groups assembled initially, but questions remain about differences in followup; measurement instruments acceptable and generally applied equally; some but not all important outcomes considered; some but not all potential confounders accounted for.

Poor: Groups assembled initially are not close to being comparable or maintained; unreliable or invalid measurement instruments used; key confounders are given little or no attention.

Cohort Studies

The following criteria were used to assess the study quality of cohort studies: assembly of comparable groups; maintenance of comparable groups; differential loss to followup; equal and reliable measurements; important outcomes considered and defined; and statistical adjustment for potential confounders.

Based on these criteria, ratings for cohort studies were defined as:

Good: Meets all criteria; comparable groups are assembled and maintained throughout study (followup at least 80 percent); reliable and valid measurement instruments used and applied equally between groups; interventions clearly defined; important outcomes defined; and appropriate statistical adjustment for confounders.

Fair: Generally comparable groups assembled initially, but questions remain about differences in followup; measurement instruments acceptable and generally applied equally; some but not all important outcomes considered; some but not all potential confounders accounted for.

Poor: Groups assembled initially are not close to being comparable or maintained; unreliable or invalid measurement instruments used; key confounders are given little or no attention.

Case Control Studies

The following criteria were used to assess study quality of case control studies: accurate ascertainment of cases; nonbiased selection of cases and controls; response rate; equal application of diagnostic tests to each group; accurate and equal measure of exposure to each group; and attention to potential confounders.

Based on these criteria, ratings for case control studies were defined as:

Good: Appropriate ascertainment of cases and nonbiased selection of controls; response rate $\geq$80 percent; diagnostic procedures and measurements accurate and applied equally; and appropriate attention to potential confounders.

Fair: No major selection or diagnostic bias among groups; response rate less than 80 percent; attention to some but not all potential confounders.

Poor: Major selection or diagnostic biases; response rate less than 50 percent; inaccurate or unequal exposure measurements; or inattention to potential confounders.

Data Synthesis

Overall Approaches and Meta-Analyses for Direct Comparisons

The approach adopted for evidence synthesis was inclusive to incorporate as much evidence as possible. The rationale for this approach has four primary underpinnings. First, while symptom severity varies, the experience of menopause is universal. Second, defining homogeneous populations of women within the evidence base of trials identified is potentially problematic due to varying patient characteristics, as well as reporting. For example, years since menopause was reported in 31.4 percent of trials. Thirdly, trials employed a variety of different patient-reported outcome instruments, some more commonly used than others. To apply an inclusion criterion stipulating use of particular instrument(s) could arguably introduce bias.

Lastly, combining outcomes obtained on different metrics requires calculating standardized effect measures—here standardized mean differences (SMD). Obtaining effects and some estimate of variance from trials reported in a myriad of ways is challenging. For example, as outlined below, outcomes can be reported in a host of different ways, each allowing calculation of an effect and variance. Excluding trials reporting a nonsignificant result from a pooled analysis would introduce bias and requires imputation. Further, in the end, potential reporting bias must also be considered. There are, therefore, numerous potential sources of uncertainty over and above those sometimes encountered in meta-analyses. Confidence and credible intervals for pooled estimates should be considered cautiously as their calculation does not incorporate some sources of statistical uncertainty; arguable most all should be penalized and a lower level of type I error applied than is convention. For example, normality of outcome metrics cannot be completely verified. For vasomotor symptoms, we examined qq plots according to metric which supported normality for most, but confirming for those metrics used in a few trials was not possible. Additionally, while data extraction was verified and each reverified for potential outliers e.g., (SMDs >1.0 or < -1.0) in preliminary analyses, data extraction for use in SMDs is difficult.[57] Often p-values used to calculate variances were not reported as exact by as <0.05 or <0.01 so serving as upper bounds. We accordingly adopted a purposeful, pragmatic, but cautious approach to sifting, analyzing, and interpretation of KQ1 evidence. For example, clearly identifiable outliers were excluded from main pooled estimates (as apparent on forest, funnel, and radial plots) with results also provided including those estimates. Outliers had implausibly large or small estimated standardized effects. Pooling was also performed with and without lesser influential observations; and attempted to include in the network meta-analyses (vasomotor symptoms and quality of life consistent effects). Finally, sensitivity analyses were liberally performed.

Use of Standardized Mean Differences

Standardized mean differences were calculated and pooled according to the EPC Program Methods Guide.[58] Calculating the SMD, which is in simplest terms (mean change treatment – mean change comparator)/pooled standard deviation, allows for comparison of results across studies using different measures. We used Hedge's G calculation for SMDs being considered less biased in small samples. Analyses were performed in R[49] using the meta,[59] compute.es,[60] and ggplot2[61] packages.

We estimated effects for each arm to calculate SMDs as follows: (1) from reported pre-post change and standard deviation (or error), (2) if baselines were similar using end of treatment means and standard deviation if reported, (3) if baselines differed with baseline and end of treatment standard deviations reported calculated change and estimated standard deviation (assuming 0.5 correlation between initial and final standard deviations), (4) using p-values (applying a t-distribution) with baseline and end of treatment value or reported change for arm-specific effect, (5) using between-arm differences, confidence intervals or p-values (applying a t-distribution) as from an ANCOVA. When more than one approach to calculating a standard deviation was feasible, we compared SMDs using from different approaches to assure consistency with trial results. If an effect was reported as nonsignificant but the trial was to be pooled, a nonsignificant p-value was imputed for pooling so not to selectively exclude nonsignificant results. Values were imputed randomly from a uniform distribution bounded by the approximate standard deviations of a normal distribution fitted to the sample of study values reported—e.g., for vasomotor symptoms 0.10 to 0.70. For trials reporting nonsignificant results

but not pooled no imputation was performed. A small number of trials reported dichotomous outcomes; when feasible they were also included.

Pooling

Analyses were performed in R[49] using the meta[59] package. For individual trials, SMDs and confidence intervals were calculated using the compute.es package.[60] Clinical heterogeneity, and appropriateness for pooling, was judged on the basis of study characteristics in concert with subject matter knowledge—as interpreted by the study team. To facilitate generalizability, the approach was inclusive performing and reporting results from sensitivity analyses limited to set(s) of trials that might inform consistencies and inconsistencies. When multi-arm trials incorporated arms with treatments similar for the purposes of analyses here (e.g., same estrogen dose) effects from arms were combined prior to any pooling. Because the goal of any pooling is to estimate unconditional effects,[62] random-effects models were used. The magnitude of statistical heterogeneity was examined by using tau^2 owing to limitations of the I^2 metric and because between-trial variances are more intuitively interpreted on the effect estimate scale.[63] Evidence of possible reporting (publication) bias was explored by using funnel plots and Egger test when results from at least 10 studies were pooled. At the protocol stage, we anticipated examining subgroup-specific effects according vasomotor symptom severity, years since menopause (age), ethnicity, and comorbidities (smoking, obesity). Given inconsistent and incomplete reporting of these variables such analyses were not conducted. In addition, other than for KQ2 trial reporting did not allow evaluating results separately for women with and without a uterus. Outcomes were summarized and reported in the order specified by therapies in the KQs.

Minimal Clinically Important Differences

To discuss the outcomes in the context of clinical relevance, attempts were made to find established thresholds for the minimal clinically important difference for each outcome. PubMed and Google Scholar were searched for minimal clinically important differences (MCID) for the following: Greene scale, MENQOL, MQOL, WHQ, Kupperman Index, hot flushes, night sweats, Hamilton Depression scale, SF-36, CES-D, McCoy scale, Menopause Rating Scale, Visual Analog Scale and WHI sleep scale. Search terms for MCID included “MCID,” “MID,” “minimal important difference,” “clinical important difference,” “clinically important difference,” “minimal difference”, “clinical difference” and “important difference.” Search terms for outcomes included “Greene scale,” “Greene,” “MENQOL,” “MQOL,” “menopause QOL,” “menopause quality of life,” “WHQ,” “WHQ scale,” “Kupperman Index,” “Kupperman,” “night sweats,” “vasomotor,” “Hamilton,” “HAMD,” “SF-36,” “RAND-36,” “CES-D,” “McCoy sex scale,” “McCoy scale,” “McCoy sex,” “Menopause Rating Scale,” “MRS,” Visual Analog Scale,” “VAS,” “WHI scale,” “WHI,” and “menopause.” Articles retrieved from the search that had a postmenopausal patient population were then searched for the MCIDs using the find function and MCID search terms. If MCIDs were not found in articles with a postmenopausal population, then articles with any patient population were searched. Table 4 summarizes the MCID for each outcome or scale.

Table 4. Minimal clinically important difference (MCID) or minimal clinically important improvement (MCII) for various scales

Article	Scale	MCID/MCII	Note
Huntley, 2003[64]	Kupperman total score	final score ≤15	Cites Kupperman, 1959[65]
Kupperman, 1959[65]	Kupperman total score	final score ≤15	
Morrison, 2004[66]	Hamilton-Depression	-3 points	
Zollner, 2005[67]	MENQOL subscales	1 point change	Cites Hilditch, 2008[68]
Hilditch, 2008[68]	MENQOL subscales	1 point change	
Lewis, 2005[69]	MENQOL subscales MENQOL summary	1 point change	
Wyrwich, 2003[70]	SF-36 general health SF-36mental health	Small change: 10 Moderate change: 20 Large change: 30 State change: 5	
Samsa, 1999[71]	SF-36	3-5 point	
Levine, 2005[72]	WHI Insomnia Scale	1/2 a SD change	
DeRogatis, 2009[73]	Satisfying sexual episodes	+1 episode/4-week period	

MENQOL: Menopause Quality of Life; VAS: visual analog scale; WHI: Women's Health Initiative

Indirect Comparisons With Mixed Treatment Comparisons Techniques

A random-effects network meta-analysis was performed pooling standardized mean differences in a Bayesian model described by Chaimani (www.mtm.uoi.gr/). Models were fitted in OpenBUGS 3.2.2 using noninformative priors and convergence assessed using the Brooks-Gelman-Rubin plot and statistic (no value exceeded 1.002 in the model). A burn-in of 20,000 samples was discarded and subsequent 40,000 analyzed. Rankings were estimated for the probability a treatment was most effective, next most effective, and so on. SMDs and accompanying 95% credible intervals were obtained from the samples. To evaluate consistency we compared available pairwise estimates to the network results[74] and explored graphically (www.mtm.uoi.gr/). We examined all pairwise comparisons individually in random effects models and graphically using forest plots.

Outcome Measures

Key Questions 1 and 4

Outcomes for KQ1 and KQ4 were categorized into the following menopausal symptom categories: vasomotor symptoms, sleep disturbance, psychological symptoms, urogenital atrophy symptoms, sexual function, and quality of life. Outcomes were self-reported, from daily diaries or derived from validated survey instruments. Survey instrument details appear in each of the results sections.

There existed a wide variety of potential outcome measures for each of the categories, so abstraction was limited to the more common outcomes. The following outcomes, by category, were abstracted for analyses:

Vasomotor symptoms: self-reported hot flushes, night sweats, and severity of hot flushes; vasomotor subscores from instruments such as the Greene Climacteric Scale (GCS), the Kupperman Menopausal Index (KI), Women's Health Questionnaire (WHQ), and the Menopause-specific Quality of Life (MENQOL)

Sleep disturbance: self-reported insomnia and sleep problems; Women's Health Initiative Insomnia Rating Scale, and sleep subscales from GCS, KI, or MENQOL

Psychological symptoms: anxiety, depressive symptoms, and global measures; subscales from the larger menopause-related survey instruments such as KI, GCS, MENQOL, or from psychological survey instruments such as Beck and Hamilton

Urogenital atrophy: self-reported vaginal dryness; urogenital atrophy or vaginal atrophy subscale scores from KI, GCS, and MENQOL

Sexual function: dyspareunia, satisfying sexual episodes, number of sexual episodes; McCoy Sex Scale, and sexual function subscales from GCS, KI, WHQ, and MENQOL

Quality of life: total scores from GCS, KI, MENQOL

Some investigators devised their own scales rather than using the above standardized scales. We included outcomes that used these other scales as well.

Key Questions 2 and 3

Outcomes included heart disease (myocardial infarction, angina), stroke, or venous thromboembolism; cholecystitis; osteoporotic fractures; or endometrial, breast, colorectal, or ovarian cancer.

Strength of the Body of Evidence

Strength of evidence (SOE) assessments were based on the EPC approach,[75] which is conceptually similar to the GRADE system.[56] Two reviewers graded the strength of evidence, resolving disagreements by consensus. Details for the strength of evidence approach are also available at the AHRQ Effective Health Care site, http://effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf.

We adopted a point-based approach to SOE ratings in which each assessment started at high (3 points) and downgraded by one point each for: high risk of bias, inconsistent or unknown consistency, imprecise or unknown precision, indirect body of evidence, and suspected reporting bias (Table 5). Domain ratings were entered into a spreadsheet that provided a summary SOE for each outcome. If the summary SOE remained 3 with no downgrades, strength of evidence was rated high; if the summary SOE equaled 2, strength of evidence was rated moderate; if the summary SOE equaled 1, strength of evidence was rated low; if the summary SOE was zero or lower, strength of evidence was rated insufficient. Following AHRQ guidance for assessing evidence on equivalence and noninferiority, studies can be appropriately considered individually in the presence of clinical heterogeneity—"the lack of meta-analysis does not necessarily preclude a conclusion of EQ-NI [Equivalence-noninferiority], just as it does not preclude an evaluation of the strength of evidence in relation to a particular outcome."[76]

Table 5. Downgrading of SOE according to domains from the initial SOE of high (3 points) to moderate (2 points), low (1 point), or insufficient (0 points)

Domain	Level	Change in Score
Risk of Bias	High	-1
	Medium	0
	Low	0
Consistency	Inconsistent	-1
	Unknown	-1
	Consistent	0

Table 5. Downgrading of SOE according to domains from the initial SOE of high (3 points) to moderate (2 points), low (1 point), or insufficient (0 points) (continued)

Domain	Level	Change in Score
Directness	Indirect	-1
	Direct	0
Precision	Imprecise	-1
	Unknown	-1
	Precise	0
Reporting bias	Suspected	-1
	Undetected	0

We imposed one departure from the SOE ratings. In the presence of a large number of trials ($n \geq 10$), even when a majority of the trials were rated poor quality, risk of bias was assigned medium rather than low. If there were 10 or more trials with consistent effects and no suspected reporting bias, we concluded that low trial quality did not justify a lower strength of evidence.

For KQ1, when sufficient trials allowed for evidence synthesis, strength of evidence was determined by outcome (vasomotor symptoms, quality of life, psychological symptoms, sexual function, urogenital atrophy symptoms, and sleep disturbance) and by comparators. *For outcomes and comparator groups without poolable data represented by single trials, strength of evidence was deemed insufficient and not reported.*

For KQ2, strength of evidence was determined by outcome (breast cancer; gallbladder disease; colorectal cancer; coronary heart disease, stroke, and venous thromboembolism; endometrial cancer; osteoporotic fractures, and ovarian cancer), and by treatment regimen (either estrogens alone or estrogens with progestogens).

For KQ 3, strength of evidence was determined by outcome (breast cancer; gallbladder disease; colorectal cancer; coronary heart disease, stroke, and venous thromboembolism; endometrial cancer; osteoporotic fractures, and ovarian cancer), and by treatment regimen (SSRI/SNRIs, isoflavones, and vitamin E).

For KQ 4, strength of evidence was determined by outcome (vasomotor symptoms, quality of life, psychological symptoms, sexual function, urogenital atrophy, and sleep dysfunction), by subgroup (age, body mass index, race, severity of symptoms, time since menopause, and uterine status), and by treatment regimen (estrogens, other prescription treatments, and nonprescription treatments). *For outcomes and comparator subgroups represented by single trials, strength of evidence was deemed insufficient and not reported.*

Applicability

Applicability is defined as the extent to which treatment effects observed in published studies reflect expected results when treatments are applied to these populations in the real world. The population of interest for this review is women experiencing symptoms accompanying natural menopause (during perimenopausal or postmenopausal periods) or surgically induced menopause (during the postmenopausal period). Potential factors which may affect applicability in this body of evidence include:

- Study populations may consist of all menopausal women, regardless of presence of symptoms

- Study populations may combine results on menopausal women with and without a uterus
- Study populations may consist of menopausal women with different levels of symptom severity
- Study populations may have a larger proportion of older menopausal women

Limitations in the applicability of individual studies were identified. When there were questions applying results from randomized controlled trials for KQ2, we reviewed observational studies from the original literature search seeking more comparable populations. As suggested by the AHRQ Methods Guide, when applicability issues occurred, they were highlighted and clearly discussed following the evidence tables.

Peer Review and Public Commentary

Key Informants are the end-users of research, including participants and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicited input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants were not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants disclosed any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore trial questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts disclosed any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers

do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers also disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Peer review comments were addressed formally with revisions to the review and text as appropriate. Following peer review and literature search update, some changes from the draft report are important to note. For KQ1, results from 29 previously not included trials were added. Additionally, published results contributing to different KQ1 outcomes were identified for another 16 trials. With the exception of the analysis for satisfying sexual episodes, all results required updating and conducted considering AHRQ's finalized guidance for continuous outcomes.[77] For vasomotor symptoms, an analysis translating SMDs to hot flush frequencies was performed. Additional sensitivity analyses were also included, particularly for the network result. Ospemifene for urogenital atrophy symptoms was not included in the protocol, but obtained FDA approval and so was added. Finally, we supplemented the analyses of sleep outcomes with network analysis to provide some comparison of agents generally used to treat menopausal symptoms with a sedative hypnotic agent, eszopiclone.

Results

Overview

Agents

Almost 20 specific agents were included in the literature search. Additional unique nonpresprescription agents were identified as well. Agents were categorized according to the scheme in Table 6. Hormones were further classified according to estrogen dose and route of administration (see Appendix D for dose categorization by route of administration). The hormone general category in the table below includes estrogen alone, estrogen/progestogen, testosterone, and progesterone alone. "Menopausal hormone therapy" in the text refers to estrogen (for women without uteri) and estrogen/progestogen (for women with intact uteri). When testosterone or progesterone was used alone, this was explicitly stated. No trials of compounded estrogen formulations met inclusion criteria. A discussion of compounded hormone therapies appears at the end of the KQ1 results section.

Table 6. Agents and categorizations for purposes of review

Estrogen Dose	Agent	General Category	Route	
High Standard Low/Ultralow	Estrogen alone Estrogen/Progestin Estrogen/Testosterone Estrogen/Bazedoxifene	Hormone	Oral	
			Transdermal Patch Skin Spray Skin Cream Skin Gel	Topical
			Vaginal Cream Vaginal Gel Vaginal Ovule Vaginal Tablet	Vaginal
			Vaginal Pessary/Suppository Vaginal Ring	Vaginal Vehicle
Not Applicable	Testosterone Progestin		Intranasal Spray	Nasal
Not Applicable	SSRI/SNRI	Antidepressant	Oral	
	Eszopiclone Clonidine Methyldopa Gabapentin Ospemifene	Other Prescription	Oral	
	Isoflavones Black Cohosh St. John's Wort Ginseng Flax Seed Vitamin E Dong Quai DHEA Others	Nonprescription Nonhormone	Oral	
	Placebo	Placebo	Any	

Results are organized by Key Question. For KQ1, the results are presented by the six outcome categories: vasomotor symptoms, quality of life, psychological symptoms, sexual function, urogenital atrophy, and sleep disturbance. Within each of these six categories, there are the following sections: a summary table of the included trials; a presentation of the quantitative synthesis (either network meta-analysis or pairwise comparisons) for those trials with data that was amenable to pooling; a strength of evidence assessment for the evidence that was synthesized; a summary of the trials that were not amenable to a quantitative synthesis; and key points.

KQ2 and KQ3 results are presented by condition: breast cancer; gallbladder disease; colorectal cancer; coronary heart disease, stroke, and venous thromboembolism; endometrial cancer; osteoporotic fractures; and ovarian cancer. KQ3 includes an additional discussion of adverse events.

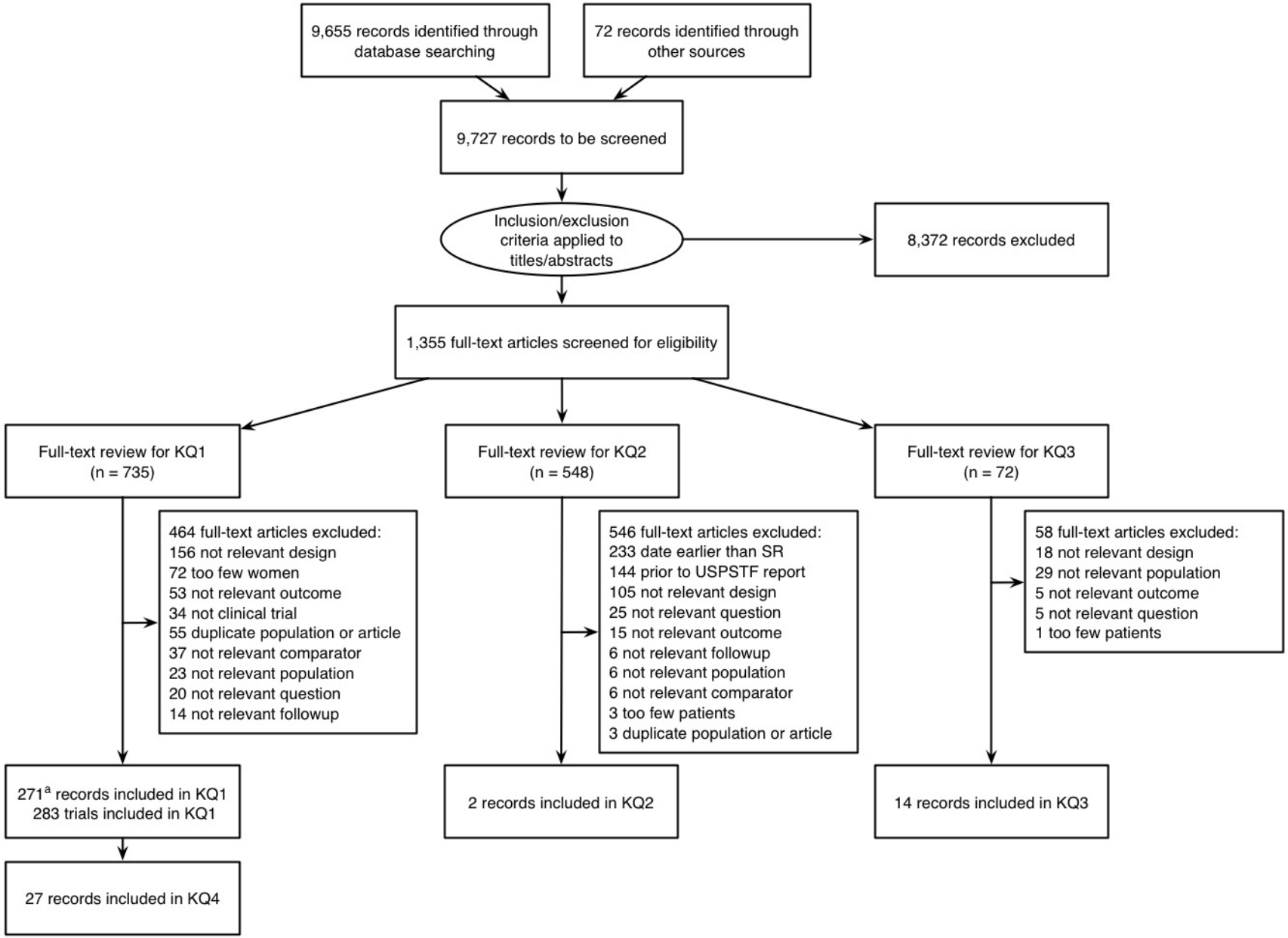
KQ4 results are organized by the six outcome categories, as listed in the KQ1 description.

Results of Literature Searches

The literature search identified 9,655 records, with an additional 72 records identified through the gray literature search and hand searching of bibliographies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[78] diagram shown in Figure 2 depicts the flow of search screening and study selection. From the total 9,727 abstracts screened, 1,355 full text articles were assessed for inclusion. For KQ1, 735 full text articles were screened, with 271 records included. Twelve of those records presented results for two distinct trials, so those publications were given two unique reference numbers and were counted as two trials, for a total of 283 trials included in KQ1. For KQ 2, a systematic review by Nelson et al.[28] published in May 2012, contained the most current literature review addressing the same outcomes in this Key Question. This systematic review therefore became the primary source for KQ2. For KQ3, 72 articles were screened, with 14 studies included: eight RCTs, two cohort studies, and four case control studies. Twenty-seven trials from KQ1 included subgroup analyses of interest and were the evidence base for KQ4.

The list of excluded studies with reasons for exclusion is presented in Appendix B.

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram



MA: meta-analysis; SR: systematic review; USPSTF: United States Preventive Services Task Force
[a] 12 records presented results from two distinct patient populations and were divided into 2 trials each

Key Question 1. Effectiveness of Different Treatments for Postmenopausal Symptoms

Description of Included Studies

Two hundred and fifty-four trials were included in this Key Question, providing results for the following outcomes: vasomotor symptoms (187 trials), quality of life (108 trials), psychological symptoms (90 trials), sexual function (76 trials), urogenital atrophy (63 trials), and sleep disturbance (48 trials). Some trials contributed results to more than one outcome.

Evidence synthesis was dependent on the number of trials with comparators and outcomes that could be appropriately pooled. When the number of trials allowed for a synthesis of outcomes by comparator group, either meta-analyses or pairwise comparisons were performed. Strength of evidence was then determined. When there were not enough trials for certain comparators and outcomes, synthesis was not possible and strength of evidence was not determined. Descriptions of these trials are provided.

Results for KQ1 are presented by outcome. Within each of these six categories, there are the following sections: a summary table of the included trials; a presentation of the quantitative synthesis (network meta-analysis and/or pairwise comparisons) for trial data amenable to pooling; a strength of evidence rating for synthesized evidence; a summary of the trials that were not amenable to a quantitative synthesis; and key points.

Navigating Key Question 1 Results

Owing to the use of different outcome scales all results were quantified in a standardized effect metric or a standardized mean difference (SMD). Interpreting results when continuous effect measures and multiple scales are used is challenging; it is difficult to infer proportions of women achieving minimally clinically important improvements.[79, 80] The GRADE Working Group has suggested alternative approaches to SMDs for analysis and interpretation of continuous outcomes—transformation to a common scale, conversion to relative or absolute effects, ratios of mean, and analysis in minimally important difference (MID) units. Still, none is a substitute for differences in clinically meaningful response between treatments. With the exception of vasomotor symptoms, the alternative approaches were judged less than satisfactory, owing to the large number of instruments used (e.g., the need to define an MID for each).

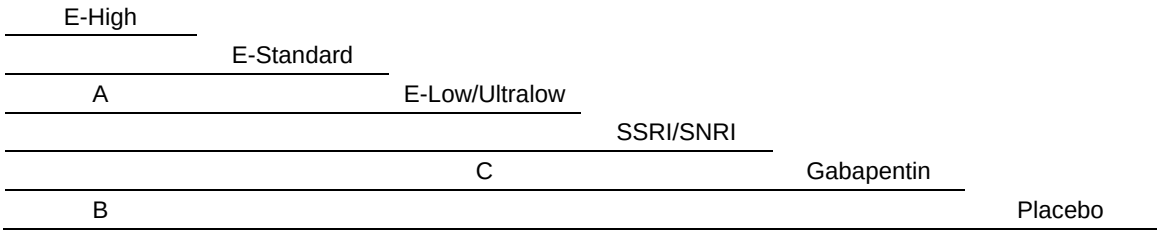
Still, as a guide for interpretation and as noted in the methods, with control-group event rates of 20 to 60 percent, SMDs can be expressed as odds ratios—magnitudes of -0.2, -0.3, -0.4, -0.5, 0.3, 0.6, and 0.75 corresponding to odds ratios of 0.7, 0.6, 0.5, 0.4, 2, 3, and 4 respectively. For example, the placebo response rate of women with vasomotor symptoms can range from approximately 20 to 40 percent.[81-83]

Except for sexual function and psychological outcomes, results are displayed first as a grid or matrix displaying comparisons among multiple treatments or agents. When a network meta-analysis was performed (vasomotor symptoms, quality of life, and sleep outcomes), all comparisons are represented as estimated by the model—direct and indirect. For pairwise results, only direct comparisons are displayed. Table 7 displays how comparisons are presented in the grid or matrix form. Forest plots for pairwise comparisons can be found in the appendixes. When a network meta-analysis was performed, a table of rank efficacy for treatments is shown. Finally, a graphical representation is provided as a caterpillar plot that summarizes all pooled estimates or

forest plots, which can be found in appendices. Note that for the network meta-analyses, the plot incorporates all possible comparisons between agents in the analyses, whereas for others, only pairwise pooled (not single-trial) comparisons are shown.

Strength of evidence ratings are provided in the text and in tabular form for comparisons with placebo involving multiple trials and between active comparators where multiple trials were able to be pooled (e.g., between different estrogen doses or routes of administration). All comparisons represented by single trials were judged insufficient.

Table 7. Comparison matrix example[a]



E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

[a] Estimate A represents comparison the of E-High (high-dose estrogen) with E-Low/Ultralow (low/ultralow dose estrogen); B represents the comparison of E-High with placebo; C represents the comparison of E-Low/Ultralow with gabapentin.

Strength of Evidence Ratings—Vasomotor Symptoms

Key Points

- A total of 211 trials including over 53,000 women examined treatment of vasomotor symptoms with prescription agents (estrogen, SSRIs, SNRIs, gabapentin, progestogens, eszopiclone, and clonidine) and nonprescription agents (isoflavones, black cohosh, vitamin E, flax seed, St. John's wort, ginseng, and a variety of herbs and other agents).
- Study quality was generally rated poor (75 percent). The sole funding source was industry for 105 trials and public for 31 trials. A combination of industry and public funding was noted in 12 trials. Funding was not identified for 63 trials.
- Amelioration of vasomotor symptoms was measured using a number of different patient-reported outcomes—most trials commonly included some metric of hot flushes.
- Strength of evidence of the comparative effectiveness of agents in relieving vasomotor symptoms is as follows:
    - There is **high** strength of evidence that estrogen is the most effective agent for relieving vasomotor symptoms. Combined results of trials that included a total of more than 22,000 women showed that the SMD is -0.5 or lower, corresponding to approximately 3 or fewer hot flushes per day, compared with placebo.
    - There is **high** strength of evidence that SSRIs or SNRIs improve vasomotor symptoms compared with placebo: SMD -0.35 (95% CI: -0.46 to -0.24; 13 trials, n=4,037).
    - There is **moderate** evidence that gabapentin improves vasomotor symptoms compared with placebo: SMD -0.28 (95% CI: -0.38 to -0.19; 5 trials, n=1,936).
    - There is **low** strength of evidence that isoflavones improve vasomotor symptoms compared with placebo: SMD -0.31 (95% CI: -0.41 to -0.22; 35 trials, n=4,022) owing to inconsistency, potential bias, and potential reporting bias.
    - There is **low** strength of evidence that, black cohosh (SMD -0.31, 95% CI: -0.46 to -0.15; 4 trials, n=663) or ginseng (SMD -0.17, 95% CI: -0.43 to 0.09; 3 trials, n=513) improve vasomotor symptoms compared with placebo.
    - There is insufficient evidence on the effectiveness of other agents.
- Analyses comparing effectiveness of treatments show estrogens alleviate vasomotor symptoms best, with the following mean rankings (1 being best, 9 worst—placebo ranked 8.9): high-dose estrogens (1.9), standard-dose estrogens (1.3), and low-dose estrogens (2.9). The nonhormone treatments were ranked much lower: SSRI/SNRI (4.9), gabapentin (5.6), isoflavones (5.9), black cohosh (6.7), and ginseng (7.0).

Included Trials

Of the 283 trials included in this review for KQ1, treatment effects on vasomotor symptoms were reported in 211 trials (74.6 percent). The trials included over 53,000 women enrolled at more than 3,800 sites. Twenty-two trials (10.4 percent) were multinational whereas 189 (89.6 percent) nonmultinational trials were conducted in 30 countries including Ecuador, Estonia, Greece, Islamic Republic of Iran, Norway, Singapore, Spain, Switzerland, Ukraine, Austria, Sweden, Thailand, Japan, Finland, Hong Kong, Netherlands, Brazil, Denmark, France, India, South Korea, Taiwan, China, Turkey, Australia, Canada, Germany, United Kingdom, Italy, and the United States (in order of increasing numbers with 71 United States trials).

The mean ages of women enrolled in individual trials ranged from 43.8 to 63.5 years (not reported in 28 trials). The average number years since menopause (4.1 years overall) was reported in 70 trials (33.1 percent). Race or ethnicity was reported in 76 trials (36.0 percent) (Table 8). The presence or absence of a uterus in women was stated in 158 trials (74.9 percent) and most (n=90, 42.7 percent) enrolled women in either category. Mean body mass index was noted in approximately two thirds of trials and ranged from 17.3 to 29.3 kg/m^2. Other trial characteristics are shown in Table 8.

Approximately two-thirds of trials randomized women to 2 arms and the remainder to multiple arms. Followup ranged from 4 weeks (for trials of centrally acting agents including SSRIs, SNRIs, and gabapentin) to more than 5 years with a mean of 24.7 weeks. The most commonly studied agents were hormones (116 trials, 55.0 percent) administered by various routes and isoflavones (40 trials, 19.0 percent). Agents examined in fewer trials included SSRIs, SNRIs, eszopiclone, clonidine, methyldopa, gabapentin, isoflavones, black cohosh, St. John's wort, ginseng, flax seed, vitamin E, dong quai, DHEA, other herbal ingredients, and combinations of nonprescription agents.

Vasomotor symptoms were ascertained and reported in different ways and in 93 trials (55.9 percent) using two or three metrics. The most common metric was hot flush frequency — daily or weekly (and both), but sometimes monthly. Daily occurrence was analyzed if reported, followed by weekly, and then monthly. Other instruments and metrics included hot flush severity, night sweats, indices combining frequency and severity of hot flushes, visual analogue scales, graphic rating scales, women experiencing greater than 50 or 80 percent improvement, and vasomotor scale components (e.g., Greene Climacteric Scale, MENQOL, WHQ, MRS, Kupperman Menopausal Index). The vasomotor domains of specific scales were as follows:

- Greene Climacteric Scale includes one hot flush and one night sweat item each rated 0 (none) to 3 (severe).
- WHQ includes one hot flush and one night sweat item rated as 0 (not at all) to 3 (definitely).
- MENQOL vasomotor domain includes hot flushes, night sweats, and sweating items scaled from 0 (not at all bothered) to 6 (extremely bothered).
- Kupperman Menopausal Index includes one hot flush item, scaled from 0 (none) to 3 (severe).
- MRS includes a rating of hot flushes and sweating, scaled from 0 (none) to 4 (very severe).

Some measure of hot flush frequency was reported in 132 trials (62.6 percent), hot flush severity in 63 (29.9 percent), night sweats in 25 (11.8 percent), combined hot flush and night sweats in 19 (9.0 percent), Greene vasomotor scale in 26 (12.3 percent), Kupperman vasomotor in 21 (10.0 percent), MENQOL vasomotor in 25 (11.8 percent), WHQ vasomotor in 11 (5.2 percent), MRS in 9 (4.5 percent), and another measure in 33 (15.6 percent). We included in the analyses the most commonly reported outcome metric (hot flush frequency) followed by next most common (severity) and so on. Overall, 147 (69.7 percent) trials reported hot flush frequency, severity, and or night sweats.

Most trials were rated as poor quality (n=158, 74.9 percent); 26 (12.3 percent) fair and 24 (11.4 percent) good quality. The funding source was not stated for 63 trials (29.9 percent), 105 (49.8 percent) appeared wholly industry sponsored, 12 (5.7 percent) reported some industry

funding, and 31 (14.7 percent) funding only from public sources. Table 8 displays further detail summarizing trial and patient characteristics.

Table 8. Characteristics of trials assessing efficacy of treatment on vasomotor symptoms

	Characteristic	Value
Trial Characteristics	Number of trials	211
	Total number of women	53,477
	Number of sites from trials that specified	3,832 1 to 502 (mean 23; median 4)
	Trials described only as multicenter	21 (10.0)
	Multicenter trials	126 (59.7)
	Two-arm trials	137 (64.9)
	Multi-arm trials	74 (35.1)
	Women per trial	50 to 2,974 (mean 253; median 153)
	Range of followup (weeks)	4 to 260 (mean 24.7; median 12)
Funding	Industry only	105 (49.8)
	Public only	31 (14.7)
	Industry and public	12 (5.7)
	Not stated	63 (29.9)
Comparator Category	Placebo vs. hormone	81 (38.4)
	SSRI/SNRI vs. placebo or other SSRI/SNRI	13 (6.2)
	Placebo vs. other prescription	7 (3.3)
	Placebo vs. nonprescription	69 (32.7)
	Placebo vs. hormone vs. nonprescription	3 (1.4)
	Hormone vs. hormone	27 (12.8)
	Hormone vs. nonprescription	5 (2.4)
	Nonprescription vs. SSRI/SNRIs	1 (0.5)
	Nonprescription vs. nonprescription	5 (2.4)
Study Quality	Good	24 (11.4)
	Fair	26 (12.3)
	Poor	158 (74.9)
	Not rated (abstract or gray literature)	3 (1.4)
Patient Demographics	Mean age (years)	43.8 to 63.5 (NR 28)
	Age range (years)	26.0 to 85.0 (NR 162)
	Years since menopause	4.1 (0.6 to 13.8) (NR 141)
	Current smokers (%)	0.0 to 44.0 (NR 166)
	Mean BMI (kg/m^2)	17.3 to 29.3 (NR 76)
	White (%)	0.0 to 100.0
	Black (%)	0.0 to 58.8
	Hispanic (%)	0.0 to 16.6
	Asian (%)	0.0 to 100.0
	Other (%)	0.0 to 41.0
Uterus Status	All intact	57 (27.0)
	All absent	11 (5.2)
	Mixed	90 (42.7)
	Range, percentage intact among trials with	22.5 to 99
	Not reported	53 (25.1)

Note: Demographics were not reported in all studies.
NR: not reported; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

Evidence Synthesis

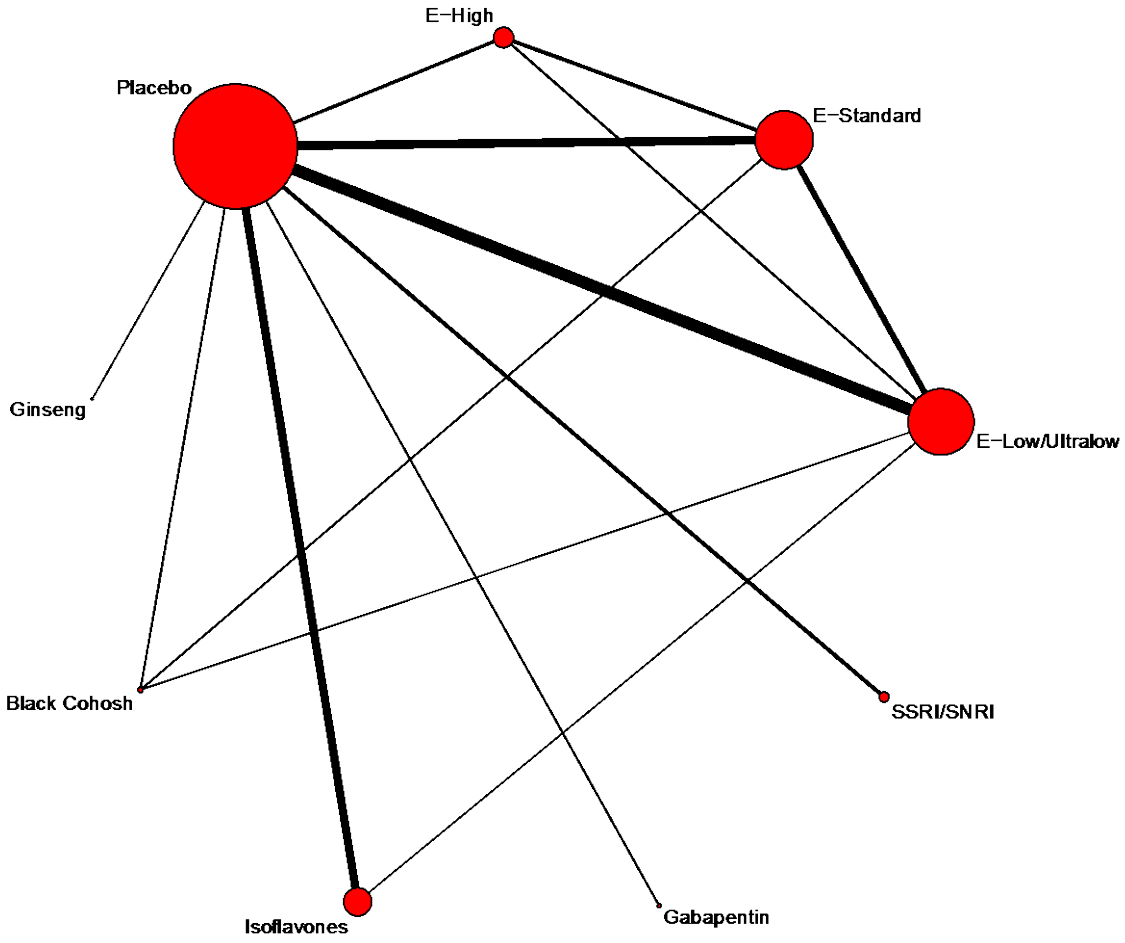
Meta-Analysis

Treatments studied in multiple trials and of likely greatest clinical interest included estrogens (high-, standard-, and low/ultralow-dose), SSRI/SNRIs, and gabapentin, isoflavones, black cohosh, and ginseng. Comparisons between one or more nonplacebo treatments were reported for all treatments except ginseng, and gabapentin. Comparative efficacy of these agents was examined in a network meta-analysis including results from 157 trials. Figure 3 displays the network of comparisons. Data were most extensive for estrogens (n=133 comparisons) followed by isoflavones (n=37), SSRI/SNRIs (n=14), black cohosh (n=8), gabapentin (n=5), and ginseng (n=3) (comparisons exceed trial total owing to multi-arm trials).

Four trials were examined only in sensitivity analyses owing to inconsistencies with the network and clinically or numerically improbable estimates. One trial[84] found black cohosh superior to fluoxetine (SMD -0.49, 95% CI: -0.94 to -0.05). SMDs from three trials were judged not numerically plausible—one reporting effectively complete resolution of hot flushes with both estrogen and isoflavones;[85] and two trials reported no placebo effect and SMD magnitudes inconsistent with other placebo comparisons (SMD -1.81 95% CI: -2.26 to -1.36 for black cohosh;[86] and -3.13, 95% CI: -4.33 to -1.94) for isoflavones[87]). The network estimates were otherwise generally consistent (Appendix F, Figure F-11 and Table F-1), but these results suggested examining the influence of black cohosh trial results. Additionally, owing to the large number of trials and their various reported characteristics, other sensitivity analyses were also performed. The set of sensitivity analyses included networks restricted to: 1) trials specifying vasomotor symptoms as a primary outcome or requiring symptoms for inclusion, 2) excluding trials judged to have included women without vasomotor symptoms, 3) excluding all black cohosh trials (owing to some evidence of inconsistency), 4) trials rated good or fair quality, 5) trials examining effects on moderate to severe hot flushes, and 6) excluding trials focused on disease prevention.

To facilitate interpreting effects across multiple scales that required pooling standardized effect sizes, we transformed effects[79, 80] to hot flush frequencies. Predicted comparative reductions in daily hot flushes corresponding to standardized effect sizes were obtained by fitting a regression model (piecewise being quadratic for SMDs less than 0 and linear otherwise) to pooled results from trials reporting hot flush reductions accompanying standard dose estrogen, low dose estrogen, and SSRI/SNRIs. The transformation from standardized effects to hot flush frequency reduction assumes that the relationship between SMDs and hot flushes can apply to the various scales. That assumption cannot be tested and the results therefore appropriately used to assist interpretation. However, as the majority of data pooled were obtained from some hot flush measure, the predicted estimates are plausibly accurate values, and are similar in magnitude reported in placebo comparison meta-analyses restricted to studies reporting hot flush frequencies.[25] Finally, these results were similar restricting the conversion to only trials reporting moderate-to-severe hot flushes.

Figure 3. Network of comparisons included in vasomotor analyses[a]



E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.
[a] Line thickness and circle area are proportional to the number of comparisons.

Table 9 and Figure 4 display estimated SMDs and 95% credible intervals from the fitted model. Negative values represent comparative improvements in vasomotor symptoms. In Table 10, the bottom row shows SMDs comparing each treatment with placebo, the next row up SMDs comparing each treatment with ginseng, and so forth. Of all comparators, estrogens appeared the most effective relieving vasomotor symptoms; only the credible interval for the indirect comparison of low/ultralow dose estrogens with gabapentin did not exclude 0. The magnitudes of effect for SSRI/SNRIs, isoflavones, gabapentin, black cohosh, and ginseng were substantially lower. Table 10 and Figure 5 display rankings of efficacy with estrogens consistently the highest ranked, followed by SSRI/SNRIs, gabapentin, isoflavones, black cohosh, and ginseng. Similar results for effect magnitudes were obtained across the sensitivity analyses, with some differences in credible intervals and rankings attributable to smaller numbers of included trials (Appendix F, Tables F-2 through F-13).

Figure 6 displays effects transformed to comparative daily hot flush frequency reductions. Compared with placebo, estrogens were accompanied by reductions between two to three hot flushes per day, while the remainder of agents by approximately one or fewer.

Finally, Table 11 displays results from pairwise meta-analyses for all direct comparisons. Heterogeneity was evident for comparisons of standard dose estrogen and isoflavones with placebo—both including a large number of comparisons. This is most likely attributable to underlying clinical heterogeneity and samples of women having a wide range of symptoms.

Estrogen Compared With Placebo

There were 101 pairwise comparisons of placebo with estrogen—nine high-dose (one good, one fair, and seven poor quality trials), 39 standard dose (three good, six fair, and 30 poor quality trials), and 53 with low/ultralow dose (two good, nine fair, and 42 poor quality trials). The magnitudes of pooled SMDs for all doses of estrogen were comparatively large and the estimates precise. Although most trials were rated poor quality, given consistency over a large number of comparisons the strength of evidence that estrogens (of any dose) improve hot flush symptoms is rated high.

Estrogen Compared With Estrogen

Comparisons among estrogens included 12 high versus standard dose (one good, one fair, and 10 poor quality trials), five high versus low/ultralow dose (all poor quality trials), and 24 standard versus low/ultralow dose (one good, four fair, and 19 poor quality trials). Direct effects were derived from 41 trials, of which, five were rated as good or fair quality. Pooled estimates differed only between standard and low/ultralow dose categories. However, heterogeneity was substantial in the pairwise analysis (tau^2=0.02 or a between-study effect standard deviation of 0.14). Moreover, there was no apparent dose-response across high, standard, and low/ultralow dose estrogens compared with placebo—respective SMDs -0.50, -0.64, and -0.55. The strength of evidence that there is similar improvement in vasomotor symptoms across estrogen doses is rated moderate.

Isoflavones Compared With Placebo

There were pairwise comparisons of isoflavones with placebo included from 35 trials (five good, two fair, and 28 poor quality). The funnel plot and Egger test (p=0.017) were consistent with possible publication bias. Limiting the pairwise analysis to the seven fair and good quality trials yielded an SMD of -0.12 (95% CI: -0.31 to -0.08; tau^2=0.04). SMDs in seven trials favored placebo (see Figure F-5 in Appendix F). The strength of evidence that isoflavones improve hot flush symptoms compared with placebo is rated low.

Gabapentin Compared With Placebo

Comparisons of gabapentin with placebo were pooled from five trials (one good and two poor quality; two trials not rated owing to lack of complete publication). The estimated SMD was precise and significantly different from placebo. The strength of evidence that gabapentin improves hot flush symptoms compared with placebo is rated moderate**.**

SSRI/SNRI Compared With Placebo

There were 13 comparisons of SSRIs or SNRIs (including escitalopram, venlafaxine, desvenlafaxine, citalopram, fluoxetine, and paroxetine) with placebo (four good, three fair, and

six poor quality trials). The SMD was precise and effect differed from placebo (-0.37; 95% CrI: -0.51 to -0.23), was similar limited to the good and fair quality trials in a pairwise analysis (-0.33; 95% CI: -0.42 to -0.24; tau^2=0.006), or those of venlafaxine or desvenlafaxine alone (-0.36; 95% CI: -0.55 to -0.17; tau^2=0.04; 6 trials). The strength of evidence that SSRIs or SNRIs improve hot flush symptoms compared with placebo is rated high**.**

Black Cohosh Compared With SSRI

Oktem et al.[84] compared black cohosh with fluoxetine for treatment of menopausal symptoms—120 randomized women with 85 (70.1 percent) women evaluated at 12 weeks. Trial quality was rated poor. Using a "monthly hot flush score" the authors reported black cohosh superior to fluoxetine SMD of -0.49 (95% CI: -0.94 to -0.05). (As noted earlier, this trial result was not included in the network owing to inconsistency.)

Black Cohosh Compared With Placebo

Four trials compared black cohosh with placebo (two poor and two good quality) with a pooled SMD of -0.24 (95% CrI: -0.46 to -0.03). The strength of evidence that black cohosh improves hot flush symptoms compared with placebo is rated low.

Ginseng Compared With Placebo

Three trials compared ginseng with placebo (one fair and two poor quality)[88, 89] yielding a pooled SMD of -0.20 (95% CrI: -0.51 to 0.12). The strength of evidence that ginseng improves vasomotor symptoms compared with placebo is rated low.

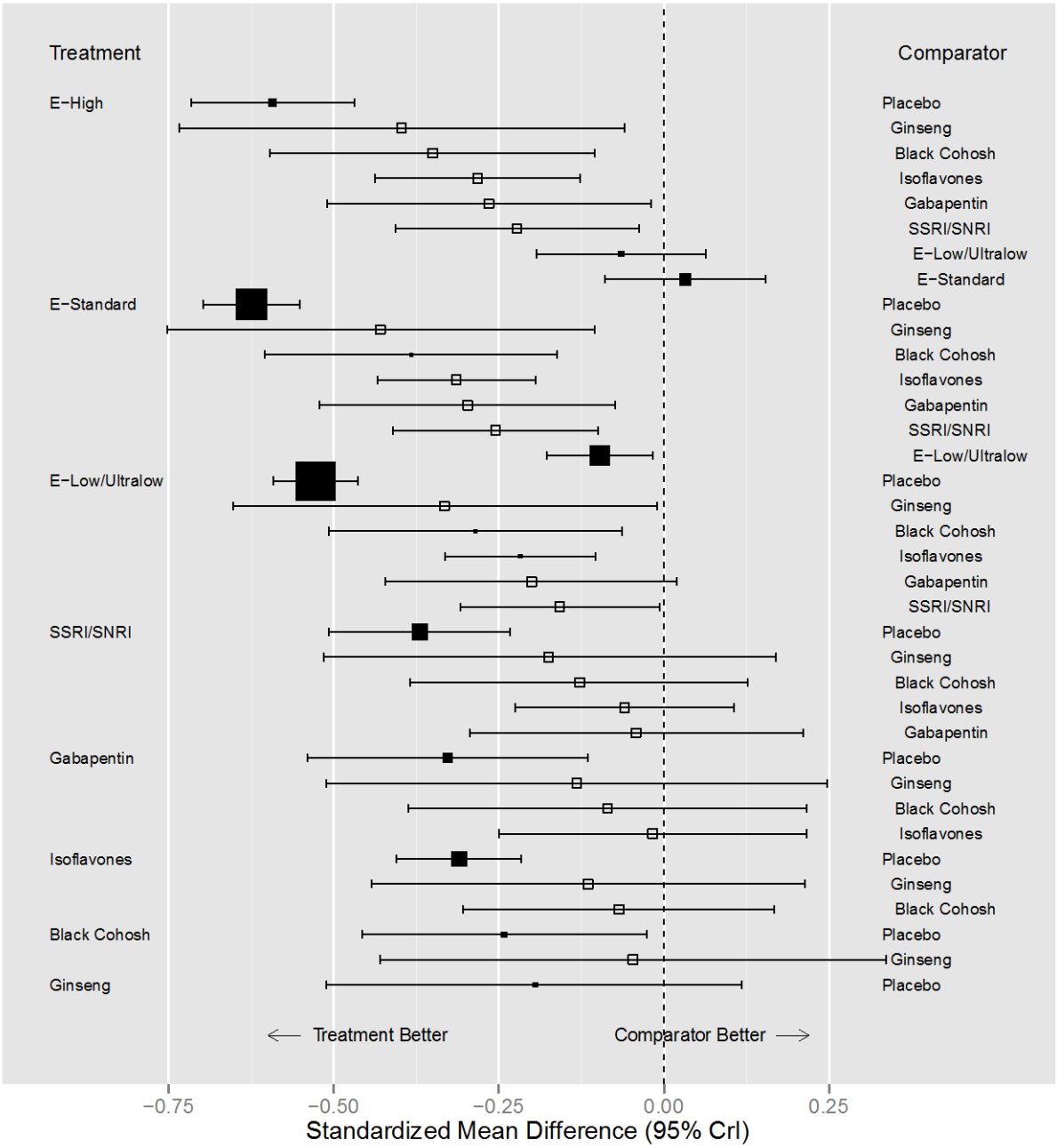
Table 9. Vasomotor symptoms estimates of comparative efficacy as standardized mean differences and 95% credible intervals from network meta-analysis[a]

E-High								
0.03 (-0.09 to 0.15)	E-Standard							
-0.06 (-0.19 to 0.06)	-0.10 (-0.18 to -0.02)	E-Low/Ultralow						
-0.22 (-0.41 to -0.04)	-0.26 (-0.41 to -0.10)	-0.16 (-0.31 to -0.01)	SSRI/SNRI					
-0.27 (-0.51 to -0.02)	-0.30 (-0.52 to -0.07)	-0.20 (-0.42 to 0.02)	-0.04 (-0.29 to 0.21)	Gabapentin				
-0.28 (-0.44 to -0.13)	-0.31 (-0.43 to -0.19)	-0.22 (-0.33 to -0.10)	-0.06 (-0.23 to 0.11)	-0.02 (-0.25 to 0.22)	Isoflavones			
-0.35 (-0.60 to -0.11)	-0.38 (-0.61 to -0.16)	-0.29 (-0.51 to -0.06)	-0.13 (-0.38 to 0.13)	-0.09 (-0.39 to 0.22)	-0.07 (-0.30 to 0.17)	Black Cohosh		
-0.40 (-0.73 to -0.06)	-0.43 (-0.75 to -0.11)	-0.33 (-0.65 to -0.01)	-0.17 (-0.52 to 0.17)	-0.13 (-0.51 to 0.25)	-0.12 (-0.44 to 0.21)	-0.05 (-0.43 to 0.34)	Ginseng	
-0.59 (-0.72 to -0.47)	-0.62 (-0.70 to -0.55)	-0.53 (-0.59 to -0.46)	-0.37 (-0.51 to -0.23)	-0.33 (-0.54 to -0.12)	-0.31 (-0.41 to -0.22)	-0.24 (-0.46 to -0.03)	-0.20 (-0.51 to 0.12)	Placebo

E: estrogen; Gabap: SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

[a] Treatments are ordered left to right generally from most to least comparative efficacy. Highlighted effects are those where the credible interval does not overlap zero. The negative effects reflect improvement (lower on the symptom scale) for the agent on the left versus comparator to its right from intersecting treatments listed on the diagonal.

Figure 4. Caterpillar plot displaying all vasomotor symptoms comparisons included in the network analysis and 95% credible intervals[a]



E: estrogen; Ulow: ultralow; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SMD: standardized mean difference; CrI: credible interval

[a] Symbol size is proportional to the number of women included in the comparison. Open squares represent effects estimated entirely through indirect comparison.

Table 10. Vasomotor symptoms rankings of comparative efficacy, standard deviations, and 95% credible intervals

Treatment	Mean Rank	SD	Median Rank	95% CrI
E-High	1.9	0.7	2	(1 to 3)
E-Standard	1.3	0.5	1	(1 to 2)
E-Low/Ultralow	2.9	0.5	3	(2 to 4)
SSRI/SNRI	4.9	1.1	5	(4 to 7)
Gabapentin	5.6	1.4	5	(3 to 8)
Isoflavones	5.9	1.0	6	(4 to 8)
Black Cohosh	6.7	1.3	7	(4 to 8)
Ginseng	7.0	1.6	8	(4 to 9)
Placebo	8.9	0.3	9	(8 to 9)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

Figure 5. Rankings and 95% credible intervals of treatments included in the network analysis from best to worst

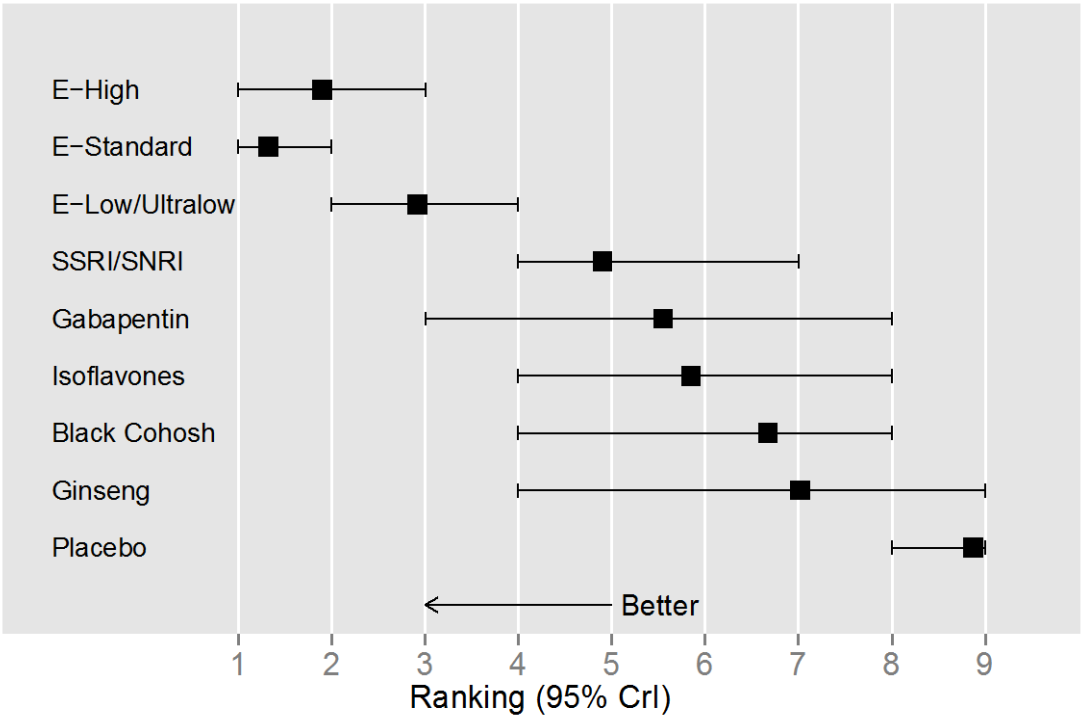
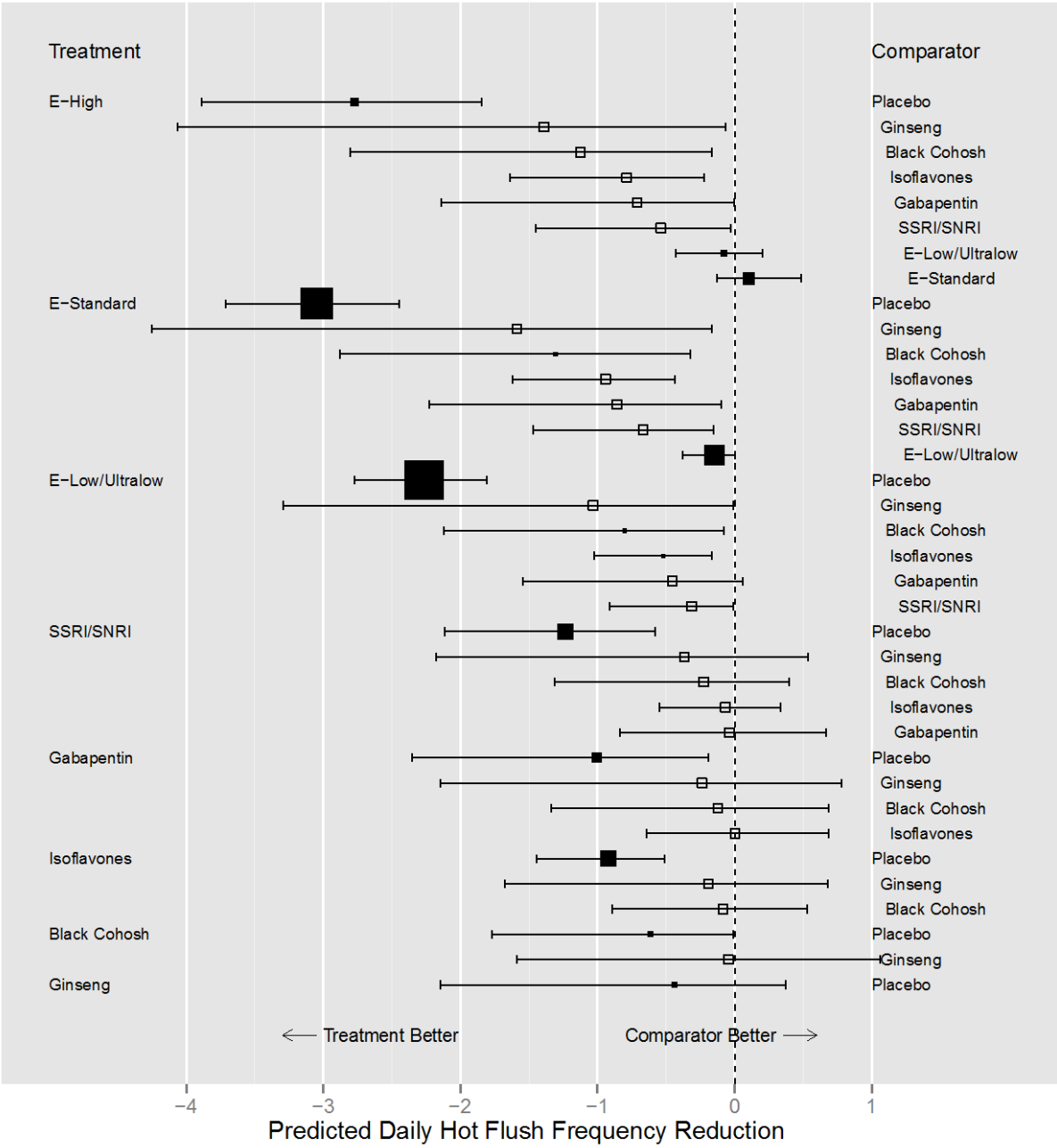


Figure 6. Caterpillar plot displaying all vasomotor symptoms comparisons included in the network analysis and 95% credible intervals as predicted difference in daily hot flush frequency reductions[a]



E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SMD: standardized mean difference; CrI: credible interval.

[a] Predicted estimates assume that the relationship between SMDs and hot flushes can extend to the scales pooled. Symbol size is proportional to the number of women included in the comparison. Open squares represent effects estimated entirely through indirect comparison.

Table 11. Vasomotor symptoms pairwise SMDs (pooled random effect estimates or single-trial effects if only data available)

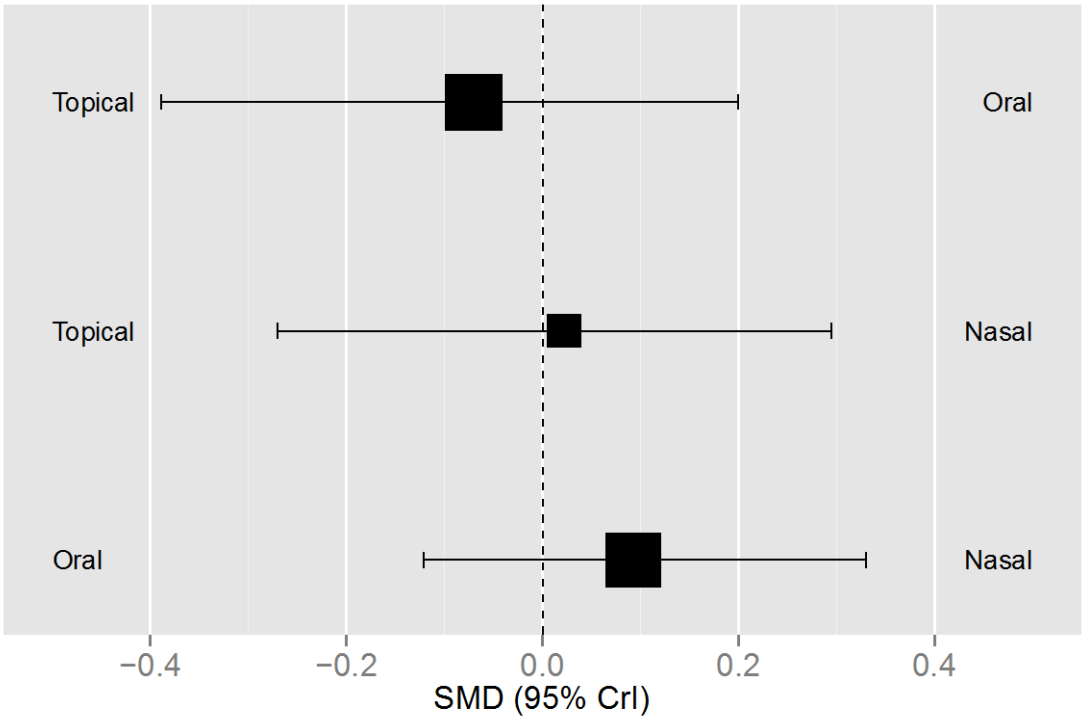
E-High								
-0.03 (-0.14 to 0.09) tau^2=0.02;n=12	E-Standard							
-0.02 (-0.17 to 0.13) tau^2=0.00;n=5	-0.14 (-0.23 to -0.05) tau^2=0.02;n=24	E-Low/Ultralow						
			SSRI/SNRI					
				Gabapentin				
		-0.38 (-0.89 to 0.13)			Isoflavones			
	-0.87 (-1.19 to -0.55) tau^2=0.00;n=2	0.08 (-0.41 to 0.57)				Black Cohosh		
							Ginseng	
-0.50 (-0.61 to -0.39) tau^2=0.00;n=9	-0.64 (-0.74 to -0.53) tau^2=0.08;n=39	-0.55 (-0.61 to -0.48) tau^2=0.03;n=53	-0.35 (-0.46 to -0.24) tau^2=0.02;n=13	-0.28 (-0.38 to -0.19) tau^2=0.00;n=5	-0.31 (-0.41 to -0.22) tau^2=0.04;n=35	-0.31 (-0.46 to -0.15) tau^2=0.00;n=4	-0.17 (-0.43 to 0.09) tau^2=0.02;n=3	Placebo

E: estrogen; Ulow: ultralow; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SMD: standardized mean difference; CrI: credible interval; N: number of trials.

Different Routes of Estrogen Administration

Ten trials[90-99] compared different routes (oral, topical, and nasal) of estrogen administration employing similar doses (one good and nine poor quality). Nine trials used a standard estrogen dose. Routes of administration were compared in network analysis demonstrating no differences between routes. Results are displayed in Figure 7. All credible intervals overlapped and SMDs were close to 0 (topical versus oral: -0.07, 95% CrI: -0.39 to 0.20; topical versus nasal: 0.02, 95% CrI: -0.27 to 0.29; oral versus nasal: 0.09, 95% CrI: -0.12 to 0.33). The strength of evidence that the effect of estrogens improving vasomotor symptoms does not differ according to route of administration is rated high.

Figure 7. Comparison of different estrogen routes on vasomotor symptoms[a]



[a] Results obtained from a network analysis of 11 different route comparisons from 10 trials. Symbol sizes proportional to the number of women included in each comparison.

Trials Not Pooled

If there were fewer than three trials with the same comparators, pooled analyses (meta-analysis or paired comparisons) could not be performed.

Progesterone and Other Hormones Compared With Placebo

Five trials (Table 12) were identified that compared progesterone in different doses, either with estrogen[100, 101] or alone,[102-104] for relief of vasomotor symptoms. Three of the trials administered progesterone through a cream,[102-104] one through a patch,[100] and one orally.[101] Among the trials using cream, one found significant vasomotor symptom relief with low doses of progesterone,[104] with a standard mean difference of -1.67 (95% CI: -2.26 to -1.06). The other two progesterone cream trials report no significant symptom relief.[102, 103] Rozenberg et al. reported that both sequential and continuous administrations of transdermal estrogens/progesterones were

as effective as a combination estrogen patch and oral progesterones.[100] Gambacciani et al. reported equally significant improvements in vasomotor symptoms among several combinations of estrogens/progesterones.[101] Because trials studied different therapy combinations, the strength of evidence was not rated.

Table 12. Trials comparing placebo with progestogens reporting vasomotor outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI); or p-value
Benster 2009[102]	Placebo	—	36	Cream	24	Fair	—
	Progesterone	5	44	Cream			-0.19 (-0.64 to 0.25)
	Progesterone	20	40	Cream			-0.21 (-0.67 to 0.24)
	Progesterone	40	37	Cream			-0.26 (-0.73 to 0.20)
	Progesterone	60	32	Cream			-0.44 (-0.92 to 0.05)
Wren 2003[103]	Placebo	—	36	Cream	12	Poor	—
	Progesterone	32	32	Cream			-0.41 (-0.85 to 0.03)
Leonetti 1999[104]	Placebo	—	47	Cream	52	Poor	—
	Progesterone	20	43	Cream			-1.66 (-2.26 to -1.06)
Rozenberg 1997[100]	Estradiol + NETA	0.05 E + 1 P	153	Oral[a]	52	Poor	—
	Estradiol + NETA	0.05 E + 0.17 P[b]	154	Patch			0.03 (-0.19 to 0.26)
	Estradiol + NETA	0.05 E + 0.35 P[b]	158	Patch			0.00 (-0.22 to 0.22)
	Estradiol + NETA	0.05 E + 0.17 P[c]	153	Patch			0.01 (-0.22 to 0.23)
	Estradiol + NETA	0.05 E + 0.35 P[c]	156	Patch			0.02 (-0.20 to 0.24)
Gambacciani 2005[101]	Estradiol + trimegestone	1 E + 0.125 P	432	Oral	104	Poor	—
	Estradiol + norethisterone	1 E + 0.5 P	242	Oral			0.04 (-0.12 to 0.19)
	Estradiol + norethisterone	2 E + 1 P	176	Oral			-0.11 (-0.28 to 0.07)

[a] The reference group was randomized 1:1 to receive an estrogen patch and the progestin orally either by 20 mg daily dydrogesterone or 1 mg for 2 weeks norethisterone
[b] Estradiol and NETA combined
[c] Estradiol and NETA sequential
SMD: standardized mean difference; CI: confidence interval; E: estrogen; NETA: norethisterone acetate; P: progestogen; NS: not significant; FU: followup; Wks: weeks.

Other Prescription Agents Compared With Placebo

One trial compared eszopiclone, a sedative hypnotic, with placebo for the relief of vasomotor symptoms (Table 13).[105] In this randomized, double-blind, placebo-controlled crossover trial, half the participants (n=30) received eszopiclone patches for four weeks, followed by a two-week washout period, and then four weeks of placebo patches. The other half of the participants (n=29) received the placebo patches first, followed by the eszopiclone patches. There was no difference between eszopiclone and placebo in the relief of vasomotor symptoms.[105]

One trial compared clonidine with placebo and reported mean change in weekly hot flushes (Table 13).[106] In this double-blind, placebo-controlled crossover trial, treatment lasted four weeks. Treatment with clonidine resulted in 19.2 fewer hot flushes per week while 13.1 fewer hot flushes per week were reported during the placebo phase. The SMD was -0.08 (95% CI: -0.51 to 0.35).

Table 13. Trials comparing placebo with other prescription agents reporting vasomotor outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Joffe 2010[105]	Placebo	—	29	Oral	4	Poor	—
	Eszopiclone	3	30	Oral			NS
Clayden 1974[106]	Placebo	—	43	Oral	4	Poor	—
	Clonidine	0.05-0.15	42	Oral			-0.08 (-0.51 to 0.35)

SMD: standardized mean difference; CI: confidence interval; NS: not significant; FU: followup; Wks: weeks.

Other Nonprescription Agents Compared With Placebo

Twenty-seven trials, not appropriate for pooling, compared nonprescription treatments with placebo for the relief of vasomotor symptoms (Table 14). Nonprescription treatments included various herbal or plant extracts,[107-125] black cohosh,[126-128] St. John's wort,[126, 128, 129] DHEA,[130] and other nutritional supplements.[131-133] Eleven of the trials showed significant improvements in vasomotor symptoms compared with placebo: two trials which combined black cohosh with St. John's wort,[126, 128] and one trial each of Nutrafem® (mung beans and eucommia bark),[108] pine extract,[110] isoflavones/lactobacilli/magnolia bark,[111] rheum rhaponticum,[112] Femal® (pollen and pistol extract),[113] Estro-G 100 (cynanchum wilfordii, phlomis umbrosa, angelica gigas),[119] Jiawei Qing'e Fang,[120] a combination of Chinese herbs,[123] and a combination of micronutrients.[133] The variety of treatments and dosages among these 27 trials did not allow for pooling effects.

Table 14. Trials comparing nonprescription agents with placebo reporting vasomotor outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Weeks	Study Quality	SMD (95% CI)
Haines 2008[107]	Placebo	—	39	Oral	26	Poor	—
	Dang gui and huang qi	3000	45	Oral			0.38 (-0.05 to 0.82)
Garcia 2010[108]	Placebo	—	28	Oral	12	Poor	—
	Nutrafem®[a]	300	103	Oral			-0.52 (-0.94 to -0.10)
van der Sluijs 2009[109]	Placebo	—	46	Oral	16	Good	—
	Plant extracts[b]	3820	46	Oral			0.12 (-0.29 to 0.53)
van Die 2009[129]	Placebo	—	50	Oral	16	Good	—
	St. John's wort	900	50	Oral			0.28 (-0.11 to 0.68)
Yang 2007[110]	Placebo	—	75	Oral	24	Poor	—
	Pine extract	200	80	Oral			-0.47 (-0.79 to -0.15)
Chung 2007[126]	Placebo	—	35	Oral	12	Poor	—
	Black cohosh/St. John's wort	84	42	Oral			-0.53 (-0.99 to -0.07)
Mucci 2006[111]	Placebo	—	45	Oral	24	Poor	—
	Isoflavones, lactobacilli, magnolia bark	60	44	Oral			-0.72 (-1.15 to -0.28)
Heger 2006[112]	Placebo	—	55	Oral	12	Poor	—
	Rheum rhaponticum	4	54	Oral			-0.64 (-1.03 to -0.26)
Winther 2005[113]	Placebo	—	27	Oral	13	Good	—
	Femal®[c]	80	26	Oral			-0.60 (-1.16 to -0.04)
Verhoeven, 2005[127]	Placebo	—	64	Oral	12	Good	—
	Isoflavones/black cohosh	50	60	Oral			-0.15 (-0.51 to 0.20)
Davis 2001[114]	Placebo	—	27	Oral	12	Poor	—
	12 Chinese herbs	—	28	Oral			0.46 (-0.08 to 1.00)
Hirata 1997[115]	Placebo	—	36	Oral	24	Poor	—
	Dong quai	4500	35	Oral			0.22 (-0.25 to 0.69)
Chenoy 1994[116]	Placebo	—	28	Oral	26	Poor	—
	Primrose oil	4000	26	Oral			NS
Hsu 2011[117]	Placebo	—	25	Oral	52	Poor	—
	Dioscorea alata	24	25	Oral			-0.41 (-0.98 to 0.15)

Table 14. Trials comparing nonprescription agents with placebo reporting vasomotor outcomes (continued)

Trial	Treatment	Dose (mg)	N	Route	FU Weeks	Study Quality	SMD (95% CI)
Uebelhack 2006[128]	Placebo	—	143	Oral	16	Good	—
	Black cohosh/St. John's wort	3.75	151	Oral			-0.85 (-1.09 to -0.61)
Dodin 2005[131]	Placebo	—	94	Oral	52	Fair	—
	Flaxseed	40,000	85	Oral			-0.05 (-0.34 to 0.24)
Barnhart 1999[130]	Placebo	—	30	Oral	12	Poor	—
	DHEA	50	30	Oral			-0.22 (-0.73 to 0.29)
Andrikoula 2011[132]	Placebo	—	33	Oral	12	Poor	—
	Nutritional supplement[d]	—	35	Oral			0.22 (-0.26 to 0.70)
Auerbach 2012[118]	Placebo	—	38	Oral	12	Poor	—
	Pomegranate seed oil	0.254	43	Oral			-0.30 (-0.75 to 0.14)
Chang 2011[119]	Placebo	—	32	Oral	12	Fair	—
	EstroG-100®[e]	—	29	Oral			-0.67 (-1.20 to -0.15)
Xia 2012[120]	Placebo	—	32	Oral	12	Good	—
	Jiawei Qing'e Fang	3500	32	Oral			-0.76 (-1.27 to -0.25)
von Hagens 2012[121]	Placebo	—	30	Oral	12	Poor	—
	Anthroposophic remedy		62	Oral			0.17 (-0.27 to 0.60)
Yang 2012[122]	Placebo	—	100	Oral	24	Poor	—
	Chinese herbal preparation[f]	Varied[f]	105	Oral			-0.13 (-0.41 to 0.14)
Zhong 2013[123]	Placebo	—	54	Oral	12	Fair	—
	Chinese herbs[g]	15,000	54	Oral			-0.40 (-0.78 to -0.01)
Plotnikoff 2011[124]	Placebo	—	59	Oral	13	Good	—
	Keishibukuryogab[h]	7,500	62	Oral			-0.07 (-0.49 to 0.35)
	Keishibukuryogab	12,500	57	Oral			-0.17 (-0.59 to 0.26)
Kohama 2013[125]	Placebo	—	77	Oral	12	Poor	—
	Maritime pine bark	30	79	Oral			-0.17 (-0.54 to 0.21)
Pandit 2012[133]	Placebo	—	25	Oral	12	Poor	—
	Micronutrient	—	29	Oral			-0.99 (-1.78 to -0.21)

SMD: standardized mean difference; CI: confidence interval; DHEA: dehydroepiandrosterone; FU; followup; NA: not applicable
[a] combination of Mung beans, Eucommia bark
[b] combination of black cohosh, er xian tang, zhi bai di huang wan
[c] combination of pure pollen, pollen/pistil extract
[d] combination of 21 vitamins and minerals
[e] combination of cynanchum wilfordii, phlomis umbrosa, angelica gigas
[f] either Gengnianningxin capsule if yin deficiency or Bushen oral liquid for yang deficiency
[g] combination of xian mao, xian ling pi, ba ji tian, dang gui, zhi mu, huang bai
[h] combination of cinnamon bark, peony root, peach kernel, poria sclerotium, and moutan bark

Estrogen Compared With a Nonprescription Agent

Two trials (Table 15) compared estrogen, with or without progestin, with a nonprescription treatment, pueraria mirifica[134] and licorice[135] in one trial each, for the relief of vasomotor symptoms. Pueraria mirifica is a highly estrogenic herb found in Thailand and licorice is a plant with estrogenic properties. In the pueraria mirifica trial, both hormone therapy and pueraria mirifica reduced hot flushes equally well. After three months of followup, pueraria mirifica reduced the average Greene score from 2.1 to 0.55 and estrogen treatment reduced the score from 2.1 to 0.35.[134] In the licorice trial, only the estrogen and progestin treatment significantly reduced the number of hot flushes, though the difference between the two treatment groups was not significant.[135]

Table 15. Trials comparing estrogen with a nonprescription agent reporting vasomotor outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Chandeying 2007[134]	CEE + MPA	0.625 E + 2.5 P	30	Oral	24	Poor	—
	Pueraria mirifica	50	30	Oral			NS
Menati 2014[135]	CEE + MPA	0.312 E + 2.5 P	26	Oral	12	Poor	—
	Licorice	1140	26	Oral			-0.18 (-0.73 to 0.37)

SMD: standardized mean difference; CI: confidence interval; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; E: estrogen; P: progestin; FU: followup; Wks: weeks.

Nonprescription Agents Compared

Four trials (Table 16) compared nonprescription agents for relief of vasomotor symptoms. In one trial, two different doses of pueraria mirifica were equally effective in relieving vasomotor symptoms,[136] and in another trial, two different doses of isoflavones were equally effective in relieving vasomotor symptoms.[137] One trial compared isoflavones alone with isoflavones and magnolia bark. Both treatments were equally effective in relieving vasomotor symptoms.[138] In a trial comparing vitamin E with isoflavones, isoflavones significantly improved vasomotor symptoms compared with vitamin E. After one year followup, 41.9 percent of the isoflavones group report no more hot flushes and 16.1 percent of the vitamin E group report no more hot flushes ($p<0.05$).[139]

Table 16. Trials comparing nonprescription agents reporting vasomotor outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Agosta 2011[138]	Isoflavones	60	301	Oral	12	Poor	—
	Isoflavones/magnolia bark	60	335	Oral			NS
Virojchaiwong 2011[136]	Pueraria mirifica	25	26	Oral	26	Poor	—
	Pueraria mirifica	50	26	Oral			-0.23 (-0.78 to 0.32)
Zervoudis 2008).[139]	Vitamin E	500 UI	31	Oral	52	Poor	—
	Isoflavones	NR	31	Oral			-0.72 (-1.38 to -0.06)
Yang 2012[137]	Isoflavones	35	57	Oral	24	Poor	—
	Isoflavones	70	50	Oral			0.08 (-0.30 to 0.46)

SMD: standardized mean difference; CI: confidence interval; NS: not significant; UI: international unit; NR: not reported; FU: followup; Wks: weeks.

Trials Without Quantifiable or Poolable Data

Five trials lacked sufficient data to estimate an effect size or would have yielded a problematic estimate. Results of these trials would not have affected the overall outcomes presented above.

Raynaud et al. conducted a three-arm trial using transdermal patches with low, standard, and high doses of estrogen.[140] All doses were considered effective, using percent reporting greater than a 50 percent reduction in weekly hot flushes as an outcome: 99.2 percent of women treated with the low dose patch, 100 percent of women treated with the standard dose patch, and 97 percent of the women treated with the high dose patch.[140]

Hidalgo et al. conducted a trial comparing two different doses of a treatment that combined isoflavones, primrose oil, and vitamin E. Both doses worked similarly in reducing the Blatt-Kuperman hot flush score.[141]

A trial comparing oral (n=35), gel (n=25), and patch (n=28) administrations of estrogen with or without progestogen collected information on complete symptom relief of vasomotor

symptoms. The authors reported the following percentages experiencing complete vasomotor symptom relief: oral 62 percent, gel 95 percent, and patch 100 percent.[99]

In the series of SMART (Selective estrogens, Menopause, And Response to Therapy) trials, low and standard doses of conjugated estrogens were combined with different doses of bazedoxifene and compared with placebo. The SMART-1 trial performed on analysis on a subset of subjects who had greater than or equal to seven moderate to severe hot flushes per day (n=216). Lobo et al. reported that all treatment dosages significantly reduced the frequency of hot flushes, but the number in each treatment group was not provided.[142]

Gupta et al. conducted a trial comparing conjugated equine estrogen, DHEA, and placebo. The authors did not report the proportions of women experiencing vasomotor symptoms at baseline for any of the groups. At followup, 36 percent of the placebo group, 12 percent of the estrogen group, and 16 percent of the DHEA group reported hot flushes.[143]

Strength of Evidence Ratings—Vasomotor Symptoms

Table 17 summarizes strength of evidence ratings.

Table 17. Strength of evidence ratings domains for vasomotor symptoms

Number of Comparisons	Comparators[a]			Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Downgrading Rationale
101	**Estrogen**	vs	Placebo	M	C	D	P	U	High	—
41	**Estrogen**	vs	**Estrogen (different dose)**	M	I	D	P	U	Mod	Standard appeared better than low/ultralow dose but a small effect size, lack of dose-response; 2 good, 5 fair, 34 poor quality trials
13	**SSRI/SNRI**	vs	Placebo	M	C	D	P	U	High	4 good, 3 fair, and 6 poor quality trials
35	**Isoflavones**	vs	Placebo	M	I	D	P	S	Low	5 good, 2 fair, and 28 low quality trials; pooled SMD in good/fair quality trials 63 percent lower; suspected publication bias; SMDs in 7 trials were greater than 0
5	**Gabapentin**	vs	Placebo	H	C	D	P	U	Mod	1 good and 2 poor quality trials; 2 trials not rated owing to lack of complete publication
4	**Black cohosh**	vs	Placebo	H	C	D	I	U	Low	2 good and 2 poor quality trials
3	**Ginseng**	vs	Placebo	H	C	D	I	U	Low	1 fair and 2 poor-quality trials; CI overlapping 0
11	**Estrogen route a**	vs	**Estrogen route b**	M	C	D	P	U	High	1 good and 9 poor quality trials (2 comparisons from 1 trial)

Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I), Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S), Undetected (U).

[a] Bold font of comparator indicates the more effective treatment; if both comparators are bold, the treatments are equivalently effective

SOE: strength of evidence; Mod: moderate; CI: confidence interval.

Quality of Life

Key Points

- A total of 125 trials including over 58,000 women reported some measure of quality of life or general well-being after treatment with prescription (estrogen, SSRIs, SNRIs) and nonprescription agents (isoflavones, black cohosh, vitamin E, flax seed, ginseng, and a variety of herbs and other agents).
- Study quality was generally rated poor (73 percent). Industry was reported as the sole funding source for 55 trials, 22 trials were supported by public funds alone, and a combination of industry and public funding in 9 trials. Funding support was not stated for 39 trials.
- Results were reported from a variety of scales—a majority used menopause-specific instruments.
- Strength of evidence of the comparative effectiveness of agents for improving measures of quality-of-life scores is as follows:
    - There is **high** strength of evidence that estrogen of any dose is effective improving measures of quality of life compared with placebo. Combined results of trials that included a total of more than 35,000 women showed SMDs between 0.40 and 0.55 compared with placebo. In a network meta-analysis estrogens of any dose consistently ranked higher than SSRI/SNRI, isoflavones, black cohosh, or ginseng.
    - There is **high** strength of evidence that SSRIs or SNRIs improve quality-of-life measures compared with placebo: SMD 0.28 (95% CI: 0.17 to 0.37; 6 trials, n=3,518).
    - Strength of evidence ratings for other agents compared with placebo were either **low** (ginseng, isoflavones) or **insufficient** (black cohosh).
- Analyses comparing effectiveness of treatments show estrogens improve quality-of-life symptoms best, with the following mean rankings (1 being best, 8 worst; placebo ranked 7.8): standard dose estrogens (1.6), high dose estrogens (1.8), and low dose estrogens (3.6). The nonhormone treatments were ranked much lower: SSRI/SNRIs (4.9), isoflavones (5.1), black cohosh (5.9), and ginseng (5.5).

Included Trials

Of the 283 trials included in this review, 125 (44.2 percent) reported general well-being or quality-of-life outcomes (69 trials specified as a primary outcome). Fifty-nine trials examined hormone treatment effects on these outcomes, including the following comparators: placebo (40 trials), other hormones (16 trials), and nonprescription treatments (three trials). Fifty-four trials examined nonprescription treatment effects including the following comparators: placebo (44 trials), other nonprescription treatments (three trials), hormones (two trials), and SSRIs (one trial). Nonprescription treatments included isoflavones, ginseng, black cohosh, DHEA, herbal extracts, and vitamins and minerals. Seven trials compared SSRI/SNRIs' effect on quality of life compared with placebo (six trials) and nonprescription treatments (one trial). Desvenlafaxine, escitalopram, and fluoxetine were the SSRI/SNRIs included in the trials.

The 125 trials were conducted in over 29 countries; 16 trials were multinational. Trials conducted in single countries were most commonly from the United States (n=19), Italy (n=10),

Germany (n=7), Australia (n=5), Brazil (n=5), and Turkey (n=5). Other countries included Austria, Canada, China, Denmark, France, Hong Kong, Netherlands, Taiwan, United, Kingdom, India, South, Korea, Thailand, Japan, Belgium, Ecuador, Estonia, Finland, Norway, Poland, Singapore, Spain, Sweden, Switzerland, and Ukraine. The trials were conducted in over 2,400 sites. Length of followup ranged from 8 to 187 weeks.

General well-being and quality-of-life outcomes were reported using a variety of scales, both general health-related quality-of-life scales and menopause-specific quality-of-life scales. A majority of the trials used menopause-specific scales (n=90), which focus on physical and psychological symptoms relating to menopause. Several trials used general health-related quality-of-life measures that include broader domains, such as the Short Form-36 (SF-36, sometimes referred to as Rand-36), EuroQol, Utian QOL, and 15D. The most common scales in the included trials were: Kupperman Menopausal Index (n=59), Greene Climacteric Scale (n=20), Menopause Rating Scale (MRS) (n=10), Menopause-specific Quality of Life (MENQOL) (n=14), and SF-36 (n=4). The following are brief descriptions of commonly used scales:

- The Kupperman Index is a numerical index that scores 11 menopausal symptoms: hot flushes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and formication. Each symptom is rated from 0 to 3 according to severity, where 0 = no symptoms and 3 = most severe. The scores are weighted and a total sum is calculated. The maximum score is 51 points, with a higher score indicating a worse quality of life.
- The Greene Climacteric Scale includes 21 questions covering five domains: anxiety, depression, somatic symptoms, vasomotor symptoms, and sexual function. Each question is answered on a four-point Likert scale (0 – "not at all"; 1 – "a little"; 2 –"quite a bit"; 3 – "extremely"). The answers to all 21 questions are summed to give a total quality-of-life measure; a higher score indicates a worse quality of life.
- MENQOL consists of 29 questions covering four domains: vasomotor, psychosocial, physical, and sexual. The scoring for each question is 1 – "No", 2 –"Yes, but not at all bothered" through 8 – "Yes, extremely bothered." The scores for each question are summed for a total quality-of-life score, in which the higher score indicates a worse quality of life.
- MRS scores 11 menopausal symptoms: hot flushes, heart discomfort, sleep problems, depressive mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems, vaginal dryness, and joint and muscular discomfort. Each item is scored from 0 – "none" to 4 – "extremely severe." The scores are summed for a total quality-of-life score, in which a higher score indicates a worse quality of life.
- SF-36, or Rand-36, is a general quality-of-life scale, not created specifically for menopausal women. This scale consists of 36 questions covering the following eight domains: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. The answer to each question is transformed linearly to a 0-100 score and then all items in one domain are averaged. This scale can be used to produce outcomes on a total quality of life, subscores for each of the domains, a physical health subscore, or a mental health subscore. For this scale, the higher the score, the better the quality of life.

Study quality was generally rated as poor (72.8 percent), with 18 good and 16 fair quality trials. Industry funding was indicated in 64 trials and public funding was reported in 31 trials. Table 18 describes additional trial and patient characteristics.

Table 18. Characteristics of trials assessing efficacy for quality-of-life outcomes

	Characteristic	Value
Trial Characteristics	Number of trials	125
	Total number of women	58,474
	Number of sites from trials that specified	2,458 1 to 502 (mean 23; median 2)
	Trials described only as multicenter	11 (8.8)
	Multicenter trials	71 (56.8)
	Two-arm trials	92 (73.6)
	Multi-arm trials	33 (26.4)
	Women per trial	50 to 16,608 (mean 468; median 142)
	Range of followup (weeks)	8 to 187 (mean 27.0; median 16)
Funding	Industry only	55 (44.0)
	Public only	22 (17.6)
	Industry and public	9 (7.2)
	Not stated	39 (31.2)
Comparator Category	Placebo vs. hormone	40 (32.0)
	SSRI/SNRI vs. placebo or other SSRI/SNRI	7 (5.6)
	Placebo vs. other prescription	0 (0.0)
	Placebo vs. nonprescription	54 (43.2)
	Placebo vs. hormone vs. nonprescription	0 (0.0)
	Hormone vs. hormone	16 (12.8)
	Hormone vs. nonprescription	3 (2.4)
	Nonprescription vs. SSRI/SNRIs	1 (0.8)
	Nonprescription vs. nonprescription	4 (3.2)
Study Quality	Good	18 (14.4)
	Fair	16 (12.8)
	Poor	91 (72.8)
	Not rated (abstract or gray literature)	0 (0.0)
Patient Demographics	Mean age (years)	43.8 to 66.8 (NR 10)
	Age range (years)	29.0 to 85.0 (NR 100)
	Years since menopause	3.7 (0.6 to 18.6) (NR 84)
	Current smokers (%)	0.0 to 41.2 (NR 101)
	Mean BMI (kg/m^2)	17.3 to 30.1 (NR 41)
	White (%)	0.0 to 100.0
	Black (%)	0.0 to 58.8
	Hispanic (%)	0.0 to 66.1
	Asian (%)	0.0 to 100.0
	Other (%)	0.0 to 41.0
Uterus Status	All intact	37 (29.6)
	All absent	7 (5.6)
	Mixed	39 (31.2)
	Range, percentage intact among trials with	22.5 to 96.9
	Not reported	42 (33.6)

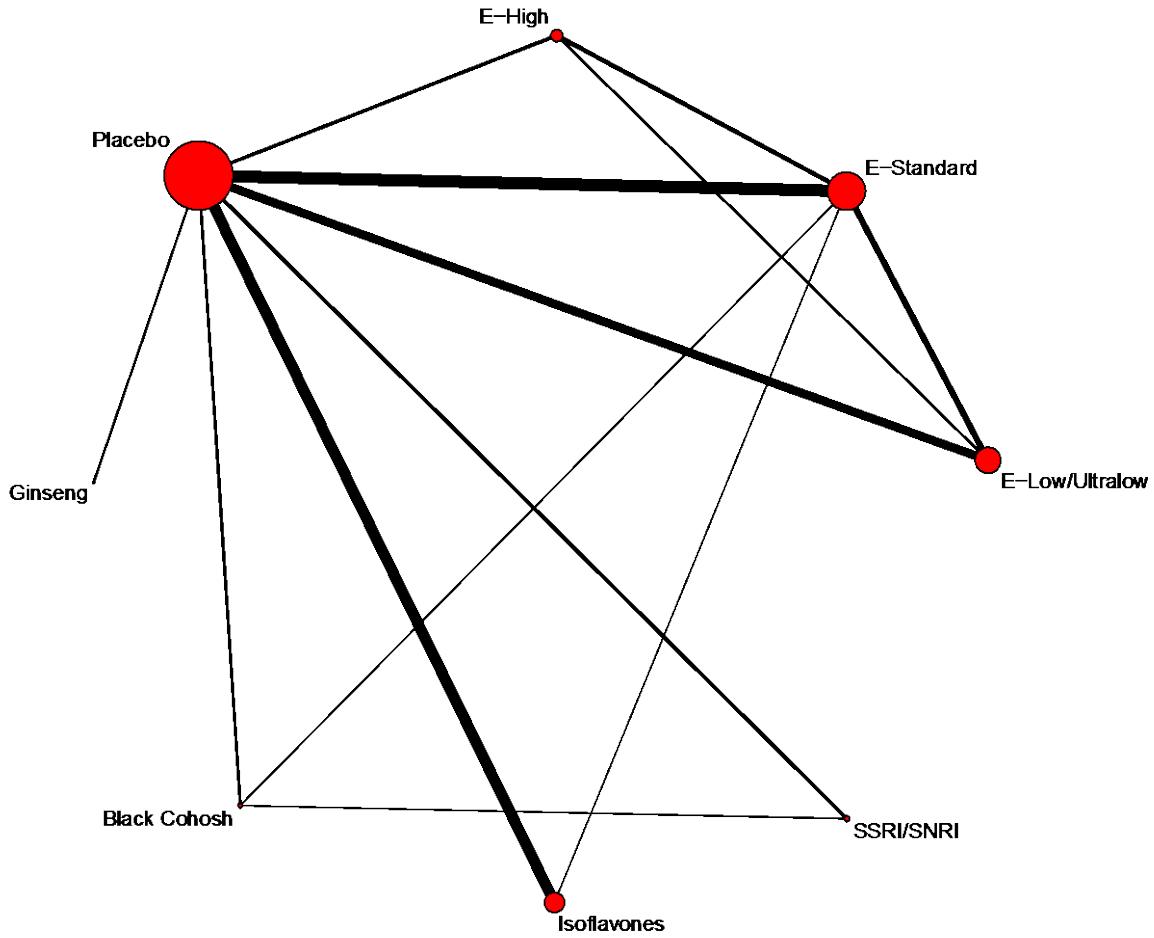
Note: Demographics were not reported in all studies.
NR: not reported; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

Evidence Synthesis for Quality of Life

Meta-Analysis

Treatments of greatest clinical interest and studied in multiple trials were compared in a network meta-analysis in addition to pairwise analyses—estrogens (according to dose), SSRI/SNRIs, isoflavones, black cohosh, and ginseng. Figure 8 displays the network and comparisons included. Data were most extensive for estrogens (72 comparisons), followed by isoflavones (24 comparisons), and SSRI/SNRIs (7 comparisons). The result from a trial concluding that women taking black cohosh had considerably better general well-being than those given fluoxetine[84] was not incorporated in the main network analysis; the effect was qualitatively (opposite effect direction) inconsistent with the other results. Finally, in sensitivity analyses, we excluded eight trials utilizing general quality-of-life measures.

Figure 8. Network of comparisons included in quality-of-life analyses[a]



E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.
[a] Line thickness and circle area are proportional to the number of comparisons.

Table 19 displays estimated standardized mean differences and 95% credible intervals from the fitted model. In the bottom row are SMDs comparing each treatment with placebo, the penultimate row are SMDs comparing each treatment with ginseng, and so forth. Compared with

placebo, the greatest improvement in quality-of-life scores were reported in women taking estrogens. The results suggested greater improvements with standard compared with low/ultralow dose estrogens (95% CrI: 0.01 to 0.29). Compared with placebo, SSRI/SNRIs and isoflavones were associated with effects of lesser magnitude different from 0. Neither black cohosh nor ginseng had statistically significant effects in the network analysis, although the pairwise result was consistent with an effect for ginseng. In a sensitivity analysis, excluding trials using general health related quality-of-life scales, resulted in comparable effect sizes and credible intervals that did not substantively change these results (Appendix G, Tables G-1 and G-2).

Figure 9 displays the estimated SMDs estimated from the network. Table 20 lists comparative treatments ranked with accompanying uncertainty; lower ranking representing greater improvement in reported quality-of-life scores. Although there is overlap of the credible intervals, estrogens appear to be superior to other agents in the network. Finally, Table 21 displays pooled effects from pairwise meta-analyses. There was little discrepancy with the network analysis indicating the network-estimated direct and indirect effects are likely accurate representations.[74]

Estrogen Compared With Placebo

There were 48 pairwise comparisons of estrogen with placebo—five with high-dose estrogen (one fair and four poor quality trials), 26 with standard dose (two good, six fair, and 18 poor quality trials), and 17 with low/ultralow dose (one good, six fair, and 10 from poor quality trials). The estimated SMDs for high, standard, and low/ultralow estrogen doses were 0.76 (95% CI: 0.48 to 1.03; tau^2=0.06), 0.55 (95% CI: 0.41 to 0.69; tau^2=0.10), and 0.36 (95% CI: 0.27 to 0.45; tau^2=0.05) (). The funnel plot of the standard dose estrogen−placebo comparison exhibited asymmetry, but was attributable to three large trials focused on prevention and using general quality-of-life instruments.[35, 144, 145] The mean ages of women in those trials were at the upper end of the distribution (62.8 to 63.6 years); excluding those trials yielded a symmetric funnel plot and an SMD of 0.64 (95% CI: 0.46 to 0.82; tau^2=0.17; 23 trials) with notable heterogeneity. Limiting the pooling further excluding poor quality trials resulted in an SMD of 0.65 (95% CI: 0.38 to 0.92; tau^2=0.09; 6 trials). The magnitudes of pooled standardized mean differences for all dose categorizations of estrogen are large and the estimates are precise. Although many trials were rated poor quality, with consistency over a large number of comparisons, the strength of evidence that estrogens of any dose improve quality-of-life scores compared with placebo is rated high.

Estrogen Compared With Estrogen

Seven trials (all poor quality) compared high with standard dose estrogens, three trials (all poor quality) compared high with low dose, and twelve trials (five fair and seven poor quality) compared standard with low dose estrogens with low-dose. Pooled estimates showed no or little differences between dose categories: high versus standard (SMD: -0.06; 95% CI: -0.16 to 0.04; tau^2=0.00); high versus low/ultralow (SMD: 0.04; 95% CI: -0.25 to 0.33; tau^2=0.04); and standard versus low/ultralow (SMD: 0.13; 95% CI: 0.02 to 0.24; tau^2=0.02). Although there was a difference between standard and low/ultralow dose estrogens, the magnitude of effect was small. Additionally, there was no evidence for dose response. The strength of evidence that changes in reported quality-of-life scores do not meaningfully differ by estrogen dose is rated moderate.

Estrogen Compared With Isoflavones

A single trial (poor quality) compared standard dose estrogens with isoflavones (SMD: 0.22; 95% CI: -0.25 to 0.70).

SSRI/SNRI Compared With Placebo

There were six trials that compared SSRI/SNRIs with placebo (three good, one fair, and two poor quality). The standardized mean difference was 0.27 (95% CI: 0.17 to 0.39; tau^2=0.01). The strength of evidence that SSRI/SNRIs improve quality of life among menopausal women is rated high.

Isoflavones Compared With Placebo

There were 24 trials comparing isoflavones with placebo (three good and 21 poor quality). The standardized mean difference was 0.27 (95% CI: 0.17 to 0.37; tau^2=0.02). Funnel plot asymmetry was notable and Egger test significant (p=0.03). The pooled SMD from the three good quality trials was 0.19 (95% CI: -0.20 to 0.57). The strength of evidence that isoflavones improve quality-of-life scores compared with placebo is rated low.

Black Cohosh Compared With Placebo

Four trials comparing black cohosh with placebo reported quality-of-life outcomes (two poor quality, one fair, and one good). The pooled SMD was 0.26 (95% CI: -0.15 to 0.66; tau^2=0.14). The strength of evidence that black cohosh improves quality-of-life scores is rated insufficient.

Ginseng Compared With Placebo

Three trials (one fair and two poor quality) including 513 women, compared ginseng with placebo resulting in a pooled SMD of 0.19 (95% CI: 0.01 to 0.36; tau^2=0.00). The strength of evidence that ginseng improves quality-of-life scores is rated low.

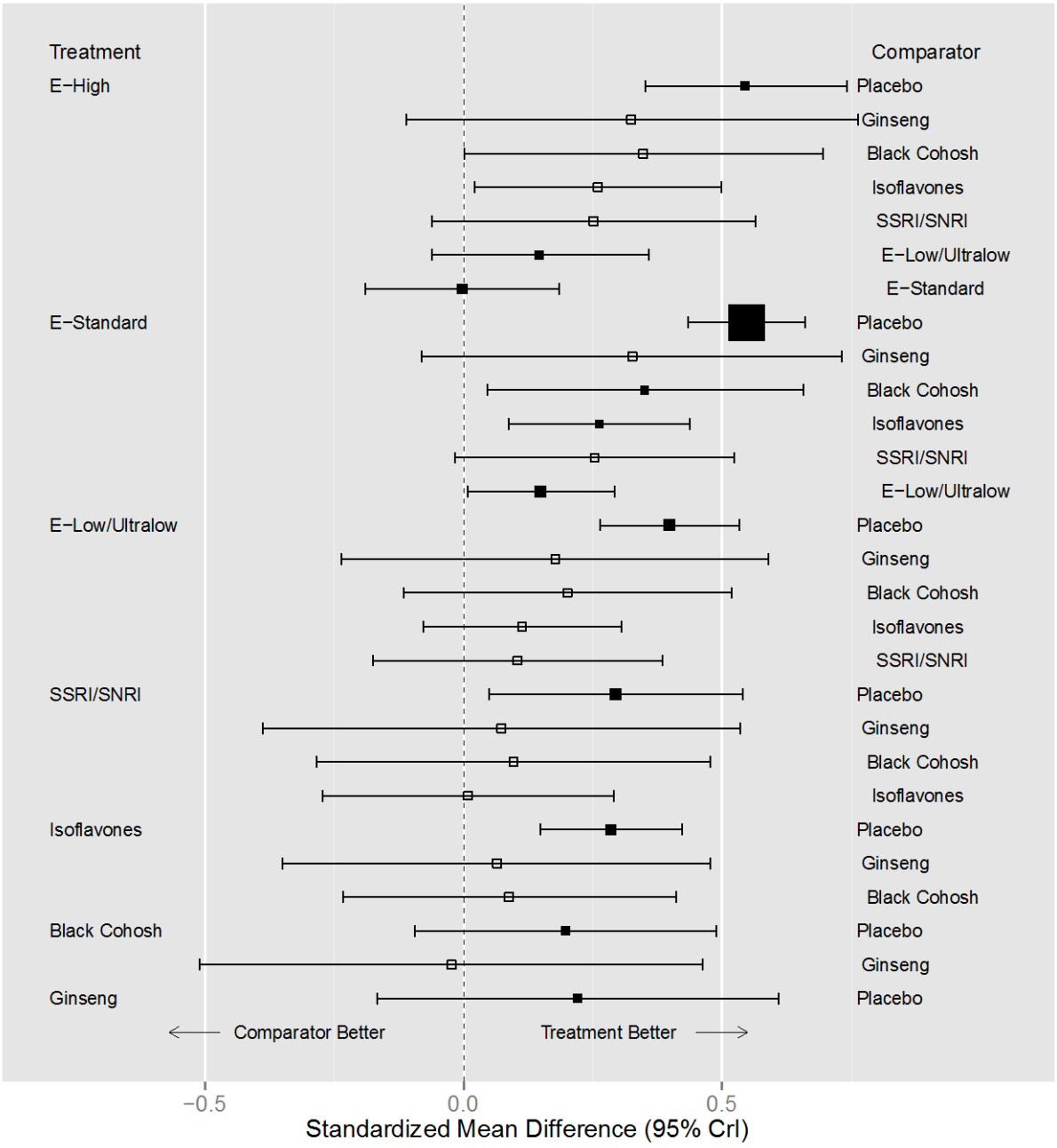
Table 19. Comparative effects on quality-of-life measures as standardized mean differences and 95% credible intervals from network meta-analysis[a]

E-High							
-0.00 (-0.19 to 0.19)	E-Standard						
0.15 (-0.06 to 0.36)	0.15 (0.01 to 0.29)	E-Low/Ultralow					
0.25 (-0.06 to 0.57)	0.25 (-0.02 to 0.52)	0.10 (-0.17 to 0.39)	SSRI/SNRI				
0.26 (0.02 to 0.50)	0.26 (0.09 to 0.44)	0.11 (-0.08 to 0.30)	0.01 (-0.27 to 0.29)	Isoflavones			
0.35 (0.00 to 0.70)	0.35 (0.05 to 0.66)	0.20 (-0.12 to 0.52)	0.10 (-0.28 to 0.48)	0.09 (-0.23 to 0.41)	Black Cohosh		
0.32 (-0.11 to 0.76)	0.33 (-0.08 to 0.73)	0.18 (-0.24 to 0.59)	0.07 (-0.39 to 0.53)	0.06 (-0.35 to 0.48)	-0.02 (-0.51 to 0.46)	Ginseng	
0.54 (0.35 to 0.74)	0.55 (0.44 to 0.66)	0.40 (0.26 to 0.53)	0.29 (0.05 to 0.54)	0.29 (0.15 to 0.42)	0.20 (-0.09 to 0.49)	0.22 (-0.17 to 0.61)	Placebo

E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

[a] Treatments are ordered left to right following a pattern of generally most to least efficacious. Highlighted effects are those where the credible interval does not overlap zero. The effects reflect improvement (higher on the scale) for the agent on the left versus comparators to its right from intersecting treatments listed on the diagonal.

Figure 9. Caterpillar plot displaying all quality-of-life comparisons included in the network analysis and 95% credible intervals[a]



[a] Symbol size is proportional to the number of women included in the comparison. Open squares represent effects estimated entirely through indirect comparison.

Table 20. Quality-of-life rankings of comparative efficacy, standard deviations, and 95% credible intervals

Treatment	Mean Rank	SD	Median Rank	95% CrI
E-High	1.8	0.9	2	(1 to 4)
E-Standard	1.6	0.6	2	(1 to 3)
E-Low/Ultralow	3.6	0.9	3	(2 to 6)
SSRI/SNRI	4.9	1.5	5	(2 to 7)
Isoflavones	5.1	1.1	5	(3 to 7)
Black Cohosh	5.9	1.4	6	(3 to 8)
Ginseng	5.5	1.9	6	(1 to 8)
Placebo	7.8	0.5	8	(7 to 8)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

Table 21. Quality-of-life pairwise effect estimates (pooled random effect estimates or single trial effects if only data available).

E-High							
-0.06 (-0.16 to 0.04) tau^2=0.00; n=7	E-Standard						
0.04 (-0.25 to 0.33) tau^2=0.04; n=3	0.13 (0.02 to 0.24) tau^2=0.02; n=12	E-Low/Ultralow					
			SSRI/SNRI				
	0.22 (-0.25 to 0.70) n=1			Isoflavones			
	0.69 (0.25 to 1.14) n=1		-0.73 (-1.18 to -0.28) n=1		Black Cohosh		
						Ginseng	
0.76 (0.48 to 1.03) tau^2=0.06; n=5	0.55 (0.41 to 0.69) tau^2=0.10; n=26	0.36 (0.27 to 0.45) tau^2=0.01; n=17	0.28 (0.17 to 0.39) tau^2=0.01; n=6	0.27 (0.17 to 0.37) tau^2=0.02; n=24	0.26 (-0.15 to 0.66) tau^2=0.14; n=4	0.19 (0.01 to 0.36) tau^2=0.00; n=3	Placebo

N: number of trials

Trials Not Pooled

Different Routes of Estrogen Administration

Seven trials compared similar estrogen doses administered through different routes (Table 22).[90-94, 146, 147] (See Appendix D for dose categorization by route of administration.) Three trials compared estrogen spray with estrogen patch, two compared oral estrogen with estrogen spray, one compared oral estrogen with estrogen patch, and one compared estrogen patches administered sequentially or combined. These trials were not included in the meta-analyses. Six of the seven trials showed no difference between the routes of administration, with all routes improving quality of life. One trial comparing an estradiol patch with an estradiol spray found that both routes significantly improved quality of life, with the spray improving significantly more than the patch.[91] These results support a conclusion, limited by trial quality, that route of administration does not determine estrogen effectiveness with respect to changes in quality-of-life scores. The strength of evidence that quality-of-life scores do not differ by route of estrogen administration is rated moderate.

Table 22. Trials comparing different routes of estrogen administration reporting quality-of-life outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Odabasi 2007[90]	Estradiol + progestogen Estradiol + progestogen	0.3 E + 90 P 0.05 E + 90 P	32 29	Spray Patch	12	Poor	— 0.20 (-0.31 to 0.71)
Davis 2005[91]	Estradiol Estradiol	0.05 0.3	60 60	Patch Spray	16	Poor	— -0.48 (-0.84 to -0.12)
Ozsoy 2002[92]	Estradiol + MPA Estradiol + MPA	2.0 E + 5.0 P 0.3 E + 5.0 P	100 101	Oral Spray	24	Poor	— -0.28 (-0.56 to 0.00)
Lopes 2001[93]	Estradiol + dydrogesterone Estradiol + dydrogesterone	0.05 E + 10 P 0.3 E + 10 P	184 174	Patch Spray	12	Poor	— -0.15 (-0.35 to 0.06)
Mattsson 2000[94]	Estradiol + dydrogesterone Estradiol + dydrogesterone	2.0 E + 10 P 0.3 E + 10 P	342 317	Oral Spray	24	Good	— -0.11 (-0.26 to 0.05)
Lubbert 1997[146]	Estradiol Estradiol	0.05 0.05	1232 1227	Patch[a] Patch[b]	12	Poor	— NS
Polvani 1991[147]	CEE + MPA Estradiol + MPA	0.625 E + 10 P 0.05 E + 10 P	170 203	Oral Patch	26	Poor	— -0.03 (-0.23 to 0.18)

[a] Combined.
[b] Sequential.
SMD: standardized mean difference; CI: confidence interval; E: estrogen; P: progestogen; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; FU: followup; Wks: weeks.

Estrogen Compared With a Nonprescription Agent

One trial compared estrogen/progestin with a nonprescription treatment, pueraria mirifica[134] and reported quality-of-life outcomes (Table 23). Pueraria mirifica is a highly estrogenic herb found in Thailand. Both hormone therapy and pueraria mirifica improved quality of life similarly. After three months of followup, pueraria mirifica reduced the total modified Greene score from 29.0 to 12.6 and estrogen/progestin treatment reduced the score from 32.3 to 9.6.[134]

Table 23. Trials comparing hormone therapy with nonprescription treatments reporting quality-of-life outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Chandeying 2007[134]	CEE + MPA	0.625 E + 2.5 P	30	Oral	24	Poor	—
	Pueraria mirifica	50	30	Oral			-0.27 (-0.78 to 0.24)

CCE: conjugated equine estrogen; CI: confidence interval; E: estrogen; FU: followup; MPA: medroxyprogesterone acetate; P: progestogen; SMD: standardized mean difference

Different Doses of Same Nonprescription Treatments

Three trials compared different doses of the same nonprescription treatments and reported quality-of-life outcomes (Table 24).[136, 137, 141] Two trials compared two doses of isoflavones and reported significant improvements in quality of life in both groups, with no between-group difference.[137, 141] The other trial compared two doses of pueraria mirifica and also reported significant improvements in quality of life in both groups, with no difference between doses.[136]

Table 24. Trials comparing different doses of the same nonprescription treatment reporting quality-of-life outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Hidalgo 2006[141]	Isoflavones	60	478	Oral	26	Poor	—
	Isoflavones	120	447	Oral			0.13 (0.00 to 0.26)
Virojchaiwong 2011[136]	Pueraria mirifica	25	26	Oral	26	Poor	—
	Pueraria mirifica	50	26	Oral			0.07 (-0.48 to 0.62)
Yang 2012[137]	Isoflavones	35	57	Oral	24	Poor	—
	Isoflavones	70	50	Oral			-0.07 (-0.45 to 0.31)

SMD: standardized mean difference; CI: confidence interval; FU: followup; Wks: weeks

SSRI/SNRIs Compared

One trial compared two different SSRI/SNRIs, desvenlafaxine and escitalopram, and reported quality-of-life outcomes (Table 25).[148] The trial was of good quality and reported that both antidepressants improved quality-of-life scores significantly, without a difference between groups.

Table 25. Trials comparing SSRI/SNRIs reporting quality-of-life outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Soares 2010[148]	Desvenlafaxine	100-200	175	oral	8	Good	—
	Escitalopram	10-20	194	oral			0.16 (-0.04 to 0.37)

SMD: standardized mean difference; CI: confidence interval; FU: followup; Wks: weeks

Nonprescription Agents Compared With Placebo

Twenty-three trials compared nonprescription treatments with placebo (Table 26). Three trials tested DHEA,[130, 149, 150] three trials used herbal extracts,[109, 119, 122] two trials combined isoflavones and black cohosh,[127, 151] two trials combined black cohosh and St. John's wort,[126, 128] two trials used dong quai,[115, 123] and two trials tested flaxseed.[131, 152] St. John's wort,[129] rheum rhaponticum,[112] pollen extract,[113] a vitamin/mineral mixture,[132] dioscorea alata,[117] green tea,[153] pomegranate seed oil,[118] maritime pine extract,[125] and ovaria bovis[121] were compared with placebo in one trial each.

The three DHEA trials (two of poor quality), with a total of 365 participants, reported inconsistent results. Two trials of oral DHEA compared with placebo did not find significant differences in quality of life among study groups.[130, 150] One trial compared three different doses of DHEA in vaginal ovules with placebo and found improvements in quality-of-life scores with two of the three doses compared with placebo.[149] The strength of evidence that DHEA improves quality-of-life scores was rated insufficient.

The two trials that combined black cohosh with St. John's wort reported significant improvements in quality of life compared with placebo. One trial with 77 women had a standard mean difference of 0.78 (95% CI: 0.31 to 1.24)[126] and the other trial with 294 women had a standard mean difference of 0.39 (95% CI: 0.16 to 0.62).[128]

Of the remaining trials, three found significant improvements in quality of life compared with placebo: a trial (n=64) using a mixture of Cynanchum wilfordii, Phlomis umbrosa, and Angelica gigas;[119] a trial (n=75) using a combination of isoflavones and black cohosh;[151] and a trial (n=108) using dong quai.[123]

Table 26. Trials comparing nonprescription treatments reporting quality-of-life outcomes

Trial	Treatment	Dose (mg)	N	Mode	FU Wks	Study Quality	SMD (95% CI)
van der Sluijs 2009[109]	Placebo	—	46	Oral	16	Good	—
	Plant extracts[a]	3820	46	Oral			-0.15 (-0.56 to 0.27)
Lewis 2006[152]	Placebo	—	28	Oral	16	Good	—
	Flaxseed	*	27	Oral			0.06 (-0.48 to 0.59)
van Die 2009[129]	Placebo	—	50	Oral	16	Good	—
	St John's wort	900	50	Oral			-0.27 (-0.66 to 0.13)
Heger 2006[112]	Placebo	—	55	Oral	12	Poor	—
	Rheum rhaponticum	4	54	Oral			0.38 (0.00 to 0.76)
Winther 2005[113]	Placebo	—	32	Oral	13	Good	—
	Femal®[b]	80	26	Oral			0.15 (-0.39 to 0.69)
Verhoeven 2005[127]	Placebo	—	64	Oral	12	Good	—
	Isoflavones/Black cohosh	50 I + 100 BC	60	Oral			0.01 (-0.34 to 0.37)
Hirata 1997[115]	Placebo	—	36	Oral	24	Poor	—
	Dong Quai	4,500	35	Oral			-0.05 (-0.52 to 0.41)
Hsu 2011[117]	Placebo	—	25	Oral	52	Poor	—
	Dioscorea alata	24	25	Oral			0.30 (-0.26 to 0.86)
Labrie 2009[149]	Placebo	—	53	Ovule	12	Poor	—
	DHEA	3.25	53	Ovule			0.58 (0.19 to 0.97)
	DHEA	6.5	56	Ovule			0.24 (-0.14 to 0.62)
	DHEA	13.0	54	Ovule			0.42 (0.04 to 0.81)
Panjari 2009[150]	Placebo	—	42	Oral	26	Good	—
	DHEA	50	43	Oral			0.16 (-0.27 to 0.59)
Dodin 2005[131]	Placebo	—	94	Oral	52	Fair	—
	Flaxseed	40,000	85	Oral			0.15 (-0.14 to 0.44)
Barnhart 1999[130]	Placebo	—	30	Oral	12	Poor	—
	DHEA	50	30	Oral			-0.05 (-0.56 to 0.46)
Andrikoula 2011[132]	Placebo	—	34	Oral	12	Poor	—
	Nutritional supplement[c]	*	36	Oral			0.12 (-0.36 to 0.59)
Chang 2011[119]	Placebo	—	32	Oral	12	Fair	—
	EstroG-100®[d]	*	29	Oral			0.67 (0.15 to 1.20)
Chung 2007[126]	Placebo	—	35	Oral	12	Poor	—
	Black cohosh/St. John's wort	—	42	Oral			0.78 (0.31 to 1.24)

Table 26. Trials comparing nonprescription treatments reporting quality-of-life outcomes (continued)

Trial	Treatment	Dose (mg)	N	Mode	FU Wks	Study Quality	SMD (95% CI)
Uebelhack 2006[128]	Placebo	—	143	Oral			—
	Black cohosh/St. John's wort	3.75 BC + 70 SJW	151	Oral	16	Fair	0.39 (0.16 to 0.62)
Shen 2010[153]	Placebo	—	44	Oral	24	Poor	—
	Green tea polyphenols	500	47	Oral			0.15 (-0.27 to 0.56)
Sammartino 2006[151]	Placebo	—	39	Oral	12	Fair	—
	Isoflavones/black cohosh	60	36	Oral			0.61 (0.14 to 1.07)
Auerbach 2012[118]	Placebo	—	38	Oral	12	Poor	—
	Pomegranate seed oil	0.254	43	Oral			0.39 (-0.05 to 0.83)
Kohama 2012[125]	Placebo	—	70	Oral	12	Poor	—
	Maritime pine extract	30	72	Oral			0.33 (0.00 to 0.66)
Von Hagens 2012[121]	Placebo	—	32	Oral			—
	Ovaria bovis	—	62	Oral	12	Poor	-0.17 (-0.60 to 0.26)
Yang 2012[122]	Placebo	—	98	Oral	24	Poor	—
	Chinese medicinal herbs	—	105	Oral			0.24 (-0.04 to 0.52)
Zhong 2013[123]	Placebo	—	54	Oral	12	Fair	—
	Dong quai	—	54	Oral			0.69 (0.30 to 1.08)

BC: black cohosh; CI: confidence interval; NS: not significant; DHEA: dehydroepiandrosterone; I: isoflavones; FU: followup; SJW: St. John's wort; SMD: standardized mean difference; Wks: weeks

The asterisk (*) denotes multicomponent agents with varying dose amounts for each component.

[a] combination of black cohosh, er xian tang, zhi bai di huang wan

[b] combination of pure pollen, pollen/pistil extract

[c] combination of 21 vitamins and minerals

[d] combination of cynanchum wilfordii, phlomis umbrosa, angelica gigas

Trials Without Quantifiable or Poolable Data

Below is a description of four trials that did not have data that could be analyzed by the standardized method or pooled because of the reporting metric. Results of these trials would not have affected the overall outcomes presented above.

The Estonian Postmenopausal Hormone Therapy Trial compared 0.625 mg estrogen plus 2.5 mg medroxyprogesterone acetate with placebo.[154] Quality of life was measured using the EQ-5D developed by the EuroQol group. No baseline measures were reported. Post-treatment median EQ-5D scores showed no significant difference in quality of life among the treatment and placebo groups.

A randomized blinded trial (n=152) compared two different doses of black cohosh (39 mg and 127.3 mg) and reported median Kupperman Index scores as a measure of quality of life.[155] Both black cohosh doses improved quality-of-life scores equally.

Foidart et al. compared a low-dose estrogen vaginal pessary with placebo and reported total Kupperman Index scores as a quality-of-life outcome. Kupperman Index scores decreased more with estrogen-alone therapy compared with the placebo.[156]

Pandit et al. compared a micronutrient supplement with placebo and reported percentage with negative well-being as an outcome. The placebo group had a baseline percentage of negative well-being of 48.3, which decreased to 24.0 after 12 weeks of followup. The group treated with micronutrients had a baseline for negative well-being of 55.2 percent, which decreased to 0.0 at followup.[133]

Strength of Evidence Ratings—Quality of Life

Table 27 summarizes strength of evidence ratings.

Table 27. Strength of evidence ratings domains for quality of life

Number of Comparisons	Comparators[a]			Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Downgrading Rationale
48	**Estrogen**	vs	Placebo	M	C	D	P	U	High	3 good, 13 fair, and 32 fair quality trials
22	**Estrogen**	vs	**Estrogen (different dose)**	M	I	D	P	U	Mod	Standard appeared better than low/ultralow dose but a small effect size, lack of dose-response; 5 fair and 17 poor quality trials
6	**SSRI/SNRI**	vs	Placebo	M	C	D	P	U	High	3 good, 1 fair, and 2 poor quality trials
24	**Isoflavones**	vs	Placebo	M	C	D	I	S	Low	3 good and 21 poor quality trials
4	**Black Cohosh**	vs	**Placebo**	H	I	D	I	U	Insuff	2 poor quality trials; confidence interval overlaps 0
3	**Ginseng**	vs	Placebo	H	C	D	I	U	Low	1 fair and 2 poor quality trials; lower bound of CI 0.01
7	**Estrogen route a**	vs.	**Estrogen route b**	H	C	D	P	U	Mod	6 poor quality trials

[a] Bold font of comparator indicates the more effective treatment; if both comparators are bold, the treatments are equivalently effective

Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I), Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S), Undetected (U); SOE: strength of evidence; Mod: moderate; CI: confidence interval; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; DHEA: dehydroepiandrosterone; Insuff: insufficient.

Psychological Symptoms

Key Points

- A total of 108 trials including over 52,000 women reported at least one psychological outcome measure (depressive symptoms, anxiety, and/or global psychological well-being) in women treated with prescription (estrogen, testosterone, SSRIs, SNRIs) and nonprescription agents (isoflavones, black cohosh, ginseng, DHEA, herbal extracts, and others).
- Study quality was generally rated poor (71 percent). Funding was reported provided by industry alone in 41 trials, public sources in 21 trials, industry and public sources in 10 trials, funding, and the type of funding was not stated for 36 trials.
- Psychological outcomes were reported using a variety of scales in three domains: global, anxiety, and depressive symptoms.
- Strength of evidence of comparative effectiveness of agents in treating psychological symptoms is as follows:
    - There is **high** strength of evidence that, compared with placebo, an SSRI or SNRI is accompanied by improved depressive symptoms: SMD -0.43, 95% CI: -0.60 to -0.26; 5 trials, n=2,882); anxiety symptoms (outcomes for SNRI only): SMD -0.31, 95% CI: -0.50 to -0.12; 3 trials, n=2,688); and global psychological well-being: SMD -0.42 (95% CI: -0.60 to -0.24; 6 trials, n=3,021).
    - There is **high** strength of evidence that, compared with placebo, that estrogens are accompanied by improved depressive symptoms: SMD -0.36 (95% CI: -0.53 to -0.20; 18 trials, n=2,104); anxiety symptoms: SMD -0.31 (95% CI: -0.50 to -0.18; 13 trials, n=1,718); and global psychological well-being: SMD -0.26 (95% CI: -0.40 to -0.13; 14 trials, n=3,386).
    - There is **low** strength of evidence that, compared with placebo, isoflavones are accompanied by improved depressive symptoms: SMD -0.29, 95% CI: -0.49 to -0.09; 7 trials, n=1,055); and global psychological well-being: SMD -0.11 (95% CI -0.22 to 0.01; 7 trials, n=1,228); and **moderate** strength of evidence for improved anxiety symptoms: SMD -0.30 (95% CI: -0.46 to -0.14; 7 trials, n=853).
    - There is **insufficient** evidence that gabapentin is accompanied by improved global psychological well-being compared with placebo: SMD -0.23 (95% CI: -0.48 to 0.02; 2 trials; n=252).
    - There is insufficient evidence on the effectiveness of other agents and comparators on psychological outcomes.

Included Trials

Of the 283 trials included in this review for KQ1, 108 (35.4 percent) trials reported psychological outcomes in three domains: global, anxiety, and depressive symptoms (50 trials specified at least one as a primary outcome). Trials often reported outcomes in more than a single domain: global (n=61), anxiety (n=48), and depressive symptoms (n=61). Fifty-two trials examined hormones compared with: placebo (34 trials), other hormones (13 trials), and nonprescription agents (five trials). Other comparators categories are shown in Table 28.

The 108 trials originated from 24 different countries and 10 trials were described as multinational. Nonmultinational trials were conducted in the United States (n=24), United Kingdom (n=7), and six each from Turkey, Italy, Germany, and Canada; other countries included China, Hong Kong, India, Taiwan, Australia, Ecuador, France, Japan, Netherlands, Norway, Poland, Singapore, Ukraine, Finland, Sweden, Austria, Denmark, and Brazil. The trials were conducted at over 2,000 sites. Length of followup ranged from four to 192 weeks.

Psychological symptoms were reported using a variety of scales. The most common scales were: Greene (12 anxiety, 12 depressive symptoms, 15 global), WHQ (10 anxiety, 18 depressive symptoms, one global), MENQOL (22 global), Beck (four anxiety, eight depressive symptoms), Hamilton (six anxiety, seven depression), SF-36 (nine global), and Kupperman (six anxiety, six depressive symptoms). Additional scales used include CES-D, Hospital Anxiety and Depression Scale, Psychological General Well-Being, MRS, Profile of Mood States, and the Bond and Lader Mood Rating Scale. The following are brief descriptions of the most commonly used scales:

- The Greene anxiety subscale consists of six items, with scores ranging from 0 to 18.[157] Questions include heart beating quickly and strongly, feeling tense or nervous, difficulty sleeping, excitable, attacks of panic, and difficulty concentrating. The Greene depressive symptom subscale consists of five items, with scores ranging from 0 to 15. Questions include feeling tired or lacking in energy, loss of interest in most things, feeling unhappy or depressed, crying spells, and irritability. Total psychological scores range from 0 to 33. Higher scores indicate more severe symptoms.
- The WHQ can be administered as a 23- or 37-item instrument. The 37-item version includes four items in the anxiety assessment: I get very frightened or panic feelings for apparently no reason at all, I feel anxious when I go out of the house on my own, I get palpitations or a sensation of "butterflies" in my stomach or chest, and I feel tense or "wound up." The depressive symptom score includes seven items: I feel miserable and sad, I have lost interest in things, I still enjoy the things I used to, I feel life is not worth living, I have a good appetite, I am more irritable than usual, and I have feelings of well-being. Total scores on subscales are 0 to 1 (some scales reversed according to the construct probed). Higher scores indicate more severe symptoms.
- The MENQOL psychosocial score is derived from seven items (scored 1 for "not bothered" to 8 for "extremely bothered"): being dissatisfied with my personal life; feeling anxious or nervous; experiencing poor memory (no or yes); accomplishing less than I used to; feeling depressed, down, or blue; being impatient with other people; and feelings of wanting to be alone. Higher scores indicate more severe symptoms.[68]
- The Beck anxiety inventory and Beck depression inventory each include 21 items, scored from 0 for "not at all" to 3 for "severely bothered," with total scores ranging from 0 to 63. The Beck anxiety inventory lists symptoms common to anxiety such as numbness, heart pounding, trembling, shaking, indigestion, and flushing.[158] The Beck depression inventory assesses mood, satisfaction, appetite, sleep, weight, and sexual activity. Higher scores indicate more psychological distress.[159]
- The Hamilton scales are completed by a health care professional following an examination of the patient. This scale measures both mental distress as well as physical complaints related to anxiety and depression.[160, 161] The Hamilton anxiety score consists of 14 items with a total score of 0 to 56. The depression scale consists

of 21 items with a total score of 0 to 52. Higher scores indicated worse psychological health.

- The SF-36 mental health score consists of five items. The items assess nervousness, cheerfulness, peacefulness, depressive symptoms, and happiness. Scores are summed, then normalized to a 0-100 scale. Higher scores indicate improvement in mental health.[162]
- Kupperman measures insomnia, nervousness, and melancholia.[163] Total scores range from 0 to 16 summed. Higher scores indicate more severe symptoms. Hospital Anxiety & Depression Scale (HADS) includes 14 items (seven depression and seven anxiety), with higher scores indicating more severe symptoms. The Psychological General Well Being is a 22-item derivative of the General Well Being Index Menopause Rating Scale, in which a higher score indicates better mental health.

In many cases, the presence of climacteric symptoms and/or anxious depressive disorders was required for inclusion in the study. However, women were often excluded if taking psychoactive drugs, had too high of a score on the assessment tool, or had suicidal thoughts. Table 28 further describes the trial and patient characteristics.

Table 28. Characteristics of trials assessing efficacy for psychological symptoms

	Characteristic	Value
Trial Characteristics	Number of trials	108
	Total number of women	52,538
	Number of sites from trials that specified	2,099 1 to 502 (mean 23; median 2)
	Trials described only as multicenter	4 (3.7)
	Multicenter trials	57 (52.8)
	Two-arm trials	79 (73.1)
	Multi-arm trials	29 (26.9)
	Women per trial	50 to 16,608 (mean 486; median 119)
	Range of followup (weeks)	4 to 192 (mean 26.5; median 16)
Funding	Industry only	41 (38.0)
	Public only	21 (19.4)
	Industry and public	10 (9.3)
	Not stated	36 (33.3)
Comparator Category	Placebo vs. hormone	34 (31.5)
	SSRI/SNRI vs. placebo or other SSRI/SNRI	10 (9.3)
	Placebo vs. other prescription	3 (2.8)
	Placebo vs. nonprescription	39 (36.1)
	Placebo vs. hormone vs. nonprescription	2 (1.9)
	Hormone vs. hormone	13 (12.0)
	Hormone vs. nonprescription	3 (2.8)
	Nonprescription vs. SSRI/SNRIs	1 (0.9)
	Nonprescription vs. nonprescription	3 (2.8)
Study Quality	Good	17 (15.7)
	Fair	13 (12.0)
	Poor	77 (71.3)
	Not rated (abstract or gray literature)	1 (0.9)

Table 28. Characteristics of trials assessing efficacy for psychological symptoms (continued)

	Characteristic	Value
Patient Demographics	Mean age (years)	46.5 to 75.6 (NR 14)
	Age range (years)	29.0 to 85.0 (NR 90)
	Years since menopause	4.2 (0.8 to 18.6) (NR 74)
	Current smokers (%)	0.0 to 41.2 (NR 82)
	Mean BMI (kg/m^2)	17.3 to 30.1 (NR 40)
	White (%)	0.0 to 100.0
	Black (%)	0.0 to 46.3
	Hispanic (%)	0.0 to 9.0
	Asian (%)	0.0 to 100.0
	Other (%)	0.0 to 41.0
Uterus Status	All intact	31 (28.7)
	All absent	7 (6.5)
	Mixed	42 (38.9)
	Range, percentage intact among trials with mixed	25 to 94.3
	Not reported	28 (25.9)

Note: Demographics were not reported in all studies.
NR: not reported; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

Evidence Synthesis for Psychological Symptoms

Standard mean differences were calculated to allow comparison of outcomes across different psychological symptom scales. Analyses were performed according to domain: anxiety, depressive symptoms, and global measures of psychological well-being. There were either few trials reporting comparisons between different estrogen doses, or in the single instance there were multiple comparisons there was little apparent difference between doses (standard versus low/ultralow doses for the global domain, SMD -0.06; 95% CI: -0.14 to 0.02; tau^2=0.00, 9 trials). Estrogens were therefore combined in the analyses (results according to dose can be found in Appendix H). Because results from large trials focused on prevention with estrogen[35, 144, 145] showed lesser effects, pooled effects including and excluding those trial results were estimated. In addition, trial results were pooled for isoflavones, SSRI/SNRIs, and gabapentin compared with placebo.

Table 29 displays effect estimates for psychological outcomes (forest plots shown in Appendix H) and Figure 10 a caterpillar plot for the comparisons.

SSRI/SNRI Compared With Placebo

Global

Six trials compared an SSRI or SNRI with placebo and reported a global measure of psychological well-being (three good and three poor quality).[164-168] Compared with placebo, the pooled SMD for improved well-being on a global scale was -0.42 (95% CI: -0.60 to -0.24; tau^2=0.03); limited to the three high quality trials -0.38 (95% CI: -0.56 to -0.20; tau^2=0.02). The strength of evidence that an SSRI or SNRI is accompanied by improved psychological well-being compared with placebo is rated high.

Depressive Symptoms

Five trials compared an SSRI or SNRI with placebo and reported depressive symptoms (two good and three poor quality).[168-172] Compared with placebo, the pooled SMD for improved reported depressive symptoms was -0.43 (95% CI: -0.60 to -0.26; tau^2=0.02); limited to the three high quality trials -0.37 (95% CI: -0.60 to -0.15; tau^2=0.02). The strength of evidence that an SSRI or SNRI is accompanied by improved depressive symptoms compared with placebo is rated high.

Anxiety

Three trials compared an SNRI (desvenlafaxine) with placebo and reported some measure of anxiety (two good and one poor quality trial).[168, 171, 172] The pooled SMD for improvement in reported anxiety symptoms for estrogen compared with placebo was -0.31 (95% CI: -0.50 to -0.12; tau^2=0.02). The strength of evidence that desvenlafaxine is accompanied by improved anxiety symptoms compared with placebo is rated high.

Estrogens Compared With Placebo

Global

Sixteen trials including one or more estrogen-placebo comparison and reported some global measure of psychological well-being (two good, six fair, and eight poor quality).[144, 145, 173-186] Compared with placebo, the pooled SMD for improved well-being on a global scale from all trials was -0.18 (95% CI: -0.27 to -0.10; tau^2=0.01), and excluding two large disease prevention focused trials -0.26 (95% CI: -0.40 to -0.13; tau^2=0.04). There was no indication for potential reporting bias. The strength of evidence that estrogens are accompanied by improved psychological well-being compared with placebo is rated high.

Depressive Symptoms

Twenty trials reported some measure of depression for estrogen compared with placebo (two good, one fair, and 17 poor quality).[35, 145, 148, 173, 174, 179, 180, 185, 187-198] Compared with placebo, the pooled SMD for fewer reported depressive symptoms was -0.31 (96 percent CI: -0.44 to -0.18; tau^2=0.05), and excluding two large disease prevention focused trials -0.36 (95% CI: -0.53 to -0.20; tau^2=0.07) with no indication of reporting bias. The strength of evidence that estrogens are accompanied by improved depressive symptoms compared with placebo is rated high.

Anxiety

Some measure of anxiety was reported in 14 trials (one good, one fair, and 12 poor quality).[35, 173, 179, 180, 185, 187, 190-192, 195-199] The pooled SMD for less reported anxiety symptoms for estrogen compared with placebo was -0.30 (95% CI: -0.48 to -0.12; tau^2=0.08), and excluding one large disease prevention focused trials -0.34 (95% CI: -0.50 to -0.18; tau^2=0.05). Reporting bias was not suspected. The strength of evidence that estrogens are accompanied by improved anxiety symptoms compared with placebo is rated high.

Gabapentin Compared With Placebo

Global

Two trials compared gabapentin with placebo and reported a global measure of psychological well-being (both rated poor quality).[42, 200]Compared with placebo, the pooled SMD for improved

well-being on a global scale was -0.23 (95% CI: -0.22 to 0.02; tau^2=0.0). The strength of evidence that gabapentin is accompanied by improved psychological well-being compared with placebo is rated insufficient.

Isoflavones Compared With Placebo

Global

Seven trials compared isoflavones with placebo and reported a global measure of psychological well-being (four good, one fair, and two poor quality trials).[152, 201-206] Pooled estimates show no significant difference in global measures compared with placebo (SMD: -0.11; 95% CI: -0.22 to 0.01; tau^2=0.00). The strength of evidence that isoflavones are accompanied by improved global mental psychological well-being compared with placebo among menopausal women is rated low.

Depressive Symptoms

Nine trials compared isoflavones with placebo and reported a measure of depressive symptoms (one good and eight poor quality).[87, 201, 202, 205, 207-211] Pooled analyses showed a significant improvement in depressive symptoms among the group treated with isoflavones compared with placebo (SMD: -0.29; 95% CI: -0.49 to -0.09; tau^2=0.05). Four of the trials, including the two largest[201, 202] showed SMDs close to 0, whereas in three of the smallest[87, 209, 210] calculated SMDs were large (-0.65 to -0.78) indicating potential for reporting bias. The strength of evidence that isoflavones are accompanied by improved depressive symptoms compared with placebo is rated low.

Anxiety

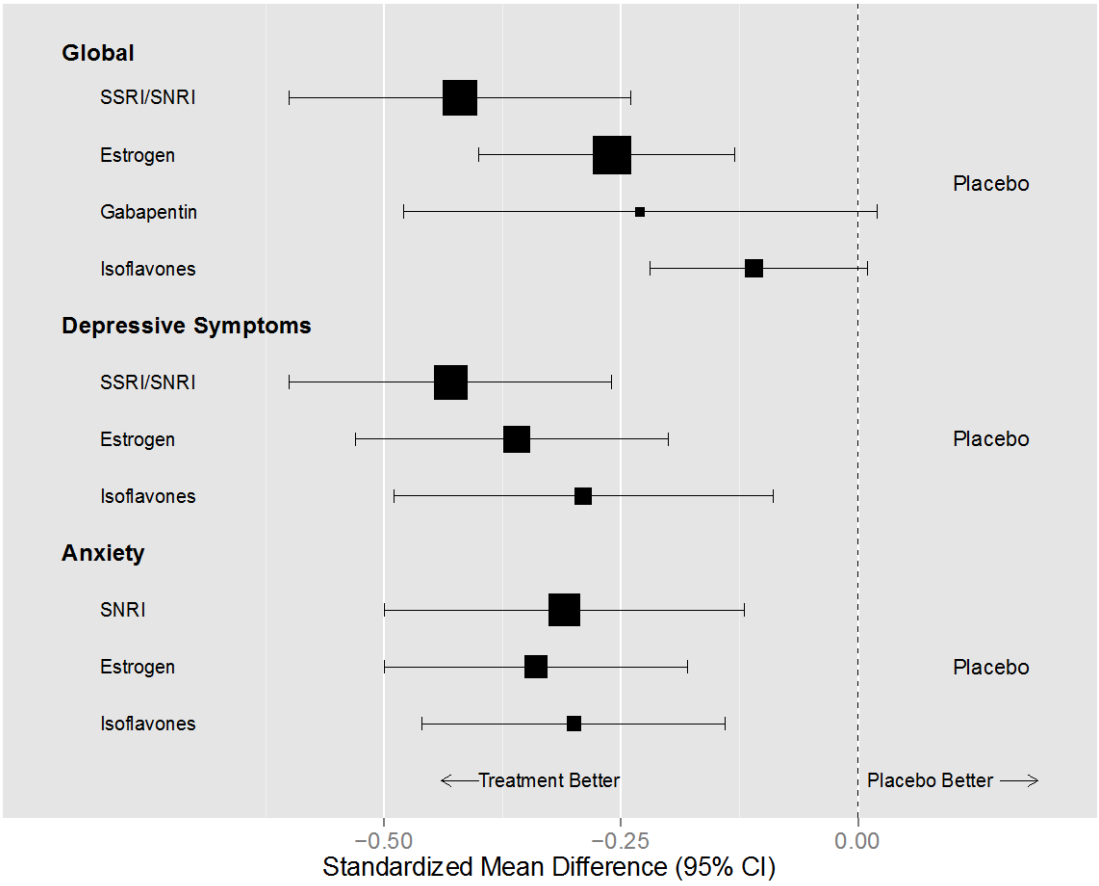
Seven trials compared isoflavones with placebo and reported a measure of anxiety symptoms (one good and six poor quality trials).[87, 201, 205, 207, 209, 210, 212] The pooled effect was consistent with an improvement in anxiety among women treated with isoflavones compared with the placebo—SMD -0.30 (95% CI: -0.46 to -0.14; tau^2=0.01). The strength of evidence that isoflavones improve reported anxiety symptoms compared with placebo among menopausal women is rated moderate.

Table 29. Psychological outcomes pairwise effect estimates (pooled random effect estimates or single trial effects if only data available)

Domain	SSRI/SNRI	Estrogen	Gabapentin	Isoflavones
Global	-0.42 (-0.60 to -0.24) tau^2=0.03; n=6	-0.26[a] (-0.40 to -0.13) tau^2=0.04; n=14	-0.23 (-0.48 to 0.02) tau^2=0.00; n=2	-0.11 (-0.22 to 0.01) tau^2=0.00; n=7
Depression	-0.43 (-0.60 to -0.26) tau^2=0.02; n=5	-0.36[b] (-0.53 to -0.20) tau^2=0.07; n=18		-0.29 (-0.49 to -0.09) tau^2=0.05; n=9
Anxiety	-0.31 (-0.50 to -0.12) tau^2=0.02; n=3	-0.34[c] (-0.50 to -0.18) tau^2=0.05; n=13		-0.30 (-0.46 to -0.14) tau^2=0.01; n=7

Including large prevention trials:
[a] -0.18 (-0.27 to -0.10) tau^2=0.01; n=16
[b] -0.31 (-0.44 to -0.18) tau^2=0.05; n=20
[c] -0.30 (-0.48 to -0.12) tau^2=0.08; n=14
N: number of trials; SSRI/SNRI: selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor

Figure 10. Caterpillar plot displaying psychological symptom comparisons and 95% confidence intervals[a]



[a] Symbol size is proportional to the number of women included in the comparison.

Trials Not Pooled

Different Routes of Estrogen Administration

Four trials (Table 30) compared similar doses of estrogen administered through different routes (see Appendix D for dose categorization by route of administration). Three of the trials reported that changes in psychological symptoms were with the following routes of administration: sequential compared with combined progestogen added to estrogen patches,[146] oral compared with transdermal patch,[98] and nasal spray compared with transdermal patch.[90] One trial compared oral, skin gel, and transdermal patch in administering estrogen. Akhila et al. reported that the skin gel and the transdermal patch significantly improved global psychological scores compared with oral estrogen.[99]

Given the different treatments and outcomes, the strength of evidence was not rated.

Table 30. Trials comparing different routes of estrogen administration reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Lubbert 1997[146]	Estradiol + progestogen Estradiol + progestogen	0.05 E+P 0.05 E+P	1232 1227	Patch cont. Patch cycl.	12	Poor	D	— -0.01 (-0.09 to 0.06)
Akhila 2006[99]	CEE + MPA Estradiol + MPA Estradiol + MPA	0.625 E+2.5 P 1.5 E+2.5 P 0.05 E+2.5 P	35 25 28	Oral Skin gel Patch	52	Poor	G	— -1.10 (-1.96 to -0.23) -1.39 (-2.23 to -0.55)
Serrano 2006[98]	CEE + MPA Estradiol + MPA	0.625 E+10 P 0.05 E+10 P	52 52	Oral Patch	52	Poor	G	— 0.00 (-0.39 to 0.39)
Odabasi 2007[90]	Estradiol + progestogen Estradiol + progestogen	0.3 E+90 P 0.05 E+90 P	32 29	Spray Patch	12	Poor	G	— -0.28 (-0.79 to 0.23)

CI: confidence interval; cont.: continuous; cycl: cycling; D: depressive symptoms; E: estrogen; P: progestogen; CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; NETA: norethisterone acetate; A: anxiety; G: global psychological well-being; FU: followup; SMD: standardized mean difference; Wks: weeks.

Estrogen Compared With Estrogen Plus Testosterone

One trial (Table 31) compared an estrogen/progestogen skin gel (n=53) with an estrogen/progestogen plus testosterone skin gel (n=53) and reported depressive symptoms, anxiety, and global psychological well-being using the Psychological General Well-Being scale.[213] The trial was rated poor quality and reported no difference between groups in depressive symptom scores. Significant improvements were reported in both anxiety scores and global scores in the testosterone group.

Table 31. Trials comparing estrogen with estrogen plus testosterone reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Nathorst-Boos 2006[213]	Estrogen + progestogen Estrogen + progestogen + testosterone	NR 10 T	53 53	skin gel skin gel	26	Poor	D	— -0.17 (-0.55 to 0.21)
							A	— -0.65 (-1.05 to -0.26)
							G	— -0.46 (-0.84 to -0.07)

A: anxiety; CI: confidence interval; D: depressive symptoms; FU: followup; G: global psychological well-being; NR: not reported; SMD: standardized mean difference; T: testosterone; Wks: weeks.

Progesterone Alone Compared With Placebo

Two trials (Table 32) compared progesterone skin cream with placebo and reported psychological outcomes. One compared four different progestin skin cream doses (5 mg, 20 mg, 40 mg, and 60 mg) with placebo skin cream and reported Greene psychological scores. The trial was rated fair quality and found no significant difference in global psychological scores between any of the doses of progesterone skin cream compared with placebo.[102] The other trial compared a 32 mg progesterone skin cream with placebo, and reported Greene anxiety and depression

scores, and MENQOL global psychological scores. None of the psychological measures improved significantly in the treatment group compared with the placebo group.[103]

Table 32. Trials comparing progestin alone with placebo reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Benster 2009[102]	Placebo	—	35	Skin cream	24	Fair	G	—
	Progesterone	5	45	Skin cream				0.04 (-0.41 to 0.48)
	Progesterone	20	40	Skin cream				0.17 (-0.29 to 0.63)
	Progesterone	40	38	Skin cream				-0.07 (-0.54 to 0.39)
	Progesterone	60	33	Skin cream				0.14 (-0.34 to 0.62)
Wren 2003[103]	Placebo	—	35	Skin cream	12	Poor	D	—
	Progesterone	32	33	Skin cream				0.00 (-0.48 to 0.48)
							A	—
								-0.31 (-0.79 to 0.17)
							G	—
								-0.02 (-0.50 to 0.46)

A: anxiety; CI: confidence interval; D: depressive symptoms; G: global psychological well-being; FU: followup; SMD: standardized mean difference; Wks: weeks.

Estrogen Compared With Nonprescription

Two trials compared hormone treatments with black cohosh and reported psychological outcomes. Both trials found psychological outcomes for black cohosh similar to hormone treatments. One 12 week 3-arm trial compared black cohosh, standard dose estrogen plus progesterone, and standard dose estrogen plus MPA. The authors reported that all three treatments were accompanied by significantly improved overall MENQOL psychological score, Hospital Anxiety Score, and Hospital Depression Score, with no statistically significant difference between the treatments.[214] The other trial compared black cohosh with an ultralow-dose estrogen/progestogen patch and reported anxiety outcomes.[215] Both treatments were accompanied by significantly improved anxiety ($p<0.001$ for both arms of the trial). There was no significant difference between the treatments (Table 33).

Table 33. Trials comparing estrogen with nonprescription treatments reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Zheng 2013[214]	Black cohosh	NR	31	Oral	12	Poor	D	—
	E2V + P	NR	30	Oral				-0.26 (-0.77 to 0.25)
	E2V + MPA	NR	28	Oral				-0.04 (-0.56 to 0.4)
							A	—
								-0.19 (-0.70 to 0.32)
								-0.03 (-0.54 to 0.49)
							G	—
								-0.25 (-0.76 to 0.26)
								-0.21 (-0.73 to 0.31)
Nappi 2005[215]	Black cohosh	40	32	Oral	13	Poor	D	—
	Estradiol + dihydrogesterone	0.00357 E + 10 P	32	Patch				0.09 (-0.40 to 0.59)
							A	—
								-0.09 (-0.58 to 0.40)

A: anxiety; CI: confidence interval; D: depressive symptoms; G: global psychological well-being; FU: followup; NR: not reported; SMD: standardized mean difference; Wks: weeks

Prescription Compared With Placebo

One randomized, double-blind trial (Table 34) compared eszopiclone, a treatment used for insomnia (n=30), with placebo (n=29) and reported the Beck anxiety score as an outcome.[105] The trial was rated poor quality and found a significant improvement in anxiety among the treatment group with a wide confidence interval (SMD: -0.57; 95% CI: -1.10 to -0.05).

Table 34. Trials comparing prescription treatments with placebo reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Joffe 2010[105]	Placebo	—	29	oral	4	poor	A	—
	Eszopiclone	3	30	oral				-0.57 (-1.10 to -0.05)

SMD: standardized mean difference; CI: confidence interval; G: global psychological well-being; FU: followup; Wks: weeks

Nonprescription Agents Compared With Placebo

Twenty-five trials (Table 35) compared various nonprescription agents with placebo and reported 41 psychological outcomes (depressive symptoms [n=11], anxiety [n=14], and global psychological well-being [n=16]) (6 good, 4 fair, and 15 poor quality). Three trials compared black cohosh with placebo.[130, 149, 150] Two trials each examined: black cohosh,[86, 216] and maritime pine extract.[110, 125] One trial each examined: Er-Xian decoction,[123] micronutrients,[133] homeopathic remedy,[121] Jiawei Qing'e Fang,[120] Chinese medicinal herbs,[122] Estro-G 100®,[119] nutritional supplement,[132] dioscorea alata,[117] green tea polyphenols,[153] St. John's wort,[129] herbal extract,[107] black cohosh with plant extracts,[109] isoflavones with magnolia bark,[111] rheum rhaponticum,[112] flaxseed,[152] black cohosh plus St. John's wort,[128] gingko biloba with ginseng,[89] and ginseng.[88]

Trials reporting significant improvements compared with placebo were: Zhong et al.—improved global psychological well-being with Er-Xian decoction (SMD: -0.56; 95% CI: -0.95 to -0.18)[123]; Schellenberg et al.—improved global psychological well-being with both doses of black cohosh (6.5 mg, SMD: -0.43; 95% CI: -0.81 to -0.05 and 13 mg, SMD: -0.96; 95% CI: -1.36 to -0.56)[86]; Chang et al.—improved depressive symptoms and anxiety with Estro-G 100® (SMD: -0.69; 95% CI: -1.22 to -0.17 and SMD: -1.04; 95% CI: -1.58 to -0.50)[119]; Hsu et al.—improved anxiety and global psychological well-being with dioscorea alata (SMD: -0.95; 95% CI: -1.50 to -0.36 and SMD: -0.78; 95% CI: -1.36 to -0.20)[117]; Labrie et al—inconsistent improvements in global psychological well-being with different doses of vaginal DHEA.[149]; Yang et al.—improved depressive symptoms and anxiety with maritime pine extract (SMD: -0.41; 95% CI: -0.73 to -0.09 and SMD: -0.81; 95% CI: -1.14 to -0.48)[110]; Mucci—improved depressive symptoms and anxiety with a combination of isoflavones and magnolia bark (SMD: -0.72; 95% CI: -1.15 to -0.28 and SMD: -0.96; 95% CI: -1.40 to -0.52)[111]; Heger et al—improved anxiety and global psychological well-being with rheum rhaponticum (SMD: -0.77; 95% CI: -1.16 to -0.38 and SMD: -0.50; 95% CI: -0.88 to -0.12)[112]; Uebelhack et al.—improved depressive symptoms and global psychological well-being with a combination of black cohosh and St. John's wort (SMD: -1.32; 95% CI: -1.57 to -1.07 and SMD: -0.39; 95% CI: -0.62 to -0.16);[128] and Osmers et al.—improved global psychological well-being with black cohosh (SMD: -0.28, 95% CI: -0.51 to -0.04).[216]

Table 35. Trials comparing nonprescription agents with placebo reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Kohama 2013[125]	Placebo	—	70	Oral	12	Poor	A	—
	Maritime pine extract	30	72	Oral				-0.31 (-0.64 to 0.03)
Zhong 2013[123]	Placebo	—	54	Oral	12	Fair	G	—
	Er-Xian decoction[a]	—	54	Oral				-0.56 (-0.95 to -0.18)
Pandit 2012[133]	Placebo	—	25	Oral	12	Poor	A	—
	Micronutrient	—	29	Oral				-0.49 (-1.10 to 0.12)
Von Hagens 2012[121]	Placebo	—	26	Oral	12	Fair	D	—
								0.14 (-0.33 to 0.61)
	Homeopathic remedy[b]	—	57	Oral			A	—
								-0.02 (-0.49 to 0.44)
							G	—
								0.36 (-0.11 to 0.83)
Schellenberg 2012[86]	Placebo	—	54	Oral	12	Fair	G	—
	Black cohosh	6.5	57	Oral				-0.43 (-0.81 to -0.05)
	Black cohosh	13	55	Oral				-0.96 (-1.36 to -0.56)
Xia 2012[120]	Placebo	—	32	Oral	12	Good	G	—
	Jiawei Qing'e Fang	3500	32	Oral				-0.41 (-0.91 to 0.09)
Yang 2012[122]	Placebo	—	98	Oral	24	Poor	G	—
	Chinese medicinal herbs[c]		105	Oral				-0.14 (-0.42 to 0.14)
Chang 2011[119]	Placebo	—	32	Oral	12	Fair	D	—
								-0.69 (-1.22 to -0.17)
	EstroG-100®[d]	257	29	Oral			A	—
								-1.04 (-1.58 to -0.50)
Andrikoula 2011[132]	Placebo	—	34	Oral	12	Poor	A	—
	Nutritional supplement[e]	—	36	Oral				0.18 (-0.30 to 0.65)
Hsu 2011[117]	Placebo	—	25	Oral	52	Poor	D	—
								-0.38 (-0.95 to 0.18)
	Dioscorea alata	24	25	Oral			A	—
								-0.95 (-1.50 to -0.36)
							G	—
								-0.78 (-1.36 to -0.20)
Shen 2010[153]	Placebo	—	44	Oral	24	Poor	G	—
	Green tea polyphenols	500	47	Oral				-0.14 (-0.56 to 0.27)
Labrie 2009[149]	Placebo	—	53	Ovule	12	Poor	G	—
	DHEA	3.25	53	Ovule				-0.51 (-0.90 to -0.12)
	DHEA	6.5	56	Ovule				-0.18 (-0.55 to 0.20)
	DHEA	13	54	Ovule				-017 (-0.56 to 0.21)
Panjari 2009[150]	Placebo	—	42	Oral	26	Good	G	—
	DHEA	50	43	Oral				0.08 (-0.51 to 0.34)
van Die 2009[129]	Placebo	—	50	Oral	16	Good	D	—
								0.16 (-0.24 to 0.55)
	St John's wort	900	50	Oral			A	—
								0.22 (-0.17 to 0.62)
							G	—
								0.21 (-0.19 to 0.60)
Haines 2008[107]	Placebo	—	39	Oral	26	Poor	G	—
	Herbal extract	3000	45	Oral				0.39 (-0.05 to 0.82)

Table 35. Trials comparing nonprescription agents with placebo reporting psychological outcomes (continued)

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Van der Sluijs 2009[109]	Placebo	—	46	Oral	16	Good	D	—
	Black cohosh + plant extracts[f]	3820	46	Oral				0.19 (-0.23 to 0.60)
							A	—
								0.28 (-0.13 to 0.70)
							G	—
								0.26 (-0.15 to 0.68)
Yang 2007[110]	Placebo	—	75	Oral	24	Poor	D	—
	Maritime pine extract	200	80	Oral				-0.41 (-0.73 to -0.09)
							A	—
								-0.81 (-1.14 to -0.48)
Mucci 2006[111]	Placebo	—	45	Oral	24	Poor	D	—
	Isoflavones + magnolia bark	60	44	Oral				-0.72 (-1.15 to -0.28)
							A	—
								-0.96 (-1.40 to -0.52)
Heger 2006[112]	Placebo	—	55	Oral	12	Poor	A	—
	Rheum rhaponticum	4	54	Oral				-0.77 (-1.16 to -0.38)
							G	—
								-0.50 (-0.88 to -0.12)
Lewis 2006[152]	Placebo	—	33	Oral	16	Good	G	—
	Flaxseed	50	33	Oral				-0.05 (-0.58 to 0.48)
Uebelhack 2006[128]	Placebo	—	143	Oral	16	Good	D	—
	Black cohosh + St John's wort	3.75+70	151	Oral				-1.32 (-1.57 to -1.07)
							G	—
								-0.39 (-0.62 to -0.16)
Osmers 2005[216]	Placebo	—	141	Oral	12	Poor	G	—
	Black cohosh	40	145	Oral				-0.28 (-0.51 to -0.04)
Hartley 2004[89]	Placebo	—	27	Oral	12	Poor	D	—
	Gingko biloba + ginseng	320	30	Oral				-0.15 (-0.68 to 0.37)
							A	—
								-0.23 (-0.75 to 0.30)
Wiklund 1999[88]	Placebo	—	191	Oral	16	Poor	D	—
	Ginseng	200	193	Oral				-0.12 (-0.32 to 0.08)
							A	—
								-0.18 (-0.38 to 0.03)
Barnhart 1999[130]	Placebo	—	30	Oral	12	Poor	D	—
	DHEA	50	30	Oral				-0.23 (-0.74 to 0.28)
							A	—
								0.16 (-0.35 to 0.67)

SMD: standardized mean difference; CI: confidence interval; DHEA: dehydroepiandrosterone; D: depressive symptoms; A: anxiety; G: global psychological well-being; FU: followup; Wks: weeks

[a] combination of xian mao, xian ling pi, ba ji tian, dang gui, zhi mu, huang bai

[b] globuli velati of saccharose coated with Apis regina tota, Argentum metallicum, and Ovaria bovis

[c] Gengnianningxin capsules if Kidney-Yin deficiency; Bushen oral liquid if Kidney-Yang deficiency

[d] combination of cynanchum wilfordii, phlomis umbrosa, angelica gigas

[e] combination of 21 vitamins and minerals

[f] combination of black cohosh, er xian tang, zhi bai di huang wan

Nonprescription Compared With Nonprescription

One trial (Table 36) compared isoflavones with isoflavones plus magnolia bark and reported depressive symptoms and anxiety outcomes.[138] and one trial compared two different doses of isoflavones.[137] The isoflavones plus magnolia bark trial was rated poor quality and found no difference in depressive symptom scores or anxiety scores between the two groups.[138] The trial comparing different doses of isoflavones reported that both doses significantly improved the Greene psychological scale scores, with no difference between the groups.[137]

Table 36. Trials comparing nonprescription agents with nonprescription agents reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Yang 2012[137]	Isoflavones	35	57	Oral	24	Poor	G	—
	Isoflavones	70	50	Oral				0.13 (-0.26 to 0.51)
Agosta 2011[138]	Isoflavones	60	300	Oral	12	Poor	D	—
	Isoflavones + magnolia bark	60	334	Oral				-0.09 (-0.24 to 0.07)
							A	—
								-0.16 (-0.31 to 0.00)

SMD: standardized mean difference; CI: confidence interval; D: depressive symptoms; A: anxiety; FU: followup; Wks: weeks.

SSRI/SNRIs Compared

One randomized double-blind trial (Table 37) compared flexible-dose desvenlafaxine (100 to 200 mg/d) with flexible-dose escitalopram (10 to 20 mg/d) and reported Hamilton depression and anxiety scores.[217] The trial was rated good quality. The antidepressants were equally effective in reducing both depressive symptoms and anxiety scores (SMD: -0.10; 95% CI: -0.30 to 0.10, and SMD: -0.05; 95% CI: -0.25 to 0.15, respectively).

Table 37. Trials comparing SSRI/SNRIs reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Soares 2010[217]	Desvenlafaxine	100-200	185	Oral	8	Poor	D	—
	Escitalopram	10-20	203	Oral				-0.10 (-0.30 to 0.10)
							A	—
								-0.05 (-0.25 to 0.15)

SMD: standardized mean difference; CI: confidence interval; D: depressive symptoms; A: anxiety; FU: followup; Wks: weeks..

SSRI Compared With Nonprescription

One trial (Table 38) compared black cohosh with fluoxetine, reporting depressive symptoms and global psychological measures.[84] After 12 weeks of followup, Oktem et al. reported that both treatments were accompanied by similar improvements in the SF-36 global mental health score and the Beck Depression Score. The trial was rated poor quality.

Table 38. Trials comparing SSRI/SNRIs with nonprescription agents reporting psychological outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Outcome	SMD (95% CI)
Oktem 2007[84]	Black cohosh	40	40	Oral	26	Poor	D	— -0.85 (-1.31 to -0.39)
	Fluoxetine	20	40	Oral			G	— 0.09 (-0.35 to 0.54)

CI: confidence interval; G: global psychological well-being; FU: followup; SMD: standardized mean difference; Wks: weeks.

Trials With No Quantifiable Data

Seven trials did not allow determination of standardized effect estimates because of reporting. Five reported depressive symptom outcomes and two reported global psychological outcomes. Results of these trials would not have affected the overall outcomes presented above.

Gupta et al. conducted a one-year trial, comparing a standard dose of oral estrogen alone (n=25), DHEA (n=25), and placebo (n=25). At baseline, no women reported depressive symptoms. At followup (unspecified time), 4 percent of the estrogen alone treatment group, 0 percent of the DHEA group, and 16 percent of the placebo group reported depressive symptoms.[143]

In a subset of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS) group, Raz et al. reported changes in the Profile of Mood States among the placebo and low-dose estrogen/progestogen groups. For this particular analysis, the oral and patch low-dose estrogen/progestogen groups were combined. Depressive symptom scores improved in 15 percent of the placebo group and in 42 percent of the treatment group.[218]

Yalamanchili et al. conducted a four-arm trial with placebo, calcitriol, standard dose estrogen/progestin, and standard dose estrogen/progestin plus calcitriol. The Geriatric Depression Scale measured depressive symptoms among the four groups. None of the treatment groups experienced significant differences compared to placebo: calcitriol (p=0.77); estrogen/progestin (p=0.46), and estrogen/progestin plus calcitriol (p=0.98).[219]

Liske et al. performed a 12-week trial comparing black cohosh with placebo and reported median Self-Rating Depression Scale scores. The placebo group had a baseline median of 44.5 and a 12 week median of 37.0. The black cohosh group had a baseline median of 44.0 and a 12 week median of 36.0.[155]

Stricklet et al. conducted a four-arm randomized trial of two different doses of raloxifene, conjugated equine estrogen, and placebo. Women's Health Questionnaire anxiety and depressive symptoms scores were measured. Estrogen alone improved psychological scores more than placebo, but statistical significance is unknown because analysis was not conducted on these arms of the trial separately.[199]

Auerbach et al. conducted a randomized trial comparing pomegranate seed oil with placebo, reporting MRS II global mental health scores. The women receiving pomegranate seed oil had a baseline median score of 4.0 and a 12 week followup score of 2.0. The women in the placebo group had a baseline median score of 6.0 and a 12 week followup score of 4.5. The baseline median scores were significantly different. There was not a significant difference in change scores between the two groups.[118]

Davis et al. performed a randomized crossover trial that compared a standard-dose estrogen spray with a standard-dose estrogen patch.[91] Both treatments significantly improved global psychological well-being scores. No significant difference between the two treatments was found. No quantifiable data between the groups were provided.

Strength of Evidence Ratings—Psychological Symptoms

Table 39 summarizes strength of evidence ratings.

Table 39. Strength of evidence ratings for psychological symptoms

Domain	Comparisons	Comparators[a]			Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Downgrading Rationale
Global	6	**SSRI/SNRI**	vs	Placebo	M	C	D	P	U	High	3 good and 3 poor quality trials
Depressive Symptoms	5	**SSRI/SNRI**	vs	Placebo	M	C	D	P	U	High	2 good and 3 poor quality trials
Anxiety Symptoms	3	**SNRI**	vs	Placebo	M	C	D	P	U	High	2 good and 1 poor quality trial
Global	14	**Estrogen**	vs	Placebo	M	C	D	P	U	High	2 good, 6 fair, and 8 poor quality trials
Depressive Symptoms	18	**Estrogen**	vs	Placebo	M	C	D	P	U	High	2 good, 1 fair, and 17 poor quality trials
Anxiety Symptoms	13	**Estrogen**	vs	Placebo	M	C	D	P	U	High	1 good, 1 fair, and 12 poor quality trials
Global	2	**Gabapentin**	vs	Placebo	H	U	D	I	U	Insuff	2 poor quality trials; consistency unknown; CI overlaps 0
Global	7	**Isoflavones**	vs	Placebo	M	I	D	I	U	Low	4 good, 1 fair, and 2 poor quality trials; CI overlaps 0
Depression	9	**Isoflavones**	vs	Placebo	H	C	D	P	S	Low	1 good and 8 poor quality trials; potential reporting bias
Anxiety Symptoms	7	**Isoflavones**	vs	Placebo	H	C	D	P	U	Mod	1 good and 6 poor quality trials

Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I), Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S), Undetected (U); SOE: strength of evidence; Mod: moderate; Insuff: insufficient; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor.

[a] Bold font of comparator indicates the more effective treatment; if both comparators are bold, the treatments are equivalently effective

Sexual Function

Key Points

- A total of 94 including over 28,000 women, reported sexual function outcomes of treatment with hormones, SSRI/SNRIs or nonprescription agents such as isoflavones, DHEA and herbal extracts.
- Study quality was generally rated poor (75 percent). Funding was provided by industry for 49 trials, public sources in 17 trials, industry and public sources in two trials, and the type of funding was not stated for 25 trials.
- Sexual function outcomes were reported using a variety of scales, representing four domains of sexual function: global, pain, interest or activity frequency.
- Strength of evidence of relative effectiveness of agents in ameliorating symptoms of sexual function is as follows:
    - There is **high** strength of evidence that vaginal estrogen reduced pain during sex compared with placebo: SMD -0.54 (95% CI -0.73 to -0.34; 10 trials, n=3,205).
    - There is **moderate** strength of evidence that oral estrogen reduces pain compared with placebo: SMD -0.22 (95% CI: -0.35 to -0.09; 4 trials, n=1,661).
    - There is **high** strength of evidence that estrogen improves global measures of sexual function compared with placebo: SMD 0.27 (95% CI: 0.19 to 0.35; 15 trials, n=4,228).
    - There is **insufficient** strength of evidence that an SSRI or SNRI improves global measures of sexual function compared with placebo.
    - There is **low** strength of evidence that isoflavones improve global measures of sexual function compared with placebo: SMD 0.24 (95% CI: -0.12 to 0.61; 4 trials, n=586).
    - There is **moderate** strength of evidence that estrogens improves measures of sexual interest compared with placebo: SMD 0.18 (95% CI: 0.01 to 0.26; 7 trials, n=2,213).
    - There is **insufficient** strength of evidence that SNRIs improve measures of sexual interest compared with placebo.
    - There is **insufficient** strength of evidence that isoflavones improve global measures of sexual interest compared with placebo.
    - There is **moderate** strength of evidence that testosterone improves measures of sexual activity compared with placebo: SSE/4 weeks 1.17 (95% CI: 0.88 to 1.46; 8 trials, n=2,820).

Included Trials

Of the 283 trials included in this review, 94 trials (33.2 percent) trials reported sexual function outcomes (39 trials specified sexual function as a primary outcome). Sixty-one trials examined hormone treatment effects and sexual function, with the following comparators: placebo (34 trials), other hormones (23 trials), and nonprescription treatments (three trials). Twenty-eight trials examined the effects of nonprescription treatments compared with placebo; nonprescription treatments included isoflavones, DHEA, herbal extracts, and ginseng. Five trials compared SSRI or SNRIs with placebo.

Trials were conducted in more than 22 countries and 18 trials were multinational. Single country trials were conducted in the United States (n=20), Australia (n=8), Italy (n=5), Canada (n=4), China (n=4), United Kingdom (n=4), Taiwan (n=4), Denmark (n=3), Brazil (n=3), and Germany (n=3), with two or fewer trials conducted in Hong Kong, India, Sweden, Turkey, Croatia, Ecuador, Japan, Netherlands, Norway, Singapore, Spain, Thailand, and Ukraine. The trials were conducted at over 2,300. Length of followup ranged from 8 to 260 weeks. Additional trial characteristics are shown in Table 40.

Sexual function was reported using a variety of measures and scales. The domains of sexual activity assessed fell into four broad categories: global (i.e., assessed two or more domains), pain (dyspareunia), interest, or activity frequency. If results for more than one domain were reported in a trial, both were included. Forty-four trials reported a global measure (MENQOL, WHQ, MRS, and McCoy scales were most common, though others were also used); 29 reported pain during intercourse, 23 interest, and eight reported frequency of satisfying sexual episodes (activity). Specific items in the different scales include:

- Greene Climacteric Scale rated a single question, "loss of interest in sex," scaled from zero (none) to three (severe)—15 trials.
- Menopause-specific Quality of Life (MENQOL) assessed sexual function in three questions scaled from zero (not bothered) to eight (extremely bothered)—22 trials.
- Women's Health Questionnaire assessed sexual function using three questions on interest, pain, and activity, rated in a 4-point scale, with higher scores indicating more severe symptoms—10 trials.
- Self-reported dyspareunia (yes/no)—21 trials.
- Satisfying sexual episodes—eight trials.
- The remaining trials used other sexual function scales.

Study quality was generally poor (74.5 percent), with 14 trials judged good and 10 trials to be fair quality. Length of followup ranged from 8 weeks to 260 weeks. Industry funding was indicated in 51 trials, public funding in 17 trials, and two trials reported both industry and public funding. Table 40 describes additional trial and patient characteristics.

Table 40. Characteristics of trials assessing efficacy for sexual function

	Characteristic	Value
Trial Characteristics	Number of trials	94
	Total number of women	28,137
	Number of sites from trials that specified	2,367 1 to 502 (mean 30; median 5)
	Trials described only as multicenter	7 (7.4)
	Multicenter trials	61 (64.9)
	Two-arm trials	73 (77.7)
	Multi-arm trials	21 (22.3)
	Women per trial	50 to 2,459 (mean 299; median 156.5)
	Range of followup (weeks)	8 to 260 (mean 25.2; median 16)
Funding	Industry only	49 (52.1)
	Public only	17 (18.1)
	Industry and public	2 (2.1)
	Not stated	25 (26.6)
Comparator Category	Placebo vs. hormone	34 (36.2)
	SSRI/SNRI vs. placebo or other SSRI/SNRI	5 (5.3)
	Placebo vs. other prescription	0 (0.0)
	Placebo vs. nonprescription	28 (29.8)
	Placebo vs. hormone vs. nonprescription	1 (1.1)
	Hormone vs. hormone	23 (24.5)
	Hormone vs. nonprescription	3 (3.2)
	Nonprescription vs. SSRI/SNRIs	0 (0.0)
	Nonprescription vs. nonprescription	0 (0.0)
Study Quality	Good	14 (14.9)
	Fair	10 (10.6)
	Poor	70 (74.5)
	Not rated (abstract or gray literature)	0 (0.0)
Patient Demographics	Mean age (years)	46.5 to 59.9 (NR 8)
	Age range (years)	26.0 to 86.0 (NR 75)
	Years since menopause	5.3 (0.7 to 9.8) (NR 58)
	Current smokers (%)	0.0 to 44.0 (NR 74)
	Mean BMI (kg/m^2)	17.3 to 29.1 (NR 31)
	White (%)	0.0 to 100.0
	Black (%)	0.0 to 46.3
	Hispanic (%)	0.0 to 10.5
	Asian (%)	0.0 to 100.0
	Other (%)	0.0 to 41.0
Uterus Status	All intact	30 (31.9)
	All absent	7 (7.4)
	Mixed	37 (39.4)
	Range, percentage intact among trials with	25 to 94.3
	Not reported	20 (21.3)

Note: Demographics were not reported in all studies.
N: not reported; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

Evidence Synthesis for Sexual Function

Standard mean differences were calculated to allow comparisons of outcomes from different sexual function scales. Analyses were conducted by domain (pain, global, activity and interest), by route of administration (oral or vaginal), and by uterine status (all intact, all absent, or mixed) when possible. Pooling was considered possible for pairwise comparisons where evidence

included at least three trials. Pooling of the following comparators and conditions was performed:

- Pain: vaginal estrogens versus placebo (n=10); oral estrogens versus placebo (n=4); all estrogens (either vaginal or oral) versus placebo (n=14)
- Global: all estrogens (either vaginal or oral) versus placebo (n=15); SSRI/SNRI versus placebo (n=2); isoflavones versus placebo (n=4)
- Activity: testosterone versus placebo in trials with women with/without uteri mixed or trials with women with intact uteri (n=4); testosterone versus placebo in trials with all women without intact uteri (n=4); testosterone versus placebo all trials combined (n=8)
- Interest: all estrogens versus placebo (n=7); isoflavones versus placebo (n=5); SNRI versus placebo (n=2)

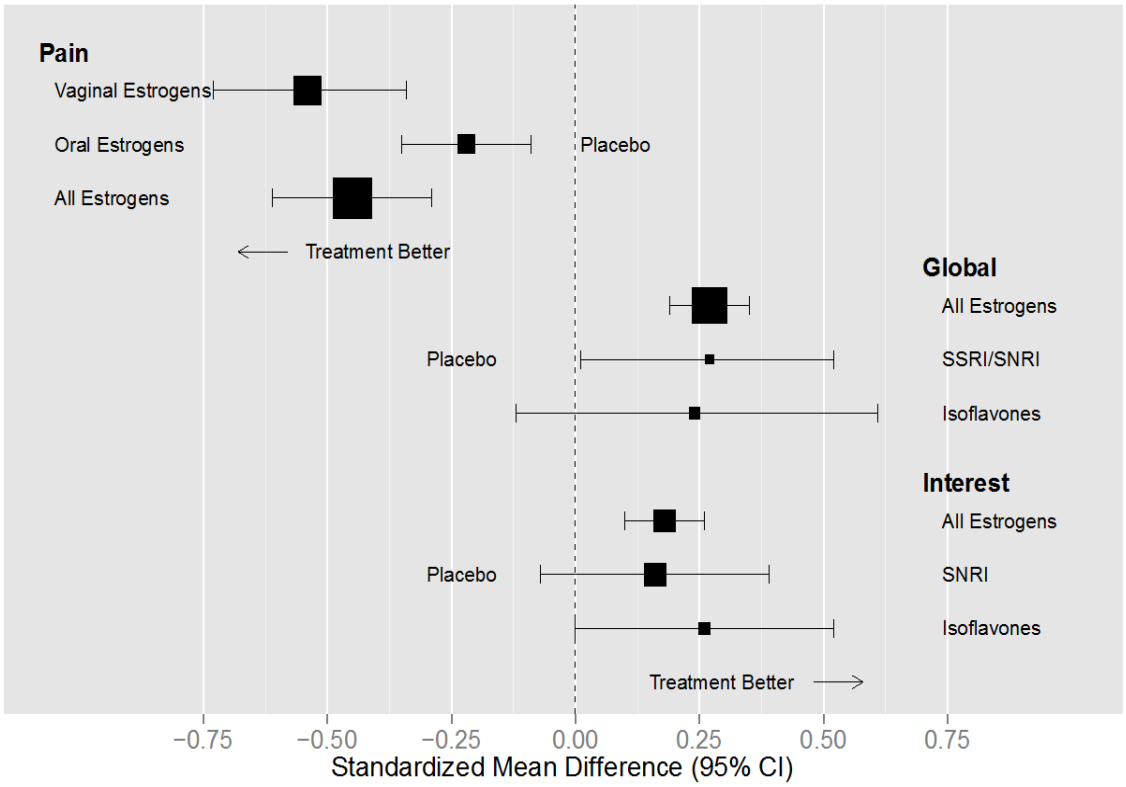
Results are shown in Table 41, Figure 11 and Figure 12.

Table 41. Pooled effect sizes from trials for improvement in sexual function

Sexual Function Domain	Comparators Versus Placebo	No. of Trials	SMD (95% CI)
Pain (lower is better)	Vaginal estrogens	10	-0.54 (-0.73 to -0.34); tau^2=0.07
	Oral estrogens	4	-0.22 (-0.35 to -0.09); tau^2=0.01
	All estrogens	14	-0.45 (-0.61 to -0.29); tau^2=0.07
Global (higher is better)	All estrogens	15	0.27 (0.19 to 0.35); tau^2=0.00
	SSRI/SNRI	2	0.27 (0.01 to 0.52); tau^2=0.00
	Isoflavones	4	0.24 (-0.12 to 0.61); tau^2=0.10
Interest (higher is better)	All estrogens	7	0.18 (0.10 to 0.26); tau^2=0.00
	SNRI	2	0.16 (-0.07 to 0.39); tau^2=0.02
	Isoflavones	5	0.26 (-.001 to 0.52); tau^2=0.06
			Mean Difference SSE/4 Weeks
Activity (higher is better)	Testosterone patch, no women with intact uteri/ovaries	4	1.05 (0.64 to 1.45); tau^2=0.00
	Testosterone (3 patch, 1 oral), women with/without intact uteri/ovaries	4	1.31 (0.89 to 1.72); tau^2=0.00
	Testosterone (7 patch, 1 oral), all trials	8	1.17 (0.88 to 1.46); tau^2=0.00

SMD: standardized mean difference; CI: confidence interval; SSE: satisfying sexual episodes.

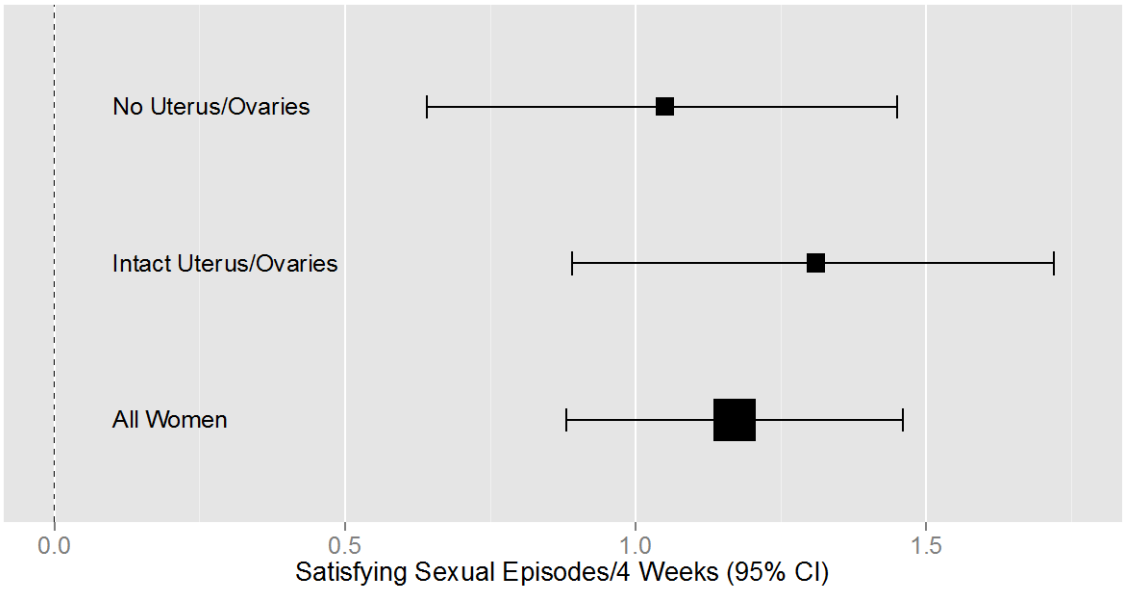
Figure 11. Caterpillar plot for sexual function: pain, global, and interest—standardized mean differences and 95% confidence intervals[a]



a

[a]Symbol size proportional to the number of women included in the comparison.

Figure 12. Caterpillar plot for sexual function: satisfying sexual episodes for testosterone compared with placebo—mean difference and 95% confidence intervals[a]



[a]Symbol size proportional to the number of women included in the comparison.

Estrogen Compared With Placebo (Pain)

Fourteen trials compared estrogens with placebo and reported pain during sex. Ten trials compared vaginal estrogens with placebo (two fair and eight poor quality)[179, 220-227] and four trials compared oral estrogens with placebo (all poor quality).[187, 228-230] In the pooled result, any estrogen improved reported pain during sex compared with placebo (SMD -0.45; 95% CI: -0.61 to -0.29; tau^2=0.07).

Analyses by route of administration was consistent with a larger effect for vaginal estrogens (SMD -0.54; 95% CI: -0.73 to -0.34; tau^2=0.07), than for oral estrogens (SMD -0.22; 95% CI: -0.22 to -0.09; tau^2=0.01).

The strength of evidence that vaginal estrogens improve reported pain during sex among menopausal women compared with placebo is rated high. The strength of evidence that oral estrogens compared with placebo improve reported pain during sex among menopausal women is rated moderate.

Estrogen Compared With Placebo (Global)

Fifteen trials compared estrogens with placebo and reported a global measure for sexual function (two good, four fair, and nine poor quality).[35, 173, 177, 181-184, 186, 187, 192, 198, 199, 231-233] Because various routes of administration were used—oral, topical, nasal, and vaginal (10, three, one, and one respectively)—all trial results were combined for analysis. Estrogens significantly improved global measures of sexual function compared with placebo (SMD 0.27; 95% CI: 0.19 to 0.35; tau^2=0.00). The strength of evidence that estrogens improve a global assessment of sexual function compared with placebo is rated high.

SSRI/SNRI Compared With Placebo (Global)

Two trials compared antidepressants with placebo and reported sexual function outcomes as a global measure (one good and one fair quality).[164, 167] The pooled SMD was 0.27 (95% CI: 0.01 to 0.52) tau^2=0.00. The strength of evidence that SNRIs improve a global assessment of sexual function compared with placebo is rated insufficient.

Isoflavones Compared With Placebo (Global)

A global measure of sexual function was reported in four trials comparing isoflavones with placebo (two good, one fair, and one poor quality).[152, 204, 206, 211] The pooled SMD was 0.24 (95% CI: -0.12 to 0.61) tau^2=0.10), accompanied by substantial heterogeneity. The strength of evidence that SNRIs compared with placebo improve a global assessment of sexual function compared with placebo is rated low.

Estrogens Compared With Placebo (Interest)

Seven trials compared estrogens with placebo and assessed interest in sex (one fair and six poor quality).[175, 179, 180, 197, 228, 230, 234] Routes of estrogen administration included oral, vaginal, and topical (oral in five trials). The pooled SMD was consistent with an increase in reported sexual interest—0.18 (95% CI: 0.10 to 0.26; tau^2=0.00). The strength of evidence that estrogens improve sexual interest compared with placebo is rated moderate.

SNRI Compared With Placebo (Interest)

Two trials compared desvenlafaxine with placebo (both good quality).[168, 235] The combined SMD from the trials was 0.16 (95% CI: -0.07 to 0.39; tau^2=0.02). The strength of evidence that desvenlafaxine improves sexual interest compared with placebo is rated insufficient.

Isoflavones Compared With Placebo (Interest)

Five trials compared isoflavones with placebo and assessed sexual interest (one good and four poor quality).[87, 201, 205, 236, 237] The pooled effect was not statistically significant, the confidence interval wide, and there was substantial heterogeneity—SMD 0.26 (95% CI: -0.001 to 0.52; tau^2=0.52). The strength of evidence that isoflavones improve sexual interest compared with placebo is rated insufficient.

Testosterone Compared With Placebo (Activity)

Eight trials compared testosterone with placebo and assessed satisfying sexual episodes (one fair and seven poor quality). The outcome was the number of episodes per four-week period. One episode per four-week period is the suggested minimal clinically important improvement.[73] Four trials, administering testosterone by patch, included only women without intact uteri and ovaries,[238-241] two trials, one patch and one oral testosterone, included only women with intact uteri and ovaries,[242, 243] and two trials, both using patches, included women with and without intact uteri and ovaries.[244, 245] Combining the eight trials showed that testosterone significantly improved sexual activity compared with placebo by 1.17 episode/4 weeks (95% CI: 0.88 to 1.46; tau^2=0.00). Analyses limited to the four trials including only women without intact uteri and ovaries also showed significant improvements in episodes compared with placebo (1.05; 95% CI: 0.64 to 1.45).

Compared with placebo, the strength of evidence that testosterone increases the number of satisfying sexual episodes compared with placebo is rated moderate.

Trials Not Pooled

Estrogen Compared With Placebo

One trial compared an ultralow dose estrogen patch with a placebo patch.[231] The MENQOL sexual subscore decreased in both groups: -0.8 (SD: 1.6) in the placebo group; -1.0 (SD: 1.7) in the estrogen group. The difference between the groups was not significant (Table 42).

Table 42. Trials comparing estrogen with placebo reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Sexual Function Domain	SMD (95% CI)
Haines 2009[231]	Placebo	—	80	Patch	12	Poor	Pain	—
	Estradiol	0.014	80	Patch				-0.20 (-0.64 to 0.24)

CI: confidence interval; SMD: standardized mean difference; Wks: weeks.

Estrogen Compared With Estrogen or Other Hormones

Five trials compared different doses of estrogen. Four of the five trials compared standard with low doses[246-249] and one trial compared standard with a high dose.[250] Two trials measured global sexual function, two measured sexual interest, and one measured pain during sexual activity. In all five trials, there were improvements in sexual function with estrogens, with no statistically significant differences among the estrogen doses (Table 43).

One trial randomized women to either 0.625 mg esterified estrogens or 0.625 esterified estrogens plus 1.25 mg methyltestosterone.[142] The outcome was a global measure of sexual function. After 16 weeks' followup, the group receiving testosterone with estrogen improved significantly compared with the estrogen alone group, with a standardized mean difference of 0.39 (95% CI: 0.12 to 0.66).

Due to the variety in outcome measures, synthesizing these data was not possible; because of treatment heterogeneity, strength of evidence was not rated.

Table 43. Trials comparing different estrogen doses reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Sexual Function Domain	SMD (95% CI)
Pitkin 2007[250]	E2V + MPA	1 E + 2.5 P	152	Oral				—
	E2V + MPA	1 E + 5 P	153	Oral				0.00 (-0.23 to 0.23)
	E2V + MPA	2 E + 5 P	154	Oral	52	Poor	Global	-0.23 (-0.45 to 0.00)
Cieraad 2006[246]	Estradiol + dydrogesterone	1 E + 10 P	97	Oral				—
	CEE + norgestrel	0.625 E + 0.15 P	89	Oral	24	Poor	Interest	0.10 (-0.19 to 0.38)
Utian 2005[247]	Estradiol + progestogen	0.9 E	77	Oral				—
	CEE + progestogen	0.625 E	84	Oral				-0.14 (-0.45 to 0.17)
	Estradiol + progestogen	1 E	80	Oral	12	Good	Pain	-0.29 (-0.60 to 0.03)
Loh 2002[248]	Estradiol + NETA	1 E + 0.5 P	42	Oral				—
	Estradiol + NETA	2 E + 1 P	39	Oral	26	Poor	Interest	0.08 (-0.36 to 0.52)
Limpaphayom 2006[249]		0.3 E + 1.5 P	291	Oral				—
	CEE + MPA	0.45 E + 1.5 P	300	Oral			Global	NS
	CEE + MPA	0.625 E + 2.5 P	286	Oral	24	Poor		NS
	CEE + MPA						Pain	—
								0.27 (-0.01 to 0.54)
								0.34 (0.07 to 0.61)
Lobo 2003[142]	Estrogen	0.625	109	Oral				—
	Estrogen + testosterone	0.625	107	Oral	16	Poor	Global	0.39 (0.12 to 0.66)

CEE: conjugated equine estrogen; CI: confidence interval; E: estrogen; E2V: estradiol valerate; MPA: medroxyprogesterone acetate; P: progestogen; SMD: standardized mean difference; Wks: weeks.

Different Routes of Estrogen Administration

Ten trials (Table 44) compared similar estrogen doses using different routes of administration. Two trials used a vaginal ring in one treatment group and vaginal cream in another[251, 252]; two trials used oral estrogens in one arm and estrogen patches in another[98, 253]; one trial used patches, either adding progestogen combined or sequential[146]; and one trial each used the following pairs of routes of administration: patch/spray,[91] oral/ring,[254] ring/tablet,[255] oral/cream,[256] and ring/pessary.[257] Five trials reported a global sexual function outcome, four reported pain, and one reported sexual interest. No trial found a significant difference in outcomes between routes of administration. These results on route of administration combined with the findings from the analysis on vaginal and oral estrogens compared with placebo in diminishing pain during sex, suggest global and pain outcomes also do not differ according to route of administration (strength of evidence moderate, Table 49).

Table 44. Trials comparing different estrogen routes of administration reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Sexual Function Domain	SMD (95% CI)
Serrano 2006[98]	CEE + MPA Estradiol + MPA	0.625 E + 10 P 0.05 E + 10 P	52 52	Oral Patch	52	Poor	Global	— 0.35 (-0.04 to 0.74)
Davis 2005[91]	Estradiol Estradiol	0.05 0.30	60 60	Patch Spray	16	Poor	Global	— -0.10 (-0.46 to 0.26)
Buckler 2003[254]	Estradiol + norethisterone Estradiol + norethisterone	1 E + 1 P 0.05 E + 1 P	75 84	Oral Ring	24	Fair	Interest	— 0.00 (-0.31 to 0.31)
Weisberg 2005[255]	Estradiol Estradiol	0.008 0.025	48 27	Ring Tablet	48	Poor	Global	— 0.01 (-0.46 to 0.49)
							Pain	— -0.45 (-0.93 to 0.03)
Lubbert 1997[146]	Estradiol, combined Estradiol, sequential	0.05 0.05	1232 1227	Patch Patch	12	Poor	Global	— 0.02 (-0.07 to 0.12)
Barentsen 1997[251]	Estradiol Estriol	0.0075 0.5	83 82	Ring Cream	12	Poor	Pain	— -0.07 (-0.40 to 0.27)
Ayton 1996[252]	Estradiol CEE	0.0075 0.625	131 63	Ring Cream	12	Poor	Pain	— -0.21 (-0.60 to 0.19)
Henriksson 1994[257]	Estradiol Estriol	0.0095 0.5	106 51	Ring Pessary	12	Poor	Pain	— -0.05 (-0.43 to 0.34)
Long 2006[256]	CEE CEE	0.625 0.625	37 36	Oral Cream	12	Poor	Pain	— -0.40 (-0.93 to 0.14)
Hilditch 1996[253]	CEE + MPA Estradiol + MPA	0.635 E + 10 P 0.014 E + 10 P	25 29	Oral Patch	14	Poor	Global	— NS

CEE: conjugated equine estrogen; CI: confidence interval; E: estrogen; FU: followup; MPA: medroxyprogesterone acetate; NS: not significant; P: progestogen; SMD: standardized mean difference; Wks: weeks.

Other Prescription Agents Compared With Placebo

One placebo-controlled trial examined ospemifene, an estrogen receptor agonist/antagonist, and measured change in severity of pain during intercourse. The ospemifene group experienced a significant decrease in pain compared with the placebo group (Table 45).[258]

Table 45. Trials comparing other prescription treatments with placebo reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Sexual Function Domain	SMD (95% CI)
Constantine 2014[258]	Placebo Ospemifene	— 60	302 303	Oral Oral	12	Fair	Pain	— -0.27 (-0.43 to -0.11)

SMD: standardized mean difference; CI: confidence interval FU: followup; Wks: weeks

Estrogen Compared With Nonprescription Agents

Two trials (Table 46) compared estrogen/progestogen therapy with nonprescription treatments. One examined pueraria mirifica for the treatment of pain relating to sexual function.[134] Pueraria mirifica is an herb considered highly estrogenic, found in Thailand. This

small study with a sample size of 60 women, did not find a significant difference between groups. The other trial compared two arms of estrogen/progestogen therapy with black cohosh.[214] The hormone therapy arms experienced more improvement in MENQOL sexual subscores compared with the black cohosh arm, but the differences between the groups was not significant.

Table 46. Trials comparing estrogens with nonprescription agents reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Sexual Function Domain	SMD (95% CI)
Chandeying 2007[134]	CEE + MPA	0.625 E + 2.5 P	30	Oral	24	Poor	Pain	—
	Pueraria mirifica	50	30	Oral				NS
Zheng 2013[214]	Black cohosh	NR	31	Oral	12	Poor	Global	—
	E2V + P	NR	30	Oral				0.51 (0.00 to 1.03)
	E2V + MPA	NR	28	Oral				0.43 (-0.09 to 0.95)

CEE: conjugated equine estrogen; CI: confidence interval; E: estrogen; FU: followup; MPA: medroxyprogesterone acetate; NR: not reported; P: progesterone; SMD: standardized mean difference; Wks: weeks.

SSRI/SNRIs Compared

One trial compared a serotonin-norepinephrine reuptake inhibitor (desvenlafaxine) with a selective serotonin reuptake inhibitor (escitalopram) and reported Change in Sexual Functioning Questionnaire as an outcome (Table 47).[148]

Table 47. Trials comparing SSRI/SNRIs reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Soares 2010[148]	Desvenlafaxine	100-200	178	oral	8	Good	—
	Escitalopram	10-20	194	oral			0.06 (-0.14 to 0.26)

CI: confidence interval; FU: followup; SMD: standardized mean difference.

Nonprescription Agents Compared With Placebo

Eighteen trials (Table 48) compared nonprescription agents with placebo and reported sexual function outcomes. The domains of the outcomes were global (n=11), interest (n=4), and pain (n=3).

Three trials compared isoflavones with placebo, and measured pain during intercourse. Two of the trials reported statistically significant improvements in pain,[87, 237] while one trial reported no difference in pain compared with placebo.[207]

Two trials compared ginseng with placebo, with one trial reporting a global sexual function outcome[88] and one reporting on sexual interest.[89] Neither trial reported significant improvements in either outcome.

Two trials compared maritime pine extract with placebo and reported global sexual function outcomes. The trial administering 200 mg pine extract reported significant improvements in sexual function compared with placebo[110], and the trial administering 30 mg pine extract reported no difference in sexual function compared with placebo.[125]

Two of the 18 trials compared DHEA with placebo and reported global sexual function outcomes.[149, 150] One was a four-arm trial with increasing doses of DHEA which were administered through a vaginal ovule and the other was a two-arm trial administering DHEA orally. The trial using vaginal ovules showed significant improvements in global sexual function

in the two higher doses compared with placebo,[149] while the trial using orally administered DHEA did not show a difference compared with placebo.[150] Due to the variety of dosages and treatments, pooling was not appropriate.

The remaining nine trials tested different treatments compared with placebo: Dang Gui Buxue Tang,[107] black cohosh with plant extracts,[109] Jiawei Qing'e Fang,[120] St. John's wort,[129] rheum rhaponticum,[112] dioscorea alata,[117] a homeopathic remedy[121] Chinese medicinal herbs,[122] and Er-Xian decoction.[123] None of these trials reported a significant improvement in the sexual function outcome measured.

Table 48. Trials comparing nonprescription agents with placebo reporting sexual function outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	Sexual Function Domain	SMD (95% CI)
Hidalgo 2005[87]	Placebo	—	53	Oral	26	Poor	Pain	—
	Isoflavones	80	53	Oral				-0.98 (-1.54 to -0.43)
Haines 2008[107]	Placebo	—	39	Oral	26	Poor	Global	—
	Dang Gui Buxue Tang	3000	45	Oral				0.10 (-0.33 to 0.53)
Van der Sluijs 2009[109]	Placebo	—	46	Oral	16	Good	Interest	—
	Black cohosh plus plant extracts[a]	3820	46	Oral				0.04 (-0.37 to 0.45)
Xia 2012[120]	Placebo	—	32	Oral	12	Good	Global	—
	Jiawei Qing'e Fang	3500	32	Oral				0.18 (-0.31 to 0.68)
Van Die 2009[129]	Placebo	—	50	Oral	16	Good	Interest	—
	St John's wort	900	50	Oral				-0.21 (-0.61 to 0.18)
Yang 2007[110]	Placebo	—	75	Oral	24	Poor	Global	—
	Maritime pine extract	200	80	Oral				0.50 (0.18 to 0.82)
Heger 2006[112]	Placebo	—	55	Oral	12	Poor	Global	—
	Rheum rhaponticum	4	54	Oral				0.38 (0.00 to 0.76)
Hsu 2011[117]	Placebo	—	25	Oral	52	Poor	Interest	—
	Dioscorea alata	24	25	Oral				-0.10 (-0.66 to 0.46)
Wiklund 1999[88]	Placebo	—	191	Oral	16	Poor	Global	—
	Ginseng	200	193	Oral				-0.04 (-0.24 to 0.16)
Hartley 2004[89]	Placebo	—	27	Oral	12	Poor	Interest	—
	Ginseng	120	30	Oral				0.49 (-0.04 to 1.03)
Labrie, 2009[149]	Placebo	—	53	V ovule	12	Poor	Global	—
	DHEA	3.25	53	V ovule				0.80 (-0.41 to 1.20)
	DHEA	6.5	56	V ovule				0.39 (0.01 to 0.77)
	DHEA	13	54	V ovule				0.73 (0.34 to 1.13)
Panjari 2009[150]	Placebo	—	40	Oral	26	Good	Global	—
	DHEA	50	41	Oral				0.23 (-0.21 to 0.67)
Kotsopoulos 2000[207]	Placebo	—	41	Oral	13	Poor	Pain	—
	Isoflavones	118	34	Oral				0.26 (-0.20 to 0.71)
Kohama 2013[125]	Placebo	—	70	Oral	12	Poor	Global	—
	Maritime pine extract	30	72	Oral				-0.12 (-0.61 to 0.37)
Von Hagen 2012[121]	Placebo	—	30	Oral	12	Poor	Global	—
	Homeopathic remedy[b]	—	60	Oral				-0.17 (-0.61 to 0.28)
Yang 2012[122]	Placebo	—	98	Oral	24	Poor	Global	—
	Chinese medicinal herb[c]	—	105	Oral				0.18 (-0.9 to 0.46)
Zhong 2013[123]	Placebo	—	54	Oral	12	Fair	Global	—
	Er-Xian decoction[d]	—	54	Oral				0.28 (-0.10 to 0.66)
Colacurci 2013[237]	Placebo	—	62	Oral	52	Poor	Pain	—
	Isoflavones	60	62	Oral				-0.60 (-0.96 to -0.24)

CI: confidence interval; DHEA: dehydroepiandrosterone; FU: followup; SMD: standardized mean difference; V: vaginal; Wks: weeks.
[a] combination of black cohosh, er xian tang, zhi bai di huang wan
[b] globuli velati of saccharose coated with Apis regina tota, Argentum metallicum, and Ovaria bovis
[c] Gengnianningxin capsules if Kidney-Yin deficiency; Bushen oral liquid if Kidney-Yang deficiency
[d] combination of xian mao, xian ling pi, ba ji tian, dang gui, zhi mu, huang bai

Trials With No Quantifiable Data

Six trials did not have data that could be analyzed by the standardized effect size methods. Results of these trials would not have affected the overall outcomes presented above.

In a double-blind trial, women were randomized to either a progesterone skin cream (n=38) or a placebo skin cream (n=42), and were followed for 12 weeks. Sexual function outcomes were measured by the Greene sexual function subscore and reported as baseline median and post-treatment median. Similar improvements were seen in both study groups.[103]

In a trial comparing a mixture of 12 Chinese herbs (n=28) with placebo (n=27), the sexual function subscore for the MENQOL was reported. Followup was 12 weeks. Baseline measures were provided for both the placebo and treatment groups, but followup measures were provided for only the group treated with the Chinese herbs. The authors report that there was no statistical difference in sexual function between the two groups.[114]

Nathorst-Boos et al. conducted a 26-week, double-blind, crossover trial of 53 women, adding a testosterone skin gel or a placebo gel to already existing hormone treatments. Median values of components of the McCoy sex questionnaire were reported. Pain during intercourse did not improve significantly with the testosterone treatment compared with placebo. However, frequency of sexual activity increased significantly more in the testosterone treatment group.[213]

Long et al. conducted a 12-week randomized trial on hysterectomized women, comparing a standard dose of oral estrogen alone (n=37) with a standard dose of estrogen administered through a vaginal cream (n=36). The oral estrogen group reported 63 percent dyspareunia at baseline, 33.3 percent at followup. The estrogen vaginal cream group reported 66.7 percent dyspareunia at baseline, 20.0 percent at followup. Neither route of administration increased the number of satisfying sexual episodes per week.[256]

Lima et al. conducted a 12-week randomized trial, comparing an isoflavone vaginal gel with a placebo vaginal gel. At baseline, 100 percent of the women reported dyspareunia. At followup, 40% of the placebo group reported dyspareunia and 3.3 percent of the women receiving the isoflavone gel reported dyspareunia.[259]

Gupta et al. conducted a one-year trial, comparing a standard dose of oral estrogen alone (n=25), DHEA (n=25), and placebo (n=25). At baseline, no women reported a loss of libido. At followup (unspecified time), 4 percent of the estrogen alone treatment group, 0 percent of the DHEA group, and 36 percent of the placebo group reported a loss of libido.[143]

Strength of Evidence Ratings—Sexual Function

Table 49 summarizes strength of evidence ratings.

Table 49. Strength of evidence ratings domains for sexual function

Number of Comparisons	Comparators[a]			Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Downgrading Rationale
Pain										
10	**Vaginal estrogen**	vs.	Placebo	M	C	D	P	U	High	2 fair and 8 poor quality trials
4	**Oral estrogen**	vs.	Placebo	H	C	D	P	U	Mod	4 poor quality trials
Global										
15	**All estrogens**	vs.	Placebo	M	C	D	P	U	High	2 good, 4 fair, and 9 poor quality trials
2	**SSRI/SNRI**	vs.	Placebo	H	U	D	I	U	Insuff	1 good and 1 poor quality trial; wide confidence interval
4	**Isoflavones**	vs	Placebo	M	I	D	I	U	Low	2 good, 1 fair, 1 poor quality trials; wide confidence interval and substantial heterogeneity
Interest										
7	**All estrogens**	vs	Placebo	H	C	D	P	U	Mod	1 fair, 6 poor quality trials
2	**SNRI**	vs	Placebo	H	I	D	I	U	Insuff	1 poor and 1 good quality trial; confidence interval includes 0
5	**Isoflavones**	vs	Placebo	H	I	D	I	U	Insuff	1 good and 4 poor quality trials; wide confidence interval; heterogeneity
Activity										
8	**Testosterone**	vs.	Placebo	H	C	D	P	U	Mod	1 fair and 7 poor quality trials
Pain, interest, global										
10	**Estrogen route a**	vs.	**Estrogen route b**	M	C	D	U	U	Mod	Precision unknown with 3 domains assessed

Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I) Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S) Undetected (U); SOE: strength of evidence; Mod: moderate; Insuff: insufficient; SMD: standardized mean difference; CI: confidence interval; SSRI: selective serotonin reuptake inhibitor.

[a] Bold font of comparator indicates the more effective treatment; if both comparators are bold, the treatments are equivalently effective. Only the last entry has both comparators bold, estrogen route a and estrogen route b. The other entries show only the first comparator in bold.

Urogenital Atrophy

Key Points

- Seventy-one trials including more than 20,000 women, reported on urogenital atrophy outcomes of treatment with estrogen, ospemifene, or nonprescription agents such as isoflavones, black cohosh and herbal extracts.
- Study quality was typically rated as poor (80 percent). Industry was the only funding source for 31 trials and public sources for 9 trials. Both public and industry funding was reported for 2 trials and support not stated for 29 trials.
- Results were reported using a variety of scales. The most common outcome was vaginal dryness.
- Strength of evidence of relative effectiveness of agents in ameliorating symptoms of vaginal atrophy is as follows:
    - There is **high** strength of evidence that vaginal estrogens improve urogenital atrophy symptoms compared with placebo: SMD -0.44 (95% CI: -0.65 to -0.23; 12 trials, n=3,419).
    - There is **high** strength of evidence that nonvaginal estrogens improve urogenital atrophy symptoms compared with placebo: SMD -0.36 (95% CI: -0.35 to -0.26; 14 trials, n=5,141).
    - There is **high** strength of evidence that ospemifene improves urogenital atrophy symptoms compared with placebo: SMD -0.75 (95% CI: -1.05 to -0.45; 3 trials, n=1,889).
    - There is **low** strength of evidence that isoflavones improve symptoms of urogenital atrophy compared with placebo.
    - There is insufficient evidence to determine whether any other nonprescription agent improve symptoms of vaginal atrophy compared with placebo.

Included Trials

Of the 283 total included trials in this review, 71 (25.1 percent) reported urogenital atrophy outcomes (40 trials specified urogenital atrophy symptoms as a primary outcome). Forty-seven trials examined effects of hormones including the following comparators: placebo (28 trials), other hormones (16 trials), and nonprescription treatments (two trials). Twenty trials examined the effects of nonprescription treatments such as isoflavones, black cohosh, and herbal extracts.

Ten trials were multinational and the remainder performed in over 25 different countries including the United States (n=14), Italy (n=7), Germany (n=6), Brazil (n=2), Hong Kong (n=2), South Korea (n=2), Taiwan (n=2), Thailand (n=2), United Kingdom (n=2), and single trials in 12 other countries (Austria, Belgium, Canada, China, Croatia, Ecuador, France, Netherlands, Norway, Spain, Turkey, Ukraine). The trials were conducted at over 1,900 sites with followup ranging from 12 to 260 weeks.

Urogenital atrophy outcomes were reported using a variety of metrics, the most common were:

- Vaginal dryness on a dichotomous scale.
- Vaginal dryness severity score, ranging from 0 (none) to 3 (severe).
- The Menopause Rating Scale (MRS) with a single item rating vaginal dryness on a five-point scale from 0 (none) to 4 (extremely severe).

- Several researchers devised their own outcome measurement for urogenital symptoms, either patient or physician assessed. Different researchers used different combinations of the following symptoms, assigning scores, resulting in an overall urogenital score: vaginal discomfort, loss of libido, dyspareunia, vaginal dryness, vaginal itching, and incontinence.
- Dryness improvement.
- The Modified Greene Climacteric Scale including a single item assessing vaginal dryness on a scale from 0 (none) to 3 (most severe).
- Visual analog scale
- The Kupperman Menopausal Index vaginal dryness on a scale from 0 (none) to 3 (most severe).

Forty-nine trials (69.0 percent) reported some measure of vaginal dryness, 16 (22.5 percent) vaginal atrophy, 4 (45.6 percent) the Greene domain, 6 (8.4 percent) menopause rating scale, and 12 (16.9 percent) included or reported a different urogenital outcome measure.

Study quality was generally rated poor (80.3 percent), with nine fair and five high quality trials. Industry funding was indicated in 31 trials and public funding was reported in 11 trials. Table 50 describes other trial and patient characteristics.

Table 50. Characteristics of trials assessing efficacy for urogenital atrophy symptoms

	Characteristic	Value
Trial Characteristics	Number of trials	71
	Total number of women	20,147
	Number of sites from trials that specified	1,932 1 to 502 (mean 34; median 9)
	Trials described only as multicenter	8 (11.3)
	Multicenter trials	47 (66.2)
	Two-arm trials	56 (78.9)
	Multi-arm trials	15 (21.1)
	Women per trial	52 to 2,459 (mean 284; median 154)
	Range of followup (weeks)	12 to 260 (mean 24.5; median 13)
Funding	Industry only	31 (43.7)
	Public only	9 (12.7)
	Industry and public	2 (2.8)
	Not stated	29 (40.8)
Comparator Category	Placebo vs. hormone	28 (39.4)
	SSRI/SNRI vs. placebo or other SSRI/SNRI	0 (0.0)
	Placebo vs. other prescription	0 (0.0)
	Placebo vs. nonprescription	20 (28.2)
	Placebo vs. hormone vs. nonprescription	1 (1.4)
	Hormone vs. hormone	16 (22.5)
	Hormone vs. nonprescription	2 (2.8)
	Nonprescription vs. SSRI/SNRIs	0 (0.0)
	Nonprescription vs. nonprescription	4 (5.6)
Study Quality	Good	5 (7.0)
	Fair	9 (12.7)
	Poor	57 (80.3)
	Not rated (abstract or gray literature)	0 (0.0)
Patient Demographics	Mean age (years)	43.8 to 61.9 (NR 8)
	Age range (years)	29.0 to 86.0 (NR 53)
	Years since menopause	5.3 (0.6 to 10.3) (NR 48)
	Current smokers (%)	0.0 to 44.0 (NR 63)
	Mean BMI (kg/m^2)	22.1 to 29.3 (NR 31)
	White (%)	0.0 to 100.0
	Black (%)	0.0 to 15.5
	Hispanic (%)	0.0 to 10.5
	Asian (%)	0.0 to 100.0
	Other (%)	0.0 to 26.6
Uterus Status	All intact	20 (28.2)
	All absent	5 (7.0)
	Mixed	31 (43.7)
	Range, percentage intact among trials with	30.6 to 87.2
	Not reported	15 (21.1)

Note: Demographics were not reported in all studies.
NR: not reported; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

Evidence Synthesis for Urogenital Atrophy

SMDs were calculated to allow comparing outcomes across the different scales. Pooling was performed for pairwise comparisons where evidence included three or more trials. Pairwise analyses of estrogen treatments were conducted separately for vaginal and nonvaginal administration. Pooling was performed for the following comparators versus placebo: vaginal

estrogens according to dose, nonvaginal estrogens according to dose, ospemifene, isoflavones, and black cohosh. Results are displayed in Figure 13. Forest plots for pairwise comparisons are displayed in Appendix J.

Estrogen Compared With Placebo

Vaginal Estrogens

There were 13 trials that examined vaginal estrogens compared with placebo (Table 51). The routes of administration in the trials included creams, rings, ovules, and pessaries. One trial compared high-dose estrogens with placebo,[179] three trials compared standard-dose estrogens with placebo,[221, 226, 232] and nine trials compared low/ultralow dose estrogens with placebo.[156, 220, 222-225, 227, 260] One trial was rated high quality, two fair, and thirteen poor. Pooled results (Table 51) showed any vaginal estrogen significantly improved reported urogenital atrophy symptoms compared with placebo (SMD -0.44; 95% CI: -0.65 to -0.23; tau^2=0.11; 12 comparisons). One potential outlier[222] was apparent (Appendix J); including it increased the estimated effect size and heterogeneity (SMD -0.54; 95% CI: -0.77 to -0.31; tau^2=0.15). Pooled effects for standard and low/ultralow dose estrogens (Table 51) were consistent with significant improvement in urogenital atrophy symptoms compared with placebo. There was a single high-estrogen dose trial (two estrogen arms versus placebo ring);[179] in one arm a significant effect was noted (SMD -0.36; 95% CI: -0.63 to -0.09) but not the other (the result for both arms combined is shown in Table 51). SMDs for standard and low/ultralow dose vaginal estrogens compared with placebo were -0.42 (95% CI: -0.61 to -0.23; tau^2 = 0.00; three comparisons), and -0.46 (95% CI: -0.73 to -0.18; tau^2=0.18; eight comparisons), respectively. Although heterogeneity was present, the strength of evidence that vaginal estrogens improve urogenital atrophy symptoms compared with placebo symptoms is rated high.

Nonvaginal Estrogens

Fourteen trials comparing nonvaginal estrogens with placebo were pooled (Table 52). Routes of administration included oral, transdermal patch, and skin gel. One trial examined high-dose estrogens,[187] six trials standard-dose estrogens,[35, 176, 190, 228, 261, 262] and eight trials low/ultralow dose.[176, 182, 220, 229, 231, 263-265] One trial included three arms, comparing placebo with both a standard and low estrogen dose.[176] Two trials were rated good quality, one fair, and eleven poor. Analyses by estrogen dose (high, standard, and low/ultralow) showed improvement in all alleviating urogenital atrophy symptoms (Table 52) for any estrogen dose with little heterogeneity, SMD -0.35 (95% CI: -0.44 to -0.26); tau^2=0.01 (14 trials). The strength of evidence that nonvaginal estrogens improve urogenital atrophy symptoms compared with placebo is rated high.

Isoflavones Compared With Placebo

Five trials compared isoflavones with placebo.[87, 111, 207, 236, 266] Isoflavones doses ranged from 60 mg per day to 350 mg per day. Treatment arm enrollment ranged from 44 to 60 women. The pooled estimate was consistent with improved urogenital atrophy symptoms among women taking isoflavones (Table 52) SMD -0.48, 95% CI: -0.77 to -0.18; tau^2=0.07). However, all trials were rated poor quality. The strength of evidence that isoflavones compared with placebo improve urogenital atrophy symptoms is rated low.

Ospemifene Compared With Placebo

Three trials compared ospemifene with placebo for its effect on clinical signs of vulvar vaginal atrophy.[258] The trials were rated fair quality. The magnitude of pooled SMD was greater than for any other agent (-0.75, 95% CI: -1.05 to -0.45; tau^2=0.06). The strength of evidence that ospemifene compared with placebo improve urogenital atrophy symptoms is rated high.

Table 51. Pooled standardized mean differences from trials for improvement in urogenital atrophy symptoms among vaginal estrogen doses[a]

Any Estrogen	E-High			
		E-Standard		
		0.14 (-0.04 to 0.32) tau^2=0.00; n=3	E-Low/Ultralow	
-0.44[b] (-0.65 to -0.23) tau^2=0.11; n=12	-0.26 (-0.49 to -0.02) n=1	-0.42 (-0.61 to -0.23) tau^2=0.00; n=3	-0.46[c] (-0.73 to -0.18) tau^2=0.13; n=8	Placebo

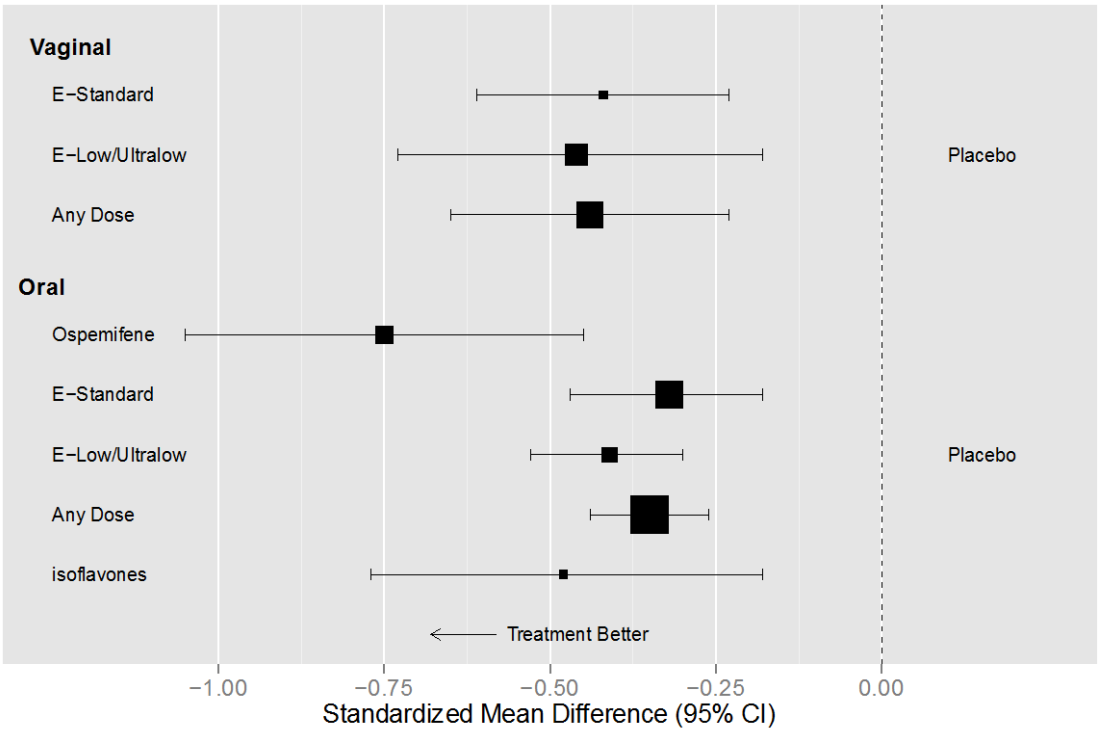
[a] The estimates represent comparison of the treatment intersecting the diagonal above it to that on the right (n is number of trials pooled). For example, the pooled standardized mean difference for standard dose estrogen versus placebo is -0.42.
[b] Including one outlier with a large SMD[222] -0.54 (-0.77 to -0.31) tau^2=0.15; n=13
[c] Including outlier [222] -0.60 (-0.90 to -0.30) tau^2=0.18; n=9
E: estrogen; N: number of trials

Table 52. Pooled standardized mean differences from single trials for improvement in urogenital atrophy symptoms among nonvaginal agents[a]

Ospemifene						
	E-High					
	-0.21 (-0.44 to 0.01) n=1	E-Standard				
		-0.06 (-0.18 to 0.06) tau^2=0.00; n=3	E-Low Ultralow			
				Isoflavones		
			-0.99 (-1.51 to -0.47) n=1		Black Cohosh	
-0.75 (-1.05 to -0.45) tau^2=0.06; n=3	-0.36 (-0.71 to 0.00) n=1	-0.32 (-0.47 to -0.18) tau^2=0.02; n=6	-0.41 (-0.53 to -0.30) tau^2=0.00; n=8	-0.48 (-0.77 to -0.18) tau^2=0.07; n=5	-0.30 (-0.53 to -0.07) n=1	Placebo

[a] The estimate in each cell represents comparison of the treatment intersecting the diagonal above it to that on the right (n is number of trials pooled). For example, the pooled standardized mean difference for standard-dose estrogen versus placebo is -0.32.
For any estrogen compared with placebo SMD -0.35 (95% CI: -0.44 to -0.26); tau^2=0.01 (14 trials)
E: estrogen; N: number of trials

Figure 13. Caterpillar plot for treatment of urogenital atrophy symptoms displaying pooled comparisons and 95% confidence intervals[a]



[a] Symbol size is proportional to the number of women included in the comparison.

Trials Not Pooled

Estrogen Compared With Placebo

One trial (Table 53) compared low-dose estrogen alone with placebo, administered through vaginal rings.[224] The estrogen treatment did not improve urogenital symptoms compared with placebo.

Table 53. Trials of hormone therapies compared with placebo reporting urogenital atrophy outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Casper 1999[224]	Placebo	—	27	Ring	24	Poor	—
	Estradiol	0.0075	23	Ring			-0.11 (-0.58 to 0.79)

CI: confidence interval; FU: followup; SMD: standardized mean difference

Estrogen Compared With Other Hormones

One trial (Table 54) compared estrogen/progestin versus estrogen/progestin plus testosterone.[243] Estrogen/progestin doses were identical in both groups, with the experimental

group receiving 2 mg testosterone. Both groups reported significant improvements in vaginal dryness. There was no difference in the magnitude of improvement between the groups.

Table 54. Trials comparing hormone therapies reporting urogenital atrophy outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Penteado 2008[243]	CEE + MPA	0.625 E + 2.5 P	24	Oral	52	Poor	—
	CEE + MPA + testosterone	0.625 E + 2.5 P + 2 T	27	Oral			-0.33 (-0.97 to 0.27)

SMD: standardized mean difference; CI: confidence interval; CEE: conjugated equine estrogen; E: estrogen; MPA: medroxyprogesterone acetate; P: progestin; T: testosterone; FU: followup; Wks: weeks.

Different Routes of Estrogen Administration

Eight trials compared similar estrogen doses administered by different routes (Table 55)[90, 99, 146, 251, 255-257, 267] (see Appendix G for dose categorization by route). One trial showed a significant improvement in urogenital symptoms administering estrogen via pessary compared with tablet.[267] A three-armed trial reported that a vaginal gel and a patch significantly improved urogenital symptoms compared with oral estrogens.[99] All other trials reported no difference between the routes of administration. Given the heterogeneity among routes of administration in these trials, no strength of evidence ratings were assigned.

Table 55. Trials comparing different routes of estrogen administration reporting urogenital atrophy symptoms

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Odabasi 2007[90]	Estradiol + progesterone	0.3 E + 90 P	32	Spray + vaginal cream	12	Poor	—
	Estradiol + progesterone	0.05 E + 90 P	29	Patch + vaginal cream			-0.26 (-0.76 to 0.25)
Weisberg 2005[255]	Estradiol	0.008	101	Ring	48	Poor	—
	Estradiol	0.025	54	Tablet			-0.17 (-0.55 to 0.20)
Dugal 2000[267]	Estradiol	0.025	48	Tablet	24	Poor	—
	Estriol	0.5	48	Pessary			-0.82 (-1.24 to -0.40)
Lubbert 1997[146]	Estradiol + progestogen	0.05 E + P[a]	1232	Patch – continuous	12	Poor	—
	Estradiol + progestogen	0.05 E + P	1227	Patch – cyclical			0.05 (-0.06 to 0.16)
Barentsen 1997[251]	Estradiol	0.0075	83	Ring	12	Poor	—
	Estriol	0.5	82	Cream			0.11 (-0.23 to 0.45)
Henriksson 1994[257]	Estradiol	0.0095	101	Ring	12	Poor	—
	Estriol	0.5	45	Pessary			0.66 (0.16 to 1.15)
Long 2006[256]	CEE	0.625	27	Oral	12	Poor	—
	CEE	0.625	30	Cream			-0.39 (-1.04 to 0.27)
Akhila 2006[99]	CEE + MPA	0.625 E + 2.5 P	35	Oral	52	Poor	—
	Estradiol + MPA	1.5 E + 2.5 P	25	Gel			-1.61 (-2.76 to -0.46)
	Estradiol + MPA	0.05 E + 2.5 P	28	Patch			-1.65 (-2.80 to -0.51)

[a] Recommended 5 mg/day dose but various agents and doses used.

SMD: standardized mean difference; CI: confidence interval; CEE: conjugated equine estrogen; E: estrogen; MPA: medroxyprogesterone acetate; P: progestogen; FU: followup; Wks: weeks.

Nonprescription Agents Compared With Placebo

Eleven trials (Table 56) compared nonprescription agents with placebo. Four trials examined plant extracts,[112, 115, 119, 123] two dehydroepiandrosterone (DHEA),[130, 149] and one trial each tested isoflavones gel,[259], isoflavones and berberine[111] St. John's wort and black cohosh mix,[128] a homeopathic remedy,[121] and black cohosh alone.[216] The two isoflavones trials report significant improvements in urogenital symptoms compared with placebo.[111, 259] Findings among the two DHEA trials were inconsistent, with one trial noting significant improvements in urogenital symptoms[149] and the other reporting a nonsignificant finding.[130] Heger et al. reported significant improvements using rheum rhaponticum,[112] Uebelhack et al. reported significant improvements with the St. John's wort and black cohosh combination,[128] and Osmers et al. reported significant improvements with black cohosh alone.[216] Due to the variety of dosages and treatments, pooling was not appropriate.

Table 56. Trials comparing nonprescription agents with placebo reporting urogenital atrophy symptoms

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Heger 2006[112]	Placebo	—	55	Oral	12	Poor	—
	Rheum rhaponticum	4	54	Oral			-1.32 (-1.74 to -0.90)
Hirata 1997[115]	Placebo	—	36	Oral	24	Poor	—
	Dong quai	4,500	35	Oral			-0.84 (-1.90 to 0.20)
Labrie 2009[149]	Placebo	—	53	Ovule	12	Poor	—
	DHEA	3.25	53	Ovule			-0.78 (-1.18 to -0.38)
	DHEA	6.5	56	Ovule			-0.51 (-0.90 to -0.13)
	DHEA	13	54	Ovule			-0.71 (-1.10 to -0.31)
Barnhart 1999[130]	Placebo	—	30	Oral	12	Poor	—
	DHEA	50	30	Oral			-0.06 (-0.57 to 0.45)
Osmers 2005[216]	Placebo	—	141	Oral	12	Poor	—
	Black cohosh	40	145	Oral			-0.30 (-0.53 to -0.07)
Chang 2011[119]	Placebo	—	32	Oral	12	Fair	—
	EstroG-100®[a]	257	29	Oral			-0.51 (-1.02 to 0.01)
Lima 2012[259]	Placebo	—	25	V. gel	12	Poor	—
	Isoflavone gel	50	30	V. gel			-1.52 (-2.73 to -0.32)
Mucci 2006[111]	Placebo	—	45	Oral	24	Poor	—
	Isoflavones mix[b]	60	44	Oral			-0.55 (-0.98 to -0.13)
Uebelhack 2006[128]	Placebo	—	143	Oral	16	Fair	—
	Black cohosh + St. John's wort	3.75	151	Oral			-0.25 (-0.48 to -0.02)
Von Hagens 2012[121]	Placebo	—	30	Oral	12	Poor	—
	Ovaria bovis	—	62	Oral			0.00 (-0.44 to 0.44)
Zhong 2013[123]	Placebo	—	54	Oral	12	Fair	—
	Dong quai	—	54	Oral			-0.22 (-0.60 to 0.16)

SMD: standardized mean difference; CI: confidence interval; DHEA: dehydroepiandrosterone; FU: followup; V: vaginal; Wks: weeks.

[a] combination of cynanchum wilfordii, phlomis umbrosa, angelica gigas

[b] combination of isoflavones, lactobacilli, magnolia bark, vitamin D, and calcium

Nonprescription Agents Compared With Nonprescription Agents

One trial (Table 57) compared isoflavones versus isoflavones combined with pine bark extract,[138] one trial compared two different doses of isoflavones,[137] and one trial compared different dosages of pueraria mirifica.[136] Agosto et al. reported a minimal improvement with the

addition of pine bark extract to isoflavones compared with isoflavones alone. The other two trials reported no difference between dosages.

Table 57. Trials comparing nonprescription agents reporting urogenital atrophy outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Agosta 2011[138]	Isoflavones	60	300	Oral	12	Poor	—
	Isoflavones/pine bark extract	60	334	Oral			-0.16 (-0.31 to 0.00)
Virojchaiwong 2011[136]	Pueraria mirifica	25	26	Oral	26	Poor	—
	Pueraria mirifica	50	26	Oral			0.11 (-0.44 to 0.66)
Yang 2012[137]	Isoflavones	35	57	Oral	24	Poor	—
	Isoflavones	70	50	Oral			-0.17 (-0.55 to 0.22)

SMD: standardized mean difference; CI: confidence interval; FU: followup; Wks: weeks.

Trials With No Quantifiable Data

Publications from six trials lacked sufficient data to estimate effect sizes (SMD or other). Results of these trials would not have affected the overall outcomes presented above. One trial was rated fair quality[268] and the remainder rated poor quality.

Schulman et al.[268] compared placebo with a low dose estrogen patch given with two different progestin doses. Only post-treatment data were reported, and after 12 weeks, vaginal dryness was less frequent in both treatment arms compared with placebo (p=0.013 and p=0.016).

Le Donne et al. conducted a 3-month, randomized, double-blind trial comparing 5 mg hyaluronic acid (n=31) with 97 µg genistein (n=31), administered through vaginal suppository.[269] Outcomes were reported as median genital score and both treatments provided significant relief of symptoms.

A randomized, double-blind trial compared the effect of pomegranate seed oil (n=43) with placebo (n=38).[118] Outcomes were reported as pre- and post-median scores in the urogenital domain of the Menopause Rating Scale. Women in the treatment and placebo arms experienced the same improvement in scores.

A trial comparing menopausal hormone therapy (n=30) with pueraria mirifica (n=30) reported that neither treatment affected vaginal dryness significantly.[134] The outcome was measured by the modified Greene Climacteric Scale.

Buckler et al. conducted a 24-week trial comparing a low-dose estrogen/progestin oral treatment with a high-dose estrogen/progestin vaginal ring. Both treatments lowered the vaginal dryness symptom intensity score, but no variance estimates or p-values were provided.

Gupta et al. conducted a trial comparing a standard dose of oral estrogen, 25 mg of DHEA, and placebo. The authors report a lower frequency of vaginal dryness in the treatment groups compared with placebo. No baseline frequencies were provided.[143]

Strength of Evidence Ratings—Urogenital Atrophy

Table 58 summarizes strength of evidence ratings for urogenital atrophy.

Table 58. Strength of evidence ratings domains for urogenital atrophy

Number of Comparisons	Comparators[a]			Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Downgrading Rationale
12	**Estrogen vaginal**	vs.	Placebo	M	C	D	P	U	High	1 good, 2 fair, and 13 poor quality trials
14	**Estrogen oral**	vs.	Placebo	M	C	D	P	U	High	2 good quality, 1 fair, and 11 poor quality trials
5	**Isoflavones**	vs.	Placebo	H	C	D	I	U	Low	All poor quality trials; wide confidence interval for pooled effect
3	**Ospemifene**	vs.	Placebo	M	C	D	P	U	Mod	3 fair quality trials

Risk of Bias: High (H), Medium (M) Low (L); Consistency: Inconsistent (I) Unknown (U) Consistent (C); Directness: Indirect (I) Direct (D); Precision: Imprecise (I) Unknown (U) Precise (P); Reporting Bias: Suspected (S) Undetected (U); SOE: strength of evidence.

[a] Bold font of comparator indicates the more effective treatment; if both comparators are bold, the treatments are equivalently effective. All entries show only the first comparator in bold.

Sleep Disturbance

Key Points

- A total of 56 trials including over 44,000 women reported on sleep outcomes in women treated with prescription agents (estrogen, SSRIs, gabapentin) and nonprescription agents (isoflavones, St. John's Wort, pine bark extract, rheum rhaponticum, ginseng, dioscorea alata, DHEA, pomegranate seed oil, and herbal extract)
- Forty-five of 56 trials were rated as poor quality. Eighteen trials reported only industry funding, 10 were publicly funded, seven trials were funded by both industry and public sources, and funding support was not noted in 21 trials.
- Results were reported from a variety of scales. The most common outcome reported was the proportion with insomnia (13 trials).
- Strength of evidence of relative effectiveness of agents on improving measures of sleep is as follows:
    - There is **high** strength of evidence that estrogens are accompanied by improved measures of sleep compared with placebo: SMD 0.32 (95% CI: 0.24 to 0.46; 22 trials)
    - There is **moderate** strength of evidence from placebo-controlled trials and direct comparisons that there is no significant difference between standard and low/ultralow dose estrogens in their effect on sleep measures.
    - There is **low** strength of evidence that SSRIs, gabapentin, or isoflavones are accompanied by improved measures of sleep compared with placebo.
    - There is **insufficient** evidence to determine whether any other agent, prescription or nonprescription, is effective in improving measures of sleep compared with placebo or other agent.

Included Trials

Of the 283 trials included in this review, 56 (20.5 percent) reported sleep outcomes (26 as a primary outcome). The most common nonplacebo comparators included hormones (n=28), isoflavones (n=6), and nonprescription agents such as ginseng and herbal extracts (Table 59).

Seven trials were multinational and the others performed in over 22 different countries including Australia (n=3), and South American (n=3), with the most from Europe (n=17), and the United States (n=11). The trials were conducted at over 1,551 sites with followup ranging from 4 weeks in the gabapentin trials to 260 weeks.

Sleep outcomes were reported using a variety of measures and scales. The most commonly reported was the proportion with insomnia (13 trials). Other measurements included subscales of the Women's Health Questionnaire (WHQ) (10 trials), Kupperman Menopausal Index (10 trials), Greene Climacteric Scale (eight trials), WHI Insomnia Rating Scale (two trials), and Menopausal Rating Scale (MRS) (two trials). Other trials reported sleep using graphic rating scales. Following are brief descriptions of the most commonly used scales:

- WHQ consists of nine domains, with three questions comprising the sleep domain: waking early, sleeping badly for the rest of the night, and difficulty in falling asleep. A 4-point scale is used to answer the questions, the answers are converted to binary scores, then the total score is divided by number of questions per domain. WHQ domain scores range from 0 to 1, with higher scores indicating more severe symptoms.[270]

- Kupperman Index assesses 11 menopausal symptoms, including insomnia. Each symptom is scored from 0 (no symptoms) to 3 (most severe).[163]
- Greene Climacteric Scale has a single question about difficulty in sleeping, which is scored on a 4-point scale, from 0 (none) to 3 (severe).
- WHI Insomnia Rating Scale consists of four questions: trouble falling asleep, waking several times at night, waking up earlier than planned, and trouble falling back asleep. A 5-point scale is used to answer the questions and is coded so that the higher score indicates more severe insomnia.[72]
- MRS includes one question encompassing difficulty in falling asleep, difficulty in sleeping through the night, and waking up early, scaled from 0 (none) to 4 (extremely severe).

Study quality was generally rated as poor (45 of the 56 trials). Funding sources were unreported in 21 trials, industry funding was noted in 25 trials, and solely public funding was cited in 10 trials. Table 59 summarizes trial and patient characteristics.

Table 59. Characteristics of trials assessing efficacy for sleep outcomes

	Characteristic	Value
Trial Characteristics	Number of trials	56
	Total number of women	44,433
	Number of sites from trials that specified	1,551 1 to 502 (mean 36; median 2)
	Trials described only as multicenter	6 (10.7)
	Multicenter trials	31 (55.4)
	Two-arm trials	43 (76.8)
	Multi-arm trials	13 (23.2)
	Women per trial	50 to 16,608 (mean 793; median 142.5)
	Range of followup (weeks)	4 to 260 (mean 34.2; median 23)
Funding	Industry only	18 (32.1)
	Public only	10 (17.9)
	Industry and public	7 (12.5)
	Not stated	21 (37.5)
Comparator Category	Placebo vs. hormone	21 (37.5)
	SSRI/SNRI vs. placebo or other SSRI/SNRI	2 (3.6)
	Placebo vs. other prescription	3 (5.4)
	Placebo vs. nonprescription	20 (35.7)
	Placebo vs. hormone vs. nonprescription	1 (1.8)
	Hormone vs. hormone	5 (8.9)
	Hormone vs. nonprescription	1 (1.8)
	Nonprescription vs. SSRI/SNRIs	0 (0.0)
	Nonprescription vs. nonprescription	3 (5.4)
Study Quality	Good	5 (8.9)
	Fair	5 (8.9)
	Poor	45 (80.4)
	Not rated (abstract or gray literature)	1 (1.8)
Patient Demographics	Mean age (years)	43.8 to 63.6 (NR 8)
	Age range (years)	34.0 to 81.0 (NR 47)
	Years since menopause	2.8 (0.6 to 4.7) (NR 43)
	Current smokers (%)	0.0 to 44.0 (NR 41)
	Mean BMI (kg/m^2)	22.8 to 30.1 (NR 22)
	White (%)	0.0 to 100.0
	Black (%)	0.0 to 58.8
	Hispanic (%)	0.0 to 6.1
	Asian (%)	0.0 to 100.0
	Other (%)	0.0 to 41.0
Uterus Status	All intact	18 (32.1)
	All absent	5 (8.9)
	Mixed	15 (26.8)
	Range, percentage intact among trials with	47.7 to 94.3
	Not reported	18 (32.1)

Note: Demographics were not reported in all studies.
NR: not reported; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor

Evidence Synthesis for Sleep Disturbance

Standardized mean differences were calculated to allow comparing outcomes across different sleep scales. Pairwise pooling was performed for comparisons where evidence was available from two or more trials. To summarize the body of evidence, results from trials and treatments included in the pairwise analyses, with estrogens included as a single category, were incorporated in a network meta-analysis providing both direct and indirect estimates. To facilitate clinical interpretation for reference we included results from the single eszopiclone trial—an agent approved for use in insomnia. Forest plots are displayed in Appendix K.

Estrogen Compared With Placebo

Estrogen-placebo comparisons were performed in 22 trials (24 comparisons). One trial compared high-dose estrogens with placebo,[187] 14 trials compared standard-dose estrogens with placebo (two good, two fair and 10 poor quality),[35, 144, 145, 154, 173, 181, 183, 186, 190, 191, 196, 199, 228, 261] and nine trials compared low-dose estrogens with placebo (two fair and seven poor quality).[181, 183, 186, 192, 198, 263-265, 271] Analyses according to estrogen dose showed improvements in sleep compared with placebo in each category—standard dose SMD of 0.24 (95% CI: 0.17 to 0.31) or low/ultralow dose SMD of 0.46 (95% CI: 0.29 to 0.64) (Table 60). Excluding trials focused on disease prevention from the standard estrogen dose category yielded an SMD of 0.45 (95% CI: 0.29 to 0.62; tau^2=0.03). When any estrogen dose was compared with placebo the estimated SMD was 0.32 (95% CI: 0.24 to 0.46; tau^2=0.02). The strength of evidence that estrogen improves sleep disturbance compared with placebo is rated as high.

Estrogen Compared With Estrogen

Five trials included comparisons of standard with low/ultralow dose estrogen (two fair and three poor quality).[181, 183, 186, 249, 272] No difference was apparent in effect on sleep metrics with a confidence interval including 0—SMD -0.08 (95% CI: -0.16 to 0.01; tau^2=0.00). The strength of evidence that standard and low/ultralow dose estrogens do not differ in improving sleep disturbance is rated as moderate.

SSRIs Compared With Placebo

Two trials[167, 169] comparing SSRIs with placebo and assessed sleep outcomes (one rated good and one rated poor quality). Sleep metrics were improved with treatment compared with placebo—SMD 0.46 (95% CI: 0.24 to 0.68). The strength of evidence that SSRIs improve sleep disturbance compared with placebo is rated as low.

Gabapentin Compared With Placebo

Two trials [42, 273] compared gabapentin treatment with placebo (one fair and one poor quality) yielding a pooled SMD of 0.37 (95% CI: 0.18 to 0.49). The strength of evidence that gabapentin improve sleep disturbance compared with placebo is rated low.

Isoflavones Compared With Placebo

Six trials compared isoflavones with placebo (one good and five poor quality).[87, 207, 210, 211, 266, 274] The pooled SMD (0.37, 95% CI: 0.10 to 0.67) was consistent with better reported sleep, with some heterogeneity (tau^2=0.06 or tau=0.25) and a wide confidence interval. The strength of evidence that isoflavones improve sleep disturbance compared with placebo is rated as low.

Ginseng Compared With Placebo

Two trials[88, 89] compared ginseng with placebo (both rated poor quality). The pooled SMD suggested no effect on measures of sleep disturbance—SMD 0.13 (95% CI: -0.05 to 0.32). The strength of evidence that ginseng improves sleep disturbance compare with placebo is rated as insufficient.

Eszopiclone Compared With Placebo

One randomized, double-blind trial compared eszopiclone, a treatment used for insomnia (n=30), with placebo (n=29) and reported Insomnia Severity Index scores.[105] The trial was rated as poor quality with a substantial effect (SMD: 1.08; 95% CI: 0.53 to 1.62).

Network Meta-Analysis

Table 61 and Figure 14 summarize SMDs from the network meta-analysis and Table 62 displays treatment rankings. Although the effect of eszopiclone on sleep is direct, for the other agents impact might be plausibly exerted through treatment of menopausal symptoms alone (e.g., estrogens) or by both symptom relief and sedative effect (e.g., SSRI and gabapentin). The SMDs and ranking results suggest that whatever the mechanism, effects on sleep disturbances are similar when estrogens, SSRIs, or gabapentin, are used to treat menopausal symptoms.

Table 60. Pairwise pooled estimates of standardized mean differences from trials for sleep disturbance[a]

Eszopiclone								
	E-High							
	0.13 (-0.06 to 0.33) n=1	E-Standard						
		-0.08 (-0.16 to 0.01) tau^2=0.00 n=5	E-Low/Ultralow					
				SSRI				
					Gabapentin			
						Isoflavones		
							Ginseng	
1.08 (0.53 to 1.62) n=1	0.61 (0.24 to 0.97) n=1	0.24[b] (0.17 to 0.31) tau^2=0.01 n=14	0.46 (0.29 to 0.64) tau^2=0.04 n=9	0.46 (0.24 to 0.69) tau^2=0.00 n=2	0.33 (0.18 to 0.49) tau^2=0.00 n=2	0.37 (0.10 to 0.64) tau^2=0.06 n=6	0.13 (-0.05 to 0.32) tau^2=0.00 n=2	Placebo

[a] The estimate in each cell represents comparison of the treatment intersecting the diagonal above it to that on the right (n=number of trials pooled). For example, the pooled standardized mean difference for standard dose estrogen versus placebo is 0.24.
[b] Excluding five large trials focused on prevention[144, 145, 154, 196, 228] 0.45 (95% CI: 0.29 to 0.62); tau^2=0.03; n=9.
E: estrogen; N: number of trials.

Table 61. Comparative efficacy for reported measures of sleep as standardized mean differences and 95% credible intervals from network meta-analysis[a]

Eszopiclone						
0.71 (-0.01 to 1.41)	Estrogen					
0.62 (-0.20 to 1.43)	-0.09 (-0.51 to 0.34)	SSRI				
0.71 (-0.11 to 1.51)	-0.00 (-0.43 to 0.43)	0.09 (-0.50 to 0.67)	Gabapentin			
0.70 (-0.05 to 1.44)	-0.01 (-0.30 to 0.29)	0.08 (-0.41 to 0.57)	-0.01 (-0.50 to 0.48)	Isoflavones		
0.98 (0.16 to 1.79)	0.27 (-0.16 to 0.72)	0.36 (-0.22 to 0.95)	0.27 (-0.31 to 0.87)	0.29 (-0.21 to 0.79)	Ginseng	
1.07 (0.36 to 1.76)	0.36 (0.24 to 0.49)	0.45 (0.04 to 0.86)	0.36 (-0.05 to 0.78)	0.37 (0.11 to 0.64)	0.09 (-0.34 to 0.51)	Placebo

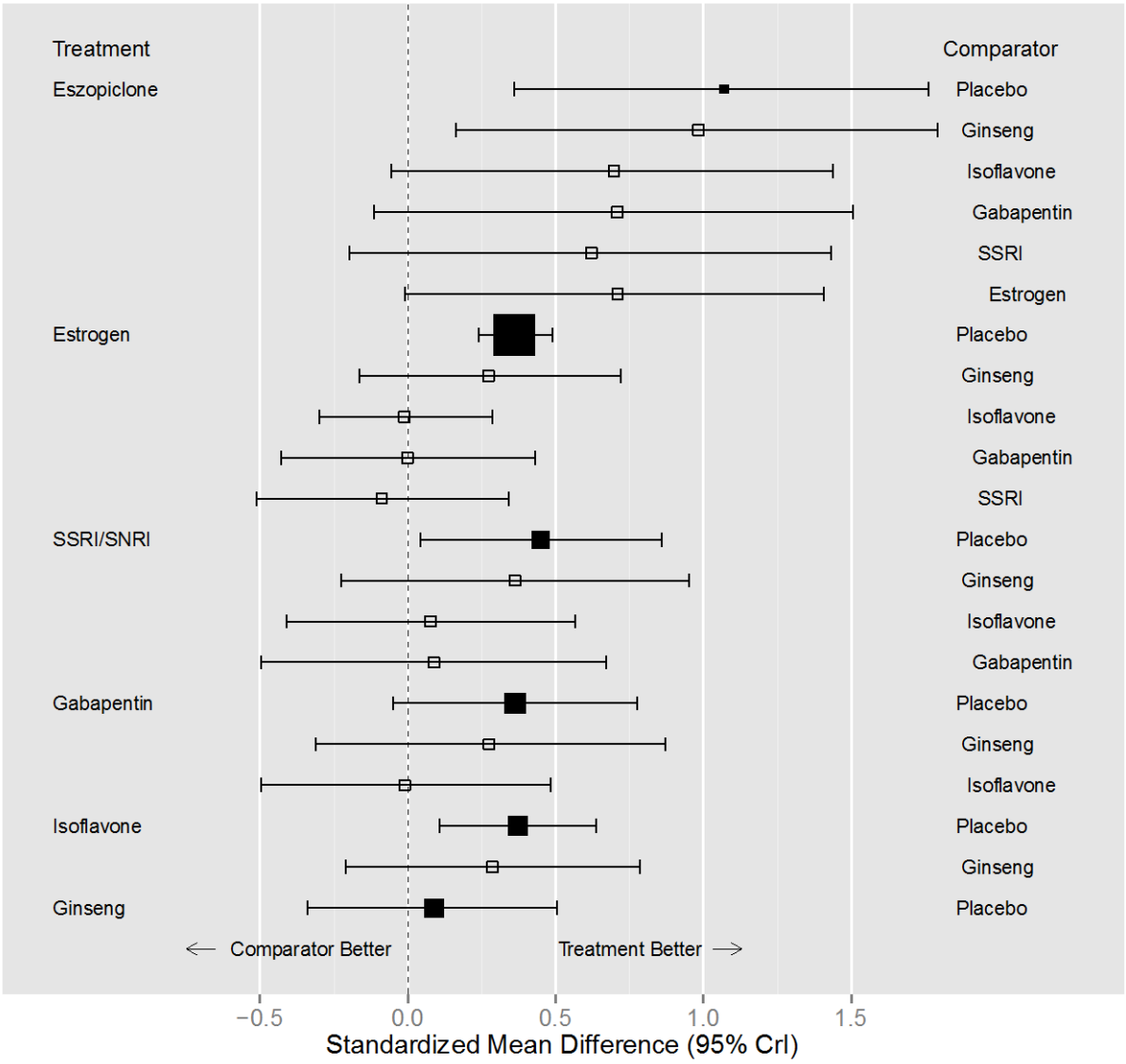
[a] Highlighted effects are those where the credible interval does not overlap zero. The positive effects reflect improvement with the agent on the left versus comparators to its right from intersecting treatments listed on the diagonal.

Table 62. Sleep outcome rankings of comparative efficacy, standard deviations, and 95% credible intervals[a]

Treatment	Mean Rank	SD	Median Rank	95% CrI
Eszopiclone	1.2	0.7	1	(1 to 4)
Estrogen	3.8	1.0	4	(2 to 6)
SSRI/SNRI	3.1	1.4	3	(1 to 6)
Gabapentin	3.8	1.5	4	(1 to 7)
Isoflavone	3.7	1.2	4	(2 to 6)
Ginseng	5.8	1.3	6	(2 to 7)
Placebo	6.6	0.5	7	(6 to 7)

[a] Credible intervals are integer values because they arise from a distribution of integers.
SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor

Figure 14. Caterpillar plot for sleep outcomes displaying network of comparisons and 95% credible intervals[a]



[a] Symbol size is proportional to the number of women included in the comparison; open squares represent indirect comparisons; no mixed direct and indirect effects were included.

Trials Not Pooled

Estrogens

One trial compared estrogen in similar doses and reported sleep outcomes (Table 63). The trial compared a vaginal ring and a vaginal tablet, both delivering low estrogen doses. The authors report that neither improved sleep outcomes significantly.[255]

Table 63. Trials comparing similar estrogen doses and reporting sleep outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Weisberg 2005[255]	Estradiol	0.008	101	Ring	48	Poor	—
	Estradiol	0.025	54	Tablet			-0.02 (-0.35 to 0.31)

SMD: standardized mean difference; CI: confidence interval; NS: not significant; FU: followup; Wks: weeks.

Other Nonprescription Agents Compared With Placebo

Nine trials compared nonprescription agents with placebo (Table 64): St. John's wort,[129] pine bark extract,[110] rheum rhaponticum,[112] isoflavones,[111] dioscorea alata,[117] DHEA,[130] herbal extract,[119] ovaria bovis,[121] and black cohosh.[86] St. John's wort, DHEA, and ovaria bovis did not improve sleep outcomes significantly, compared with placebo.[121, 129, 130] Pine bark extract,[110] rheum rhaponticum,[112] isoflavones,[111] dioscorea alata,[117] herbal extract,[119] and black cohosh (two different doses)[86] were reported to significantly improve sleep compared with placebo.

Table 64. Trials comparing nonprescription agents with placebo and reporting sleep outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Van Die 2009[129]	Placebo	—	50	Oral	16	Good	—
	St. John's wort/Chaste tree	900	50	Oral			0.00 (-0.39 to 0.39)
Yang 2007[110]	Placebo	—	75	Oral	24	Poor	—
	Pine bark extract	200	80	Oral			0.54 (0.21 to 0.86)
Heger 2006[112]	Placebo	—	55	Oral	12	Poor	—
	Rheum rhaponticum	4	54	Oral			0.77 (0.38 to 1.1.6)
Mucci 2006[111]	Placebo	—	45	Oral	24	Poor	—
	Isoflavones	60	44	Oral			0.80 (0.30 to 1.30)
Hsu 2011[117]	Placebo	—	25	Oral	52	Poor	—
	Dioscorea alata (yam)	24	25	Oral			0.75 (0.17 to 1.33)
Barnhart 1999[130]	Placebo	—	30	Oral	12	Poor	—
	DHEA	50	30	Oral			0.02 (-0.49 to 0.53)
Chang 2011[119]	Placebo	—	32	Oral	12	Fair	—
	EstroG-100®[a]	251	29	Oral			0.67 (0.15 to 1.20)
Von Hagens 2012[121]	Placebo	—	30	Oral	12	Poor	—
	Ovaria bovis	—	62	Oral			-0.35 (-0.80 to 0.09)
Schellenberg 2012[86]	Placebo	—	54	Oral	12	Fair	—
	Black cohosh	6.5	57	Oral			0.61 (0.23 to 1.00)
	Black cohosh	13	55	Oral			0.90 (0.50 to 1.29)

SMD: standardized mean difference; CI: confidence interval; NS: not significant; FU: followup; Wks: weeks.
[a] combination of cynanchum wilfordii, phlomis umbrosa, angelica gigas

Nonprescription Agents Compared

Two trials (Table 65) compared nonprescription treatments with other nonprescription treatments. One trial compared isoflavones with isoflavones plus magnolia bark, and reported that the treatment group with magnolia bark experienced marginally significant improvements in sleep compared with the group treated with isoflavones alone.[138] Another trial compared two different dosages of isoflavones combined with vitamin E. The group treated with higher doses of isoflavones experienced better sleep outcomes compared to the lower isoflavones dose group.[141]

Table 65. Trials comparing nonprescription agents and reporting sleep outcomes

Trial	Treatment	Dose (mg)	N	Route	FU Wks	Study Quality	SMD (95% CI)
Agosta 2011[138]	Isoflavones	60	300	Oral	12	Poor	—
	Isoflavones + magnolia bark	60	334	Oral			0.16 (0.00 to 0.31)
Hidalgo 2006[141]	Isoflavones + vitamin E	60	478	Oral	26	Poor	—
	Isoflavones + vitamin E	120	447	Oral			0.19 (0.06 to 0.32)

SMD: standardized mean difference; CI: confidence interval; NS: not significant; FU: followup; Wks: weeks; NR: not reported

Trials With No Quantifiable Data

Publications from seven trials lacked sufficient data to estimate effect sizes (SMD or other). Results of these trials would not have affected the overall outcomes presented above. One trial was not rated because it was an abstract,[139] the remaining trials were rated poor quality.

Lubbert et al. compared two standard dose estradiol/progestogen transdermal patches, one continuous and one cyclical.[146] Using the Menopause Rating Scale, the groups reported similar percentages in sleep improvement: 84.6 percent in the continuous group and 84.1 percent in the cyclical group.

In a trial comparing standard dose estrogen/progestin with 50 mg pueraria mirifica, both groups reported improvements in the modified Greene insomnia subscale.[134] The estrogen group experienced a mean change score of -1.8 and the pueraria mirifica group reported a mean change score of -1.2; there was not a significant difference between the groups.

Zervoudis et al. compared isoflavones with vitamin E and reported insomnia after 52 weeks of followup.[139] Insomnia decreased in 35.4 percent of the isoflavones group and in 16.1 percent of the vitamin E group. The difference between the groups was not significant.

Auerbach et al. compared pomegranate seed oil with placebo and used the Menopause Rating Scale sleeping disorder score as an outcome.[118] Median scores were reported at baseline and at 12 weeks followup. Both groups had a median score of 3.0 at baseline, with the placebo group reporting a score of 2.0 and the pomegranate seed oil group reporting a score of 1.0 after 12 weeks of followup.

Pandit et al. compared a micronutrient supplement with placebo and reported insomnia rates as an outcome.[133] The placebo group reported 64 percent with insomnia at baseline and 60 percent after 12 weeks. The micronutrient supplement group reported 51.7 percent insomnia at baseline and 24.1 after 12 weeks of treatment.

Gupta et al. compared a standard dose of conjugated equine estrogen, DHEA, and placebo and reported insomnia rates as an outcome.[143] The placebo group reported 0 percent insomnia at baseline, and 20 percent after followup. Both the estrogen group and the DHEA group reported 0 percent at baseline and 0 percent after followup. The trial was conducted for 52 weeks, though the time the followup measures were taken was not specified.

Kohama et al. compared 30 mg maritime pine extract with placebo and used the WHQ sleep domain (four items) as an outcome.[125] The placebo group experienced 21 percent improvement in sleep scores, which was statistically significant. The maritime pine extract group experienced 27.8 percent improvement in sleep scores, which was also statistically significant. The authors report that the difference between groups was also statistically significant (p=0.0025).

Strength of Evidence Ratings—Sleep Outcomes

Table 66 summarizes the strength of evidence ratings.

Table 66. Strength of evidence ratings domains for sleep outcomes

Number of Comparisons	Comparators[a]			Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Downgrading Rationale
24	**Estrogen**	vs	Placebo	M	C	D	P	U	High	Comparisons from 2 good, 4 fair, and 18 poor quality trials
5	**Estrogen (standard)**	vs	**Estrogen (low/ultralow)**	H	C	D	P	U	Mod	2 fair and 3 poor quality trials
2	**SSRI**	vs	Placebo	H	C	D	I	U	Low	1 good and 1 poor quality trial
2	**Gabapentin**	vs	Placebo	H	C	D	I	U	Low	1 poor and 1 fair quality trial
6	**Isoflavones**	vs	Placebo	H	C	D	I	U	Low	1 good and 5 poor quality trials; heterogeneity for pooled SMD
2	**Ginseng**	vs	Placebo	H	U	D	I	U	Insuff	2 poor quality trials; CI for pooled SMD overlaps 0

Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I), Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S), Undetected (U); SOE: strength of evidence; Insuff: insufficient; SMD: standardized mean difference; CI: confidence interval.
[a] Bold font of comparator indicates the more effective treatment; if both comparators are bold, the treatments are equivalently effective

Key Question 2. Long-Term Effects of Menopausal Hormone Therapy Preparations

This Key Question addresses the long-term effects of hormone therapies on breast cancer; gallbladder disease; colorectal cancer; coronary heart disease, stroke, and venous thromboembolism; endometrial cancer; osteoporotic fractures; and ovarian cancer among women taking hormone therapies for menopausal symptom relief. Systematic reviews and meta-analyses provided the evidence base.

As detailed in the Methods, selection was based on AHRQ guidance on incorporating existing SRs in comparative effectiveness reviews[275] and on a modified version of the AMSTAR tool.[52] First, systematic reviews and meta-analyses identified from the literature search were screened for relevance. Next, the selected AMSTAR criteria were added as inclusion criteria to enable the assessment of potential bias: (1) at least two electronic sources were searched and key words and/or MeSH® terms were stated, (2) trial inclusion/exclusion criteria were adequately described, and (3) trial quality (risk for bias) of included studies was assessed and documented. Thirty SRs met these criteria. Out of the 30 systematic reviews, that with the most current literature search was the 2012 review conducted by Nelson et al. for the U.S. Preventive Services Task Force (USPSTF) comparing menopausal hormone therapy with placebo for the prevention of chronic conditions.[28] This report was comprehensive, addressing most outcomes included in this Key Question. Accordingly, this report was adopted as the primary source for KQ2.

The Nelson et al. systematic review included 51 publications from nine RCTs collectively enrolling over 36,000 participants: the Women's Health Initiative (WHI) combination estrogen plus progestin trial (referred to hereafter as "estrogen/progestin,"[15, 276-279] WHI estrogen-alone trial,[277, 280, 281] WHI Memory Study (WHIMS),[282] WHI Study of Cognitive Aging (WHISCA),[283]

Heart and Estrogen/Progestin Replacement Study (HERS and HERS-II),[284, 285] Women's International Study of Long Duration Oestrogen After Menopause (WISDOM),[286] Oestrogen in the Prevention of Reinfarction Trial (ESPRIT),[287] Estrogen Memory Study (EMS),[288] and Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA).[289] The report also included a WHI followup published subsequent to the literature search.[290]

Among the trials identified by Nelson et al., four met our inclusion criteria for this Key Question: WHI estrogen/progestin, WHI estrogen-alone, HERS/HERS-II, and ESPRIT. WHIMS and WHISCA were excluded because outcomes were not those included in this Key Question. ULTRA was excluded due to a sample size of less than 250 women per arm, and WISDOM and EMS were excluded because of short followup periods. Hazard ratios and 95% confidence intervals were abstracted from nine articles from the four trials (Table 67). Nelson et al. rated the overall quality of the body of evidence as fair, based on the number, quality, and size of studies; consistency of results between studies; and directness of effect.[51] Details of the study quality ratings from the nine articles included can be found in Appendix L, quality assessments.

Women enrolled in the trials were on average older than the target population of this review. Although there is overlap in the age groups, women seeking symptom relief are in general younger than the populations of WHI (mean age of 63 years) and HERS (mean age of 67 years). We identified observational studies from the original literature search enrolling peri- and recently menopausal women in order to inform the applicability discussion. The clinical content expert was also queried regarding relevant publications. Consistency among trials with older populations and observational studies with younger populations was addressed in the strength of evidence discussion. These steps were added to those outlined in AHRQ guidance (which notes "the exact process needs to be flexible and will likely evolve").[37]

Subsequent to our initial literature search, the Cochrane Collaboration published a review of long-term menopausal hormone therapy effects.[291] Although the literature search included trials through February 2012, three months later than the Nelson report, this review derived a majority of data (70 percent) from the WHI and HERS trials, just as the Nelson report did. Attributable risks calculated in the Cochrane review were similar to those reported by Nelson et al. For those reasons, the Nelson report remained the primary source for this Key Question.

Also subsequent to our initial literature search, the Danish Osteoporosis Prevention Study (DOPS) results were published. DOPS was a prospective, randomized, open-label, blinded-endpoint, or PROBE design,[292] controlled trial of recently postmenopausal white women, mean age 50 years. Half of the women enrolled were randomized to treatment or no treatment, and the remainder made a personal choice to use menopausal hormones or not. Treatment duration was 11 years and mean followup 16 years. Only results from the randomized population and only those reported separately for estrogen-only and estrogen/progestin groups were included here.

Finally, evidence concerning potential long-term benefits of hormone therapy was included as part of the decision-making process selecting treatments for menopausal symptoms. However, this review does not address the use of hormone therapy for preventing chronic conditions.

Table 67. Evidence base for long-term effects of hormone therapies

Condition	Analysis on Estrogen/Progestin	Analysis on Estrogen Alone
Breast cancer	Chlebowski 2010[276]/WHI Hulley 2002[285]/HERS/HERS–II Schierbeck 2012[293]/DOPS	LaCroix 2011[281]/WHI Schierbeck 2012[293]/DOPS
Gallbladder disease	Cirillo 2005[277]/WHI	Cirillo 2005[277]/WHI
Colorectal cancer	Heiss 2008[278] and Simon 2012[294]/WHI Hulley 2002[285]/HERS/HERS-II	LaCroix 2011[281]/WHI
Coronary heart disease, stroke, venous thromboembolism	Heiss 2008[278]/WHI	LaCroix 2011[281]/WHI Cherry 2002[287]/ESPRIT
Endometrial cancer	Heiss 2008[278]/WHI Hulley 2002[285]/HERS/HERS–II	Previously established causal association
Osteoporotic fractures	Rossouw 2002[15]/WHI Hulley 2002[285]/HERS/HERS–II	Anderson 2004[280]/WHI
Ovarian cancer	Anderson 2003[279]/WHI	Greiser 2007[295]/MA

DOPS: Danish Osteoporosis Prevention Study; ESPRIT: Estrogen in the Prevention of Reinfarction Trial; HERS/HERS II: Heart and Estrogen/Progestin Replacement Study; MA: meta-analyses; WHI: Women's Health Initiative.

Breast Cancer

Summary

Three trials in the Nelson report provided data on breast cancer incidence: WHI estrogen/progestin,[276] WHI estrogen-only,[281] and HERS-II.[285] All three trials administered oral conjugated equine estrogens (CEE) with the addition of medroxyprogesterone acetate in the estrogen/progestin trials. Mean followup ranged from 5.2 years in the WHI estrogen/progestin trial to 6.8 years in the HERS-II trial.

In the WHI trial, estrogen/progestin increased breast cancer risk compared with placebo whereas estrogen alone reduced the risk (Table 68 and Table 69). HERS-II found no significant increase in breast cancer risk in women using estrogen/progestin (Table 68).

Using only WHI data, the review by Nelson et al. estimated that the use of estrogen/progestin increased invasive breast cancer incidence by eight additional events per 10,000 woman-years (95% CI: 3 to 14). However, the use of estrogen-only reduced invasive breast cancer incidence by eight fewer events per 10,000 woman-years (95% CI: 1 to 14).[28] A 2012 update to the WHI report found consistent results for both estrogen/progestin and estrogen-only therapies.[290] The authors of this update caution that despite the risk reduction found in the estrogen-only trial, the use of estrogen for breast cancer risk reduction remains unsupported, particularly among the subgroup of women at increased breast cancer risk.

DOPS reported breast cancer incidence rates for women with natural menopause (Table 68), and for women undergoing hysterectomy (Table 69). Women experiencing natural menopause in the treatment arm received a standard dose of estradiol with the progestin NETA, and women in the treatment arm who had undergone a hysterectomy received a standard dose of estradiol. After 11 years of treatment and a total 16 years followup, compared with no treatment there were no significant differences in breast cancer incidence among those receiving estrogen/progestin or estrogen alone.[293]

Table 68. Overall breast cancer incidence among women treated with estrogen/progestin

Trial	Treatment	N	Average Followup	Results HR (95% CI); p
WHI – CEE + MPA[276]	0.625mg CEE + 2.5mg MPA	16,608	5.2 years	Overall: 1.25 (1.07 to 1.46); 0.004
HERS/HERS-II[285]	0.625mg CEE + 2.5mg MPA	2,321	6.8 years	Overall: 1.08 (0.52 to 2.24); 0.83
DOPS – estradiol + NETA[293]	2.0 mg estradiol + 1 mg NETA	814	16 years	1.05 (0.54 to 2.04)

CEE: conjugated equine estrogen; DOPS: Danish Osteoporosis Prevention Study; HERS: Heart and Estrogen/Progestin Replacement Trial; HR: hazard ratio; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative; CI: confidence interval

Table 69. Overall breast cancer incidence among women treated with estrogen alone

Trial	Treatment	N	Average Followup	Results HR (95% CI)
WHI – CEE alone[281]	0.625mg CEE	10,739	6.8 years	Intervention: 0.79 (0.61 to 1.02) Postintervention: 0.75 (0.51 to 1.09) Overall: 0.77 (0.62 to 0.95)
DOPS – estradiol alone[293]	2.0 mg estradiol	192	16 years	0.63 (0.23 to 1.78)

CEE: conjugated equine estrogen; HR: hazard ratio; DOPS: Danish Osteoporosis Prevention Study; WHI: Women's Health Initiative; CI: confidence interval

Applicability

Evidence informing breast cancer risk in younger populations can be found in secondary analyses of the WHI trial[296] and in the Million Women Study, a large observational study.[297] In addition to focusing on younger women, these studies also explored potential treatment factors modifying breast cancer risk, including hormone treatment duration and time from menopause onset to hormone initiation—the so-called "gap time" (findings summarized in Table 70).

In an analysis combining the WHI estrogen/progestin trial and the WHI observational study, women using estrogen/progestin therapy with a gap time of less than five years were at greater risk of breast cancer compared to women initiating therapy later.[296] However, there was no evidence in the WHI estrogen-only trial that women starting therapy soon after menopause were at increased breast cancer risk.[298]

The Million Women Study conducted in the United Kingdom also examined gap time and breast cancer risk, but reported some findings inconsistent with the WHI. Women taking estrogen/progestin experienced increased risk of breast cancer, whether gap time was less than five years (RR: 2.04; 95% CI: 1.97 to 2.12) or greater than five years (RR: 1.53; 95% CI: 1.38 to 1.69).[297] Women taking estrogen alone, with a gap time less than five years, experienced increased risk of breast cancer (RR: 1.43; 95% CI: 1.36 to 1.49), but did not experience an increased risk if gap time was greater than five years (RR: 1.05; 95% CI: 0.89 to 1.23).[297]

When assessing treatment duration, the WHI combined trial and observational study reported that longer use combined with a short gap time was associated with increased breast cancer risk. Among women who initiated estrogen/progestin therapy soon after menopause and had 10 years of use, the estimated HR was 2.19 (95% CI: 1.56 to 3.08).[296]

The Million Women Study reported that women using estrogen/progestin longer than five years, regardless of gap time, were at increased risk of breast cancer. However, the study also found that women using estrogen alone for longer than five years were at increased breast cancer risk only if gap time was less than 5 years.[297]

Table 70. Summary of the impact of gap time on breast cancer risk in included studies

Estrogen/Progestin				Estrogen Alone			
Study	**Gap time**	**Duration**	**Risk**	**Study**	**Gap Time**	**Duration**	**Risk**
WHI observational	<5 yrs		↑	WHI observational	<5 yrs		—
	<5 yrs	>10 yrs	↑				
Million Women	<5 yrs		↑	Million Women	<5 yrs		↑
	>5 yrs		↑		>5 yrs		—
	<5 yrs	>5	↑		<5 yrs	>5 yrs	↑
	>5 yrs	>5	↑		>5 yrs	>5 yrs	—

Trends in breast cancer incidence in relation to trends in hormone use should be noted. The WHI published a report in July 2002 explaining that the trial was stopped early because the number of invasive breast cancer events indicated that risks of menopausal hormone therapy were exceeding benefits.[15] Subsequently, the number of prescriptions for estrogen/progestogen dropped 66 percent and for estrogen dropped 33 percent in January to June 2003 compared to the previous year.[299] In 2003, invasive breast cancer incidence decreased 10.6 percent in women 60 to 64 and 14.3 percent in women 65 to 69.[300]

Conclusions

Two large RCTs, WHI[276] and HERS-II,[285] and one smaller RCT, DOPS,[293] examined breast cancer risk accompanying estrogen/progestin treatment. WHI and HERS were rated fair and DOPS poor quality. The hazard ratios are consistent showing an increased risk of breast cancer, although statistical significance was demonstrated only in the WHI trial. The measures were direct and precise. The strength of evidence is rated high that estrogen/progestin therapy increases breast cancer risk.

One large RCT, the WHI estrogen-alone trial,[281] and one small RCT, DOPS,[293] examined breast cancer risk associated with estrogen-alone treatment. The hazard ratios are consistent showing a decreased risk of breast cancer, although statistical significance was demonstrated only in the larger WHI trial. Trial quality was rated fair. An update to the WHI study cautions that results may not apply to subgroups of women, such as those at increased risk of breast cancer. The point estimate from the DOPS trials indicated a decreased breast cancer risk, but the sample size was small, resulting in a large confidence interval. The findings are also inconsistent with the results of the observational Million Women Study. The strength of evidence is rated low that estrogen alone decreases breast cancer risk.

Gallbladder Disease

Summary

Two trials reported gallbladder disease incidence: WHI estrogen/progestin[277] and WHI estrogen-only.[277] Oral conjugated estrogens (CEE) were administered in both trials with the

addition of medroxyprogesterone acetate in the estrogen/progestin trial. Women with prior gallbladder disease or cholecystectomy were excluded. Both trials found an increased incidence of gallbladder disease with estrogen/progestin and estrogen alone compared to placebo (Table 71 and Table 72).

Using WHI data, Nelson et al. calculated additional gallbladder disease events—defined as cholecystitis and cholelithiasis—attributable to menopausal hormone therapy. Estrogen/progestin use was associated with an additional 20 gallbladder disease events per 10,000 women-years (95% CI: 11 to 29); and estrogen-only therapy with an additional 33 events per 10,000 women-years (95% CI: 20 to 45).[28]

Table 71. Gallbladder disease incidence among women treated with estrogen/progestin

Trial	Treatment	N	Average Followup	Results HR (95% CI); p
WHI – CEE + MPA[277]	0.625mg CEE + 2.5mg MPA	14,203	5.2 years	1.54 (1.22 to 1.94); <0.001

CEE: conjugated equine estrogen; HR: hazard ratio; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative; CI: confidence interval

Table 72. Gallbladder disease incidence among women treated with estrogen alone

Trial	Treatment	N	Average Followup	Results HR (95% CI); p
WHI – CEE alone[277]	0.625mg CEE	8,376	6.8 years	1.80 (1.42 to 2.28);<0.001

CEE: conjugated equine estrogen; HR: hazard ratio; WHI: Women's Health Initiative; CI: confidence interval

Applicability

Though the WHI trials enrolled an older population, the increased risk of gallbladder disease among women using menopausal hormone therapy is supported by results from large observational cohort studies of younger populations. The Nurses' Health Study found a relative risk for gallbladder disease of 2.1 (95% CI: 1.9 to 2.4)[301] and the Million Women Study 1.64 (95% CI: 1.58 to 1.69) for all current menopausal hormone therapy users.[302] In the Atherosclerosis Risk in Communities Study, compared to women who never used menopausal hormone therapy, former users had an age-adjusted relative risk for gallbladder disease of 1.84 (95% CI: 1.3 to 2.6) and current users had a risk of 1.76 (95% CI: 1.3 to 2.4).[303] Finally, risks may differ according to route of administration. In an analysis of the Million Women Study, transdermal administration was found to confer a lesser relative risk (1.17, 95% CI: 1.10 to 1.24) of gallbladder disease than all users (1.64, 95% CI: 1.58 to 1.69).[302]

Conclusions

The evidence for estrogen/progestin treatment and gallbladder disease risk consists of one large RCT, the WHI trial.[277] Trial quality was rated as fair. Consistency is unknown, but results from the trial are supported by the results of several large observational studies. The measures are direct and precise. The strength of evidence is rated moderate that estrogen/progestin increases gallbladder disease risk.

The evidence for treatment with estrogen alone and gallbladder disease risk consists of one large RCT, the WHI trial.[277] Trial quality was rated fair. Consistency is unknown, but the results of the trial are supported by the results of several large observational studies. The measures are direct and precise. The strength of evidence is rated moderate that estrogen alone increases gallbladder disease risk.

Colorectal Cancer

Summary

Three trials reported colorectal cancer incidence: WHI estrogen/progestin,[278, 294] WHI estrogen-only,[281] and HERS-II.[285] Oral conjugated equine estrogen (CEE) was used in all three trials with the addition of medroxyprogesterone acetate in the estrogen/progestin trials. The WHI estrogen/progestin trial showed a protective effect on colorectal cancer incidence, while the other two trials (HERS and WHI estrogen-only) reported no effect of menopausal hormone therapy on colorectal cancer incidence (Table 73 and Table 74).

Table 73. Overall colorectal cancer incidence among women treated with estrogen/progestin

Trial	Treatment	N	Average Followup	Results HR (95% CI); p
WHI – CEE + MPA[278, 294]	0.625mg CEE + 2.5mg MPA	16,608	11.6 years	Intervention: [278] 0.62 (0.43 to 0.89) Overall:[294] 0.72 (0.56 to 0.94); 0.014
HERS/HERS-II[285]	0.625mg CEE + 2.5mg MPA	2,321	6.8 years	0.81 (0.46 to 1.45); 0.48

CEE: conjugated equine estrogen; HERS: Heart and Estrogen/Progestin Replacement Trial; HR: hazard ratio; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative; CI: confidence interval

Table 74. Overall colorectal cancer incidence among women treated with estrogen alone

Trial	Treatment	N	Average Followup	Results HR (95% CI)
WHI – CEE only[281]	0.625mg CEE	10,739	6.8 years	Intervention: 1.15 (0.81 to 1.64) Postintervention: 1.01 (0.58 to 1.79) Overall: 1.11 (0.82. to 1.50)

CEE: conjugated equine estrogen; HR: hazard ratio; WHI: Women's Health Initiative; CI: confidence interval

Applicability

Several large observational studies following younger populations also examined menopausal hormone therapy and colorectal cancer risk: the Breast Cancer Detection Demonstration Project (BCDDP),[304] the Nurses' Health Study,[305] and the Molecular Epidemiology of Colon Cancer Study.[306]

The BCDDP reported that women treated with estrogen/progestogen for 2 to 5 years had a relative risk for colorectal cancer of 0.52 (95% CI: 0.32 to 0.87), but results for women treated fewer than 2 years and women treated more than 5 years were nonsignificant.[304] Women treated with estrogen alone for more than 10 years had a relative risk of 0.69 (95% CI: 0.56 to 0.96), but no association was evident in women treated for fewer than 10 years (e.g., 5 to 9 years of use RR 0.74 [95% CI: 0.53 to 1.02]).[304] Current hormone users (75 percent of person-time was estrogen alone and 25 percent estrogen/progestogen) in the Nurses' Health Study had a colorectal cancer relative risk of 0.65 (95% CI: 0.50 to 0.83). This same relationship was not found in past users.[305] The Molecular Epidemiology of Colon Cancer Study reported an odds ratio for colon cancer among hormone users of 0.37 (95% CI: 0.22 to 0.62), adjusting for age, sex, aspirin use, statin use, sports activities, family history of colon cancer, ethnic group, and vegetable consumption level.[306]

A meta-analysis including observational studies as well as the two trials cited here (WHI and HERS), reported a relative risk for colorectal cancer of 0.83 (95% CI: 0.79 to 0.86) for ever users of estrogen alone, and a relative risk for colorectal cancer of 0.81 (95% CI: 0.75 to 0.87) for ever users of estrogen/progestogen.[307]

Although the meta-analysis showed a protective effect of menopausal hormone use, the observational studies show either no effect or a protective effect for certain subgroups of hormone users. Two of the large studies combined estrogen/progestogen and estrogen-only users into one broad category of hormone users in the analyses.

Conclusions

The evidence for estrogen/progestin therapy and colorectal cancer risk consists of two large RCTs, the WHI trial[278, 294] and HERS-II.[285] The quality of both trials was rated as fair. Results are inconsistent, with WHI reporting a protective effect and HERS-II reporting no effect. The evidence is direct. The estimates are imprecise (HERS-II with a wide confidence interval). The strength of evidence is rated low that estrogen/progestin therapy decreases colorectal cancer risk.

The evidence informing estrogen therapy alone and colorectal cancer risk consists of one large RCT, the WHI trial.[281] Trial quality was rated as fair. The results do not show a significant relationship between estrogen therapy and colorectal cancer risk. Consistency is unknown with only one trial, though intervention, postintervention, and overall measures, all show no effect. The measures are direct and precise. The strength of evidence is rated moderate that estrogen therapy alone does not affect colorectal cancer risk.

Coronary Heart Disease, Stroke, and Venous Thromboembolic Events

Summary

Three trials examined the incidence of coronary heart disease, stroke or venous thromboembolic events: WHI estrogen/progestin,[278] WHI estrogen-only,[281]and ESPRIT.[287] Oral conjugated estrogen (CEE) was administered in the WHI trials and estradiol valerate (E2V) in the ESPRIT trial. The WHI trial found that neither hormone therapies increased mortality due to coronary heart disease or myocardial infarction. However, both therapies were associated with an increased incidence of stroke (Table 75 and Table 76). Using WHI data, Nelson et al. calculated that estrogen/progestin therapy resulted in nine more strokes per 10,000 woman-years (95% CI: 2 to 15), and estrogen-only therapy resulted in 11 more strokes per 10,000 woman-years (95% CI: 2 to 20). Deep-vein thromboembolic (DVT) events were also increased with both estrogen/progestin and estrogen-only therapies. Estrogen/progestin resulted in 12 more DVT events per 10,000 woman-years (95% CI: 6 to 17) and estrogen-only therapy results in seven more DVT events per 10,000 woman-years (95% CI: 1 to 14).[28]

ESPRIT did not find significant relationships between estrogen-only treatment and stroke, pulmonary embolism, deep venous thrombosis, or mortality due to coronary heart disease, possibly due to a smaller sample size (n=1,017).

Table 75. Coronary heart disease, stroke, and venous thromboembolic events incidence among women treated with estrogen/progestin

Trial	Overall CHD	All CVD Events	Total MI	Stroke	PE	DVT	CHD Death
WHI – CEE + MPA[278] HR (95% CI)	1.22 (0.99 to 1.51)	1.13 (1.02 to 1.25)	1.26 (1.00 to 1.59)	1.34 (1.05 to 1.71)	1.98 (1.36 to 2.87)	1.88 (1.38 to 2.55)	1.04 (0.67 to 1.64)

CEE: conjugated equine estrogen; CHD: coronary heart disease; CVD: cardiovascular disease; DVT deep venous thrombosis; HR: hazard ratio; MPA: medroxyprogesterone acetate; PE: pulmonary embolism; WHI: Women's Health Initiative.

Table 76. Coronary heart disease, stroke, and venous thromboembolic events incidence among women treated with estrogen alone

Trial	Overall CHD	All CVD Events	Total MI	Stroke	PE	DVT	CHD Death
WHI – CEE alone[281] HR (95% CI)	0.95 (0.78 to 1.15)	1.11 (1.01 to 1.23)	0.98 (0.79 to 1.21)	1.36 (1.08 to 1.71)	1.37 (0.90 to 2.07)	1.47 (1.06 to 2.05)	0.98 (0.70 to 1.39)
ESPRIT[287] RR (95% CI)				1.64 (0.60 to 4.47) p=0.45	0.98 (0.20 to 4.84) p=1.00	1.96 (0.18 to 21.6) p=1.00	0.68 (0.39 to 1.19) p=0.17

CEE: conjugated equine estrogen; CHD: coronary heart disease; CVD: cardiovascular disease; DVT deep venous thrombosis; HR: hazard ratio; PE: pulmonary embolism; RR: rate ratio; WHI: Women's Health Initiative.

Applicability

Administering hormones with goals of primary or secondary CHD prevention, the WHI and HERS trials enrolled older women with ages overlapping the target population of this review. Consequently, hormone therapy was often initiated later following menopause than when used to treat menopausal symptoms. In the WHI trials, hormone therapy was begun more than 5 years after menopause in 16 percent of women previously using hormones and in 90 percent of women without prior hormone use.[47] The potential modifying effects of age and time since menopause of hormone therapy initiation on CHD incidence has been examined in secondary analyses of the WHI trials,[308] the WHI trials and observational study combined,[47] and in the Nurses' Health Study.[45]

In the WHI estrogen-only trial the hazard ratios for CHD among women less than 10 years, 10 to 19 years, and 20 or more years since menopause were 0.48 (95% CI: 0.20 to 1.17), 0.96 (95% CI: 0.64 to 1.44) and 1.12 (95% CI: 0.86 to 1.46) respectively (p=0.15 for trend).[308] In the estrogen/progestin trial, corresponding hazard ratios were 0.88 (95% CI: 0.54 to 1.43), 1.23 (95% CI: 0.85 to 1.77), and 1.66 (95% CI: 1.14 to 2.41) (p=0.05 for trend). Trends in CHD risk were not significantly modified by age at randomization in the estrogen-only (p=0.12) or estrogen-progestin (p=0.70) trials. Stroke risks were unaffected by age or years since menopause in either the WHI estrogen-only or estrogen/progestin trial.

Prentice et al[47] subsequently reexamined both the WHI trials and WHI observational study in further detail—individually and combined—according to years since menopause (less than 5, 5 to 14, 15 or more years) and whether prior hormone therapy had been taken. In the combined trial and observational study analysis, there was no evidence for modification of CHD risk by time since menopause with estrogen alone or estrogen/progestin for prior or first time hormone users. In women with prior hormone use fewer than 2 years menopausal, estrogen/progestin therapy was accompanied by an increased CHD risk (HR 3.03, 95% CI: 1.36 to 6.75).

In a novel reanalysis to account for the potential biases of observational studies, Hernán et al examined the association between estrogen/progestin therapy and CHD incidence in 35,575

women initiating estrogen/progestin in the Nurses' Health Study. CHD risk was increased in the two years following initiation (HR 1.42, 95% CI: 0.92 to 2.20) compared with 0.96 (95% CI: 0.78 to 1.18) over the entire follow-up examined. Among women with prior hormone use and fewer than 10 years since menopause, during the two years after starting estrogen/progestin the hazard ratio for CHD was 1.33 (95% CI: 0.66 to 2.64) versus 0.77 (95% CI: 0.54 to 1.09) subsequently; among women 10 or more years from menopause corresponding hazard ratios were 1.48 (95% CI: 0.83 to 2.64) and 1.05 (95% CI: 0.77 to 1.43). For women without prior hormone use generally similar findings were noted with the exception of a significant protective effect among women fewer than 10 years postmenopausal after two years of estrogen/progestin (HR 0.58, 95% CI: 0.37 to 0.90).[45]

Overall, these results including age and time since menopause support concluding that WHI CHD risks are applicable to recently menopausal women. Finally, although the WHI did not address route of administration, observational data from the Million Women Study found no increased relative risk of VTE with transdermal estrogen-only administration (0.82, 95% CI: 0.64 to 1.06).[309]

Conclusions

The evidence for estrogen/progestin therapy and coronary heart disease consists of one large RCT, the WHI trial.[278] The trial did not find a significant relationship between treatment and overall coronary heart disease, myocardial infarctions, or death from coronary heart disease. Trial quality was rated as fair. The strength of evidence is rated moderate that estrogen/progestin increases coronary heart disease risk.

The evidence for estrogen/progestin therapy and venous thromboembolic events consists of one large RCT, the WHI trial.[278] There were significant relative increases in all three outcomes: stroke, pulmonary embolism, and DVT. Trial quality was rated as fair. With one trial, consistency is unknown, although all three measures show increased risk. The strength of evidence is rated moderate that estrogen/progestin therapy increases stroke, pulmonary embolisms, and DVT risk.

The evidence concerning estrogen therapy and coronary heart disease consists of one large RCT, the WHI trial[281] and one small RCT, the ESPRIT trial.[287] The WHI trial reported total MI, CHD death, and overall CHD. The ESPRIT trial reported only CHD death. All four measures show no effect of estrogen therapy. Both trials were rated fair quality. Consistency is unknown for total MI and overall CHD because only one trial reported those measures. CHD death was consistent between the two trials. The strength of evidence is rated moderate that estrogen does not affect coronary heart disease risk.

The evidence for estrogen therapy and venous thromboembolic events consists of one large RCT, the WHI trial[281] and one small RCT, the ESPRIT trial.[287] The WHI trial found significant increases in stroke and DVT. ESPRIT also found increases in stroke and DVT events, though the increases were not significant, possibly due to the small sample size. Both trials were rated fair quality. The strength of evidence is rated high that estrogen therapy increases venous thromboembolic risk.

Endometrial Cancer

Summary

Two trials (Table 77) reported the incidence of endometrial cancer: WHI estrogen/progestin[278] and HERS/HERS-II.[285] Both trials administered oral conjugated equine estrogen (CEE) with medroxyprogesterone (MPA). Followup ranged from 5.2 years in WHI to 6.8 years in HERS/HERS-II. No significant differences in endometrial cancer incidence were observed in the trials of estrogen/progestin therapies. The increased risk of endometrial cancer when using estrogen-only therapies has previously been established.[48]

Table 77. Overall endometrial cancer incidence among women treated with estrogen/progestin

Trial	Treatment	N	Average Followup	Results HR (95% CI)
WHI – CEE + MPA[278]	0.625mg CEE + 2.5mg MPA	15,730	5.2 years	Postintervention: 0.75 (0.40 to 1.43) Overall: 0.78 (0.52 to 1.16)
HERS/HERS-II[285]	0.625mg CEE + 2.5mg MPA	2,485	6.8 years	0.25 (0.05 to 1.18)

CEE: conjugated equine estrogen; HERS: Heart and Estrogen/Progestin Replacement Trial; HR: hazard ratio; MPA: medroxyprogesterone acetate; CI: confidence interval

Applicability

Two large observational studies of younger women, the Nurses' Health Study[310] and the European Prospective Investigation into Cancer and Nutrition[311] reported that the risk of endometrial cancer accompanying menopausal hormone therapy differed, depending on whether the progestin was administered continuously or sequentially when added to estrogen therapy. The European study showed an increased risk of endometrial cancer when progestin was administered sequentially (HR: 1.52; 95% CI: 1.00 to 2.29), and a decreased risk of endometrial cancer when progestin was administered continuously (HR: 0.24; 95% CI: 0.08 to 0.77).[311] The Nurses' Health Study reported a RR of 3.00 (95% CI: 1.43 to 6.28) when progestin was added sequentially 1 to 8 days; a RR of 1.25 (95% CI: 0.76 to 2.04) when progestin was added sequentially 9 to 18 days; and a RR of 1.34 (95% CI: 0.88 to 2.04) when progestin was added continuously.[310] Further research in this area is necessary.

Conclusions

The evidence concerning estrogen/progestin therapy and endometrial cancer included two large RCTs, the WHI trial[278] and HERS/HERS-II.[285] Both trials administered estrogen with progestin added continuously. Point estimates from both trials showed a protective effect, but small numbers of cases resulted in wide nonsignificant confidence intervals. Both trials were rated as fair quality. Results are consistent between these trials. The measures are imprecise with wide confidence intervals. The strength of evidence is rated moderate that estrogen with continuous progestin therapy does not increase endometrial cancer risk.

Osteoporotic Fractures

Summary

Three trials reported the incidence of osteoporotic fractures: WHI estrogen/progestin,[15] WHI estrogen-only,[280] and HERS/HERS-II.[285] Oral conjugated estrogen (CEE) was administered in all

three trials. Followup ranged from 5.2 years in the WHI trial to 6.8 years in the HERS/HERS-II trial.

The HERS/HERS-II trial did not detect an effect on fracture incidence with estrogen/progestin therapy. In the WHI trials, both estrogen/progestin and estrogen alone were associated with lowered osteoporotic fracture incidence (Table 78 and Table 79). Based on the WHI estimates, estrogen/progestin therapy resulted in 46 fewer fractures per 10,000 woman-years (95% CI: 29 to 63), and estrogen-only therapy resulted in 56 fewer fractures per 10,000 woman-years (95% CI: 37 to 75). Decreased incidences of hip and vertebral fractures were observed for both therapies as well. Estrogen/progestin therapy resulted in 6 fewer hip fractures (95% CI: 1 to 10) and six fewer vertebral fractures (95% CI: 1 to 11). Estrogen-only therapy resulted in seven fewer hip fractures (95% CI: 1 to 12) and six fewer vertebral fractures (95% CI: 1 to 12).[28]

Table 78. Osteoporotic fracture incidence among women treated with estrogen/progestin

Trial	Total	Hip	Vertebral	Wrist	Other
WHI – CEE + MPA[15] **HR (95% CI)**	0.76 (0.69 to 0.85)	0.66 (0.45 to 0.98)	0.66 (0.44 to 0.98)		0.77 (0.69 to 0.86)
HERS/HERS-II[285] **HR (95% CI)**	1.04 (0.87 to 1.25)	1.61 (0.98 to 2.66)	0.87 (0.52 to 1.48)	0.98 (0.64 to 1.50)	0.94 (0.75 to 1.18)

CEE: conjugated equine estrogen; HERS: Heart and Estrogen/Progestin Replacement Trial; HR: hazard ratio; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative.

Table 79. Osteoporotic fracture incidence among women treated with estrogen alone

Trial	Total	Hip	Vertebral	Wrist	Other
WHI – CEE alone[280] **HR (95% CI)**	0.70 (0.63 to 0.79)	0.61 (0.41 to 0.91)	0.62 (0.42 to 0.93)		

CEE: conjugated equine estrogen; HERS: Heart and Estrogen/Progestin Replacement Trial; HR: hazard ratio; WHI: Women's Health Initiative; CI: confidence interval

Applicability

The WHI and HERS trials have older but overlapping populations compared to the target population of this review. Additional evidence for younger populations was not identified.

Conclusions

The evidence concerning estrogen/progestin therapy and osteoporotic fractures consists of two large RCTs, the WHI trial[15] and HERS/HERS-II.[285] The WHI trial found significant decreases in hip, vertebral, other, and total fractures. The HERS trial did not find significant relationships, possibly due to a small sample size, as seen with the wide confidence intervals in the estimates. Both trials were rated as fair quality. While results were inconsistent, the measures were direct, and the WHI estimates were precise. The strength of evidence is rated moderate that estrogen/progestin therapy decreases osteoporotic fracture risk.

The evidence for estrogen therapy and osteoporotic fractures consists of the WHI trial.[280] The trial reported significant reductions in hip, vertebral, and total osteoporotic fractures. Trial quality was rated as fair. Consistency is unknown with one trial. The measures are direct and precise. The strength of evidence is rated moderate that estrogen therapy decreases the risk of osteoporotic fractures.

Ovarian Cancer

Summary

One trial reported ovarian cancer incidence: WHI estrogen/progestin.[279] This trial administered oral conjugated estrogen (CEE) with the addition of medroxyprogesterone acetate. The hazard ratio was consistent with an increased risk for ovarian cancer, although the wide confidence interval includes 1.00 (Table 80).

No RCTs in the Nelson report provided evidence for an association between estrogen alone and ovarian cancer.

Table 80. Ovarian cancer incidence among women treated with estrogen/progestin

Trial	Treatment	N	Average Followup	Results
WHI – CEE + MPA [279]	0.625mg CEE + 2.5mg MPA	16,608	5.6 years	HR: 1.58; 95% CI: 0.77 to 3.24

CEE: conjugated equine estrogen; HERS: Heart and Estrogen/Progestin Replacement Trial; HR: hazard ratio; MPA: medroxyprogesterone acetate; WHI: Women's Health Initiative.

Applicability

Two large observational studies with younger populations have reported on risks of ovarian cancer among women treated with estrogen/progestogen: the European Prospective Investigation into Cancer and Nutrition and the Cancer Prevention Study II (CPS-II). Both studies found a nonsignificant relationship between estrogen/progestogen use and ovarian cancer incidence: the European study an adjusted HR of 1.20 (95% CI: 0.89 to 1.62)[312] and CPS-II an adjusted RR for former estrogen/progestogen users of 1.40 (95% CI: 0.86 to 2.28) and for current estrogen/progestogen users of 1.18 (95% CI: 0.79 to 1.76).[313]

A systematic review and meta-analysis of menopausal hormone therapy and ovarian cancer risk was conducted by Greiser et al.[295] The review included 30 case control studies, seven cohort studies, four cancer registry studies, and one randomized controlled trial. The risk of ovarian cancer with use of estrogen/progestogen is 1.1 (95% CI: 1.0 to 1.2), according to the meta-analyses by Greiser et al.[295]

The evidence reviewed was judged consistent with the WHI results.

Conclusions

The evidence concerning estrogen/progestogen therapy and ovarian cancer consists of one large RCT, the WHI trial.[279] The trial reported an increased risk of ovarian cancer, but the findings were not statistically significant. Trial quality was rated as fair. Consistency is unknown with one trial, but results from two large observational studies and a meta-analysis, also show increased but nonsignificant findings. Measures were direct. Evidence is imprecise (wide CI) due to few events. The strength of evidence is rated low that estrogen/progestin therapy increases ovarian cancer risk.

Strength of Evidence—Long-Term Effects of Menopausal Hormone Therapy Preparations

Table 81 summarizes the strength of evidence ratings for the long-term effects of menopausal hormone therapy.

Table 81. Strength of evidence assessment for long-term effects of hormone therapies[a]

Outcome	Risk[b]	Treatment vs. Placebo	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE
Breast Cancer	↑	Estrogen/Progestin	M	C	D	P	U	High
	↓	Estrogen	M	I	D	P	U	Low
Gallbladder disease	↑	Estrogen/Progestin	M	U	D	P	U	Mod
	↑	Estrogen	M	U	D	P	U	Mod
Colorectal Cancer	↓	Estrogen/Progestin	M	I	D	I	U	Low
	—	Estrogen	M	U	D	P	U	Mod
CHD	↑	Estrogen/Progestin	M	U	D	P	U	Mod
	—	Estrogen	M	U	D	P	U	Mod
VTE	↑	Estrogen/Progestin	M	U	D	P	U	Mod
	↑	Estrogen	M	C	D	P	U	High
Stroke	↑	Estrogen/Progestin	M	U	D	P	U	Mod
	↑	Estrogen	M	C	D	P	U	High
Endometrial Cancer	—	Estrogen/Progestin	M	C	D	I	U	Mod
Osteoporotic Fractures	↓	Estrogen/Progestin	M	I	D	P	U	Mod
	↓	Estrogen	M	U	D	P	U	Mod
Ovarian Cancer	↑	Estrogen/Progestin	M	U	D	I	U	Low

[a] Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I), Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S), Undetected (U).
[b] Risk: ↑ increased, ↓ decrease, — no change.
SOE: strength of evidence; Mod: moderate; CI: confidence interval; VTE: venous thromboembolic embolic events.

Key Question 3. Nonhormone Other Benefits/Harms

This Key Question addresses the long-term effects of nonhormone therapies on the following conditions: breast cancer; gallbladder disease; colorectal cancer; coronary heart disease, stroke, venous thromboembolism; endometrial cancer; osteoporotic fractures; and ovarian cancer. Eight randomized controlled trials, two cohort studies and four case-control studies formed the evidence base (Table 82 through Table 85) (detailed inclusion criteria listed in Methods section, Tables 2 and 3). We excluded population-based dietary studies and studies reporting intermediate outcomes.

Evidence examining associations of nonhormone therapies with breast cancer, colorectal cancer, coronary heart disease, stroke, and venous thromboembolism, osteoporotic fractures, and ovarian cancer was identified[314-327] (Table 82). No evidence was identified evaluating associations with endometrial cancer or gallbladder disease.

Also addressed are agent-specific harms of nonhormone therapies, summarized following the analyses on long-term effects.

Table 82. Evidence base for long-term effects of nonhormone therapies[a]

Condition	SSRI/SNRIs	Isoflavones	Vitamin E	Black Cohosh	Ginseng	St. John's Wort	Dong Quai
Breast cancer	Chien 2006[314] Wernli 2009[316]	Rebbeck 2006[327] Obi 2009[326] Brasky 2010[325]	**Lonn 2005**[317] **Lee 2005**[318] **Lin 2009**[319]	Rebbeck 2006[327] Obi 2009[326] Brasky 2010[325]	Rebbeck 2006[327]	Obi 2009[326] Brasky 2010[325]	Rebbeck 2006[327] Brasky 2010[325]
Gallbladder disease							
Colorectal cancer			**Lee 2005**[318] **Lin 2009**[319]				
Coronary heart disease, stroke, venous thrombo-embolism	**Archer 2013**[328]		**Lee 2005**[318] **Cook 2007**[324]				
Osteoporotic fractures	Spangler 2007[320]	**Maugeri 1994**[321] Passeri 1995[322] **Alexandersen 2001**[323]					
Endometrial cancer							
Ovarian cancer			**Lin 2009**[319]				

[a] RCTs are in bold. Others studies are observational. Empty cells indicate no evidence was identified. All entries in the vitamin E column are in bold. In the SSRI/SNRIs column, Archer 2013 is in bold. In the isoflavones column, Maugeri 1994 and Alexandersen 2001 are in bold.

Table 83. Study quality assessment for Key Question 3 RCTs

Study	Comparable groups	Researcher/ Subjects Blinded	Adequate Concealment	Comparable Groups Maintained	Differential Loss to Followup	Measures Equal, Reliable	Interventions Clear	Outcomes Defined	Intention to Treat Analysis	Study Quality
Alexandersen 2001[323]	Y	Y	Y	U	Y	Y	Y	Y	Y	Fair
Cook 2007[324]	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Lee 2005[318]	Y	Y	U	Y	N	Y	Y	Y	Y	Good
Lin 2009[319]	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Lonn 2005[317]	Y	Y	Y	Y	N	Y	Y	Y	Y	Good
Maugeri 1994[321]	U	Y	U	U	N	Y	Y	Y	U	Poor
Passeri 1995[322]	U	U	U	U	Y	Y	Y	Y	N	Poor
Archer 2013[328]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Fair

N: no; U: unknown; Y: yes.

Table 84. Study quality assessment for Key Question 3 cohort studies

Study	Comparable Groups	Comparable Groups Maintained	Differential Loss to Followup	Measures Equal, Reliable	Outcomes Defined	Statistical Adjustment for Potential Confounders	Study Quality
Spangler 2008[320]	Y	Y	U	Y	Y	Y	Fair (observational)
Brasky 2011[325]	Y	Y	U	Y	Y	Y	Fair (observational)

N: no; U: unknown; Y: yes.

Table 85. Study quality assessment for Key Question 3 case control studies

Study	Accurate case Ascertainment	Nonbiased Selection of Cases/Controls	Response rate	Diagnostic Tests Equal	Exposure Accurately Measured	Exposure Applied Equally	Statistical Adjustment for Confounders	Study Quality
Chien 2006[314]	Y	Y	cases 81%; controls 74%	Y	Y[a]	Y	Y	Poor (observational)
Wernli 2009[316]	Y	Y	cases 74%; controls 67%	Y	Y[a]	Y	Y	Poor (observational)
Rebbeck 2006[327]	Y	Y	cases 78%; controls 78%	Y	Y[b]	Y	Y	Poor (observational)
Obi 2009[326]	Y	Y	cases 64%; controls 43%	Y	Y[b]	Y	Y	Poor (observational)

[a] SSRI/SNRIs use determined through self-report, in structured interviews
[b] Supplement use determined through self-report, in structured interview

Breast Cancer

Summary

Many studies evaluating soy or herbal preparations and breast cancer incidence were identified, but did not meet inclusion criteria, being either population based dietary studies or reporting only intermediate outcomes (Appendix B). Included studies and results are summarized in Table 86. Two case control studies[326, 327] and one cohort study[327] examining isoflavones, black cohosh, ginseng, St. John's wort, and Dong Quai met inclusion criteria. Three studies on vitamin E intake,[317-319] and two studies on SSRI/SNRIs use,[314, 316] also met inclusion criteria.

The Health Outcomes Prevention Evaluation (HOPE) and its extension, HOPE—The Ongoing Outcomes trial (HOPE-TOO), examined vitamin E (400 IU daily) and breast cancer incidence.[317] The trial population enrolled women with vascular disease or diabetes (n=9541 in HOPE, with n=7030 continuing in HOPE-TOO). Followup in HOPE was 6 years, with an additional 4 years in HOPE-TOO. A second RCT,[318] the Women's Health Study (WHS), enrolled healthy women aged 45 years or older with a 10-year average followup. Participants in the treatment group took 600 IU of vitamin E every other day. A third RCT, the Women's Antioxidant Cardiovascular Study, administered 600 IU of vitamin E every other day to women at high risk for cardiovascular disease. Followup averaged 9.4 years.[319]

A number of studies have investigated a possible antidepressant-breast cancer association. We excluded those enrolling women of all ages because of difficulty assessing modification by age on any exposure-disease association. We also excluded studies that reported results for any antidepressants and not specifically for SSRI/SNRIs. Two case-control studies met inclusion criteria. Chien et al.[314] enrolled women aged 65 to 79 diagnosed with invasive breast cancer. Information on history of antidepressant use in the 20 years prior to the cancer diagnosis was collected, and results were reported for all antidepressants and for subgroups of antidepressants: tricyclics (TCA), SSRIs, and triazolopyridines. Wernli et al.[316] investigated women 20 to 69 years of age, but subgroup analyses for women aged 50 years or older were provided. Results were reported for all antidepressants combined, as well as for specific types of antidepressants (SSRI, TCA, and SNRI).

Rebbeck et al. conducted a population based case control study on the association of hormone related supplements and breast cancer risk.[327] Cases were women in Pennsylvania and New Jersey, 50 to 79 years of age with newly diagnosed breast cancer (n=949), matched by age and race with 1,524 controls. Prior to telephone interviews, postcards were mailed to participants with names of hormone related supplements commonly used to relieve menopausal symptoms, such as isoflavones, black cohosh, dong quai, and ginseng.[327] MARIE (Mammary carcinoma Risk Factor Investigation), a case control study in Germany, investigated associations between herbal preparations used to alleviate menopausal symptoms and breast cancer risk.[326] Cases (n=3,257) were women 50 to74 years of age identified through the Hamburg cancer registry, matched through population registries by age and region to controls (n=6,646). Breast cancer risk and the use of isoflavones, black cohosh, and St. John's wort were assessed.[326] A subset of the VITAL (Vitamins And Lifestyle) cohort study investigated the long term use of supplements and breast cancer risk.[325] Women aged 50 to 76 years, residing in the western Washington state area, were followed for a mean of six years. Vitamin and supplement use during the ten year period prior to baseline was determined. Breast cancer risk and the use of isoflavones, black cohosh, dong quai, and St. John's wort were assessed.[325]

Table 86. Nonhormone therapies and breast cancer

Condition	Treatment	Source; Evidence Type	Study Description	Comparators	Results
Breast cancer	Vitamin E	Lonn 2005[317]; RCT	HOPE conducted 1993-1999 (n=9541)[a]	Placebo: Vitamin E:	0.6% (cumulative incidence) 0.5% RR: 0.86; 95% CI: 0.50 to 1.47; p=0.58
			HOPE-TOO conducted 1999-2003 (n=7030)[a]	Placebo: Vitamin E:	0.7% (cumulative incidence) 0.5% RR: 0.73; 95% CI: 0.40 to 1.31; p=0.29
		Lee 2005[318]; RCT	WHS conducted 1994-2004 (n=39,876)	Placebo: Vitamin E:	3.1% (cumulative incidence) 3.1% RR: 1.00; 95% CI: 0.90 to 1.12; p=0.95
		Lin 2009[319];RCT	Women's Antioxidant Cardiovascular Study 1995-2005 (n=8171)[b]	Placebo: Vitamin E:	130 cases 127 cases RR: 0.98; 95% CI: 0.77 to 1.25
Breast cancer	SSRI/SNRI	Chien 2006[314]; case-control	Women aged 65 to 79 Cases (n= 975) Controls (n= 1007)	Never used SSRI: Ever used SSRI:	914 cases; 953 controls OR: 1.0 61 cases; 54 controls OR: 1.2; 95% CI: 0.8 to 1.8
		Wernli 2009[316]; case-control	Women aged 20 to 69, newly diagnosed breast cancer Cases (n= 2908) Controls (n= 2927)	Subset: women ≥ 50 years (cases=1956; controls=2027)	10.4% cases ever use SSRI 11.3% controls ever use SSRI OR: 0.88; 95% CI: 0.72 to 1.08

Table 86. Nonhormone therapies and breast cancer (continued)

Condition	Treatment	Source; Evidence Type	Study Description	Comparators	Results
Breast cancer	Isoflavones	Rebbeck 2006[327]; case-control	Women aged 50 to 79, newly diagnosed breast cancer Cases (n=949) Controls (n=1,524)	Ever used isoflavones or genistein:	1.1% cases 1.8% controls OR: 0.74; 95% CI: 0.32 to 1.67
		Obi 2009[326]; case-control	Women aged 50 to 74 Cases (n=3,257) Controls (n=6,646)	Ever used isoflavones:	0.6% cases 1.3% controls OR: 0.64; 95% CI: 0.39 to 1.05
		Brasky 2010[325]; cohort	Women aged 50 to 76, followed up for mean 6 years Cases (n=880) Non-cases (n=34,136)	Isoflavones taken for climacteric symptoms:	4.1% cases 4.6% non-cases HR: 1.04; 95% CI: 0.74 to 1.48
Breast cancer	Black cohosh	Rebbeck 2006[327]; case-control	Women aged 50 to 79, newly diagnosed breast cancer Cases (n=949) Controls (n=1,524)	Ever used black cohosh:	2.6% cases 5.0% controls OR: 0.47; 95% CI: 0.27 to 0.82
		Obi 2009[326]; case-control	Women aged 50 to 74 Cases (n=3,257) Controls (n=6,646)	Ever used black cohosh:	3.4% cases 4.8% controls OR: 0.80; 95% CI: 0.63 to 1.00
		Brasky 2010[325]; cohort	Women aged 50 to 76, followed up for mean 6 years Cases (n=880) Non-cases (n=34,136)	Black cohosh taken for climacteric symptoms:	2.4% cases 2.8% non-cases HR: 1.17; 95% CI: 0.75 to 1.82
Breast cancer	St. John's wort	Obi 2009[326]; case-control	Women aged 50 to 79, newly diagnosed breast cancer Cases (n=949) Controls (n=1,524)	Ever used St. John's wort:	0.3% cases 0.3% controls OR: 1.18; 95% CI: 0.54 to 2.57
		Brasky 2010[325]; cohort	Women aged 50 to 74 Cases (n=3,257) Controls (n=6,646)	St. John's wort formerly taken for climacteric symptoms:	3.2% cases 4.1% non-cases OR: 0.83; 95% CI: 0.55 to 1.24
				St. John's wort currently taken for climacteric symptoms	2.3% cases 2.1% non-cases OR: 1.18; 95% CI: 0.74 to 1.89

Table 86. Nonhormone therapies and breast cancer (continued)

Condition	Treatment	Source; Evidence Type	Study Description	Comparators	Results
Breast cancer	Dong quai	Rebbeck 2006[327]; case-control	Women aged 50 to 79, newly diagnosed breast cancer Cases (n=949) Controls (n=1,524)	Ever used dong quai:	2.2% cases 2.7% controls OR: 0.83; 95% CI: 0.43 to 1.59
		Brasky 2010[325]; cohort	Women aged 50 to 74 Cases (n=3,257) Controls (n=6,6446)	Dong quai taken for climacteric symptoms:	1.8% cases 1.3% non-cases HR: 1.17; 95% CI: 0.75 to 1.82
Breast cancer	Ginseng	Rebbeck 2006[327]; case-control	Women aged 50 to 79, newly diagnosed breast cancer Cases (n=949) Controls (n=1,524)	Ever used ginseng:	7.6% cases 10.8% controls OR: 0.74; 95% CI: 0.53 to 1.06

CI: confidence interval; HOPE: Health Outcomes Prevention Evaluation trial; HOPE-TOO: Health Outcomes Prevention Evaluation- The Ongoing Outcomes trial; n=number; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.
[a] Participants were at least 55 years of age with vascular disease or diabetes.
[b]Participants were women 40 years of age and older, at high risk for cardiovascular disease.

Conclusions

The evidence concerning vitamin E and breast cancer risk consists of three large RCTs.[317-319] The population of one trial[318] was healthy women over 45 years of age and the other two trials focused on women with vascular disease or diabetes.[317, 319] Participants received vitamin E supplements or placebo. The trials—with followups of up to 10 years and sample sizes of 7,030,[317] 39,876,[318] and 8,171[319]—found no significant benefit of vitamin E for preventing breast cancer. All trials were rated as good quality (Table 83). The results are consistent among all three trials. The measures are direct and the narrow confidence interval around the null in the larger trial[318] indicates precision. The strength of evidence is rated high that vitamin E does not affect breast cancer risk.

The evidence for SSRI/SNRI use and breast cancer risk consists of two case-control studies.[314, 316] The two observational studies were poor quality (Table 85). Results are consistent and direct. One study had a small sample size and imprecise measures. The strength of evidence is rated insufficient that SSRIs affect breast cancer risk.

The evidence for isoflavones and breast cancer risk consists of two case control studies[326, 327] and one cohort study.[325] None of the studies detected an association between isoflavones supplement use and breast cancer risk (Table 86). The case control studies were rated poor quality (Table 85) and the cohort study was rated fair quality (Table 84). The results among all three studies are consistent. The measures are direct, but the wide confidence intervals indicate imprecision. The strength of evidence is rated insufficient that isoflavones affect breast cancer risk.

The evidence for black cohosh and breast cancer risk consists of two case control studies[326, 327] and one cohort study.[325] One case control study reported a decreased breast cancer risk among black cohosh users.[327] The other case control study reported a point estimate suggesting a decreased risk, but the confidence interval upper limit is 1.0.[326] The cohort study finds no

association between black cohosh use and breast cancer[325] (Table 86). The case control studies were rated poor quality (Table 85) and the cohort study was rated fair quality (Table 84); in the context of observation studies all associations were weak.[329] Results were inconsistent among the three studies, but measures were direct. Wide confidence intervals indicate imprecise measures. The strength of evidence is rated insufficient that black cohosh affects breast cancer risk.

The evidence examining St. John's wort and breast cancer risk consists of one case control study[326] and one cohort study.[325] Neither study detected an association between St. John's wort and breast cancer risk (Table 86). The case control study was rated poor quality (Table 85) and the cohort study was rated fair quality (Table 84). The results are consistent between the two studies. The measures are direct, but wide confidence intervals indicate imprecision. The strength of evidence is rated insufficient that St. John's wort affects breast cancer risk.

The evidence concerning dong quai and breast cancer risk consists of one case control study[327] and one cohort study.[325] Neither of the studies reported an association between dong quai and breast cancer risk (Table 86). The case control study was rated poor quality (Table 85) and the cohort study was rated fair quality (Table 84). The results are consistent. The measures are direct and imprecise. The strength of evidence is rated insufficient that dong quai affects breast cancer risk.

The evidence for ginseng and breast cancer risk consists of one case control study.[327] The study reports no association between ginseng and breast cancer (Table 86). The study was rated poor quality (Table 85). Consistency is unknown with a single study. The measure was direct. The confidence interval is wide indicating imprecision. The strength of evidence is rated insufficient that ginseng affects breast cancer risk.

Gallbladder Disease

No studies evaluating associations between nonhormone therapies used for menopausal symptom relief and gallbladder disease were identified.

Colorectal Cancer

Summary

Two included studies (Table 87) evaluated vitamin E and colorectal cancer. Dietary studies of soy and colorectal cancer incidence and one study reporting results in men and women combined were excluded.

One large RCT,[318] the Women's Health Study (WHS), investigated the long-term effects of taking 600 IU of vitamin E every other day. The trial population was healthy women aged 45 years or older and followup an average of 10 years. The second trial, the Women's Antioxidant Cardiovascular Study, also administered 600 IU of vitamin E every other day. The trial enrolled women aged 40 years or older with cardiovascular disease risk factors. Average followup was 9.4 years.[319]

Table 87. Nonhormone therapies and colorectal cancer

Condition	Treatment	Source; Evidence Type	Trial Description	Comparators	Results
Colorectal cancer	Vitamin E	Lee 2005[318]; RCT	WHS conducted 1994-2004 (n=39,876)	Placebo: Vitamin E:	0.5% (cumulative incidence) 0.5% RR: 1.00; 95% CI: 0.77 to1.31); p=0.99
		Lin 2009[319]; RCT	Women's Antioxidant Cardiovascular Study 1995-2005[a] (n=8171)[a]	Placebo: Vitamin E:	27 cases 17 cases RR: 0.63; 95% CI: 0.34 to 1.15

[a] Participants were women 40 year and older, at high risk for cardiovascular disease.

Conclusions

Two large RCTs examined the effect of vitamin E on colorectal cancer. One trial, with a sample size of 39,876 and a followup of 10 years, found no statistically significant benefit of vitamin E in the prevention of colon cancer (RR=1.00).[318] The second trial with a sample size of 8171 and a followup of 9.4 years, reports a protective effect (RR=0.63), but the estimate was not statistically significant (95% CI: 0.34 to 1.15).[319] The trials were rated as good quality (Table 83). The estimates were consistent and direct. The measure for the large study was precise, though the smaller study had a larger confidence interval. The strength of evidence is rated high that vitamin E does not affect colorectal cancer risk.

Coronary Heart Disease, Stroke, or Venous Thromboembolism

Summary

The literature examining the potential effect of soy (isoflavones) on the prevention of cardiovascular disease is large, but limited to population based dietary studies or those reporting intermediate outcomes. Consequently, the studies were excluded. Three RCTs were identified that met inclusion criteria: two administered vitamin E[318, 324] and one examined desvenlafaxine (Table 88).[328]

The Women's Health Study,[318] examined vitamin E supplementation and cardiovascular disease among healthy women, aged 45 years or older. The average length of followup was 10 years. Outcomes included overall cardiovascular events, myocardial infarction, stroke, and cardiovascular death. In the Women's Antioxidant Cardiovascular Study 600 IU vitamin E was prescribed every other day to women over age 40 at increased risk for cardiovascular disease.[324] The average followup was 9.4 years and outcomes included myocardial infarction, stroke, and cardiovascular death.

One RCT investigated the safety of desvenlafaxine given to healthy postmenopausal women who were seeking treatment for vasomotor symptoms.[328] This phase 3 RCT administered desvenlafaxine 100 mg per day and followed the participants for one year. Safety outcomes measured were: coronary heart disease related deaths, new myocardial infarctions, new onset unstable angina requiring hospitalization, and unscheduled revascularization procedures.

Table 88. Nonhormone therapies and CHD, stroke, or venous thromboembolism

Condition	Treatment	Source; Evidence Type	Trial Description		Results
CHD, stroke, or thrombo-embolism	Vitamin E	Lee 2005[318]; RCT	WHS conducted 1994-2004 (n=39,876)	CV events:	RR: 0.93; 95% CI: 0.82 to 1.05 p = 0.26
				MI:	RR: 1.01; 95% CI: 0.82 to 1.23 p = 0.96
				Stroke:	RR: 0.98; 95% CI: 0.82 to 1.17 p = 0.82
				CV death:	RR: 0.76; 95% CI: 0.59 to 0.98; p = 0.03
		Cook 2007[324]; RCT	Women's Antioxidant Cardiovascular Study 1995-2005 (n=8171)[a]	CV events:	RR; 0.94; 95% CI: 0.85 to 1.0 p=0.23
				MI:	RR: 0.91; 95% CI: 0.72 to 1.15 p=0.44
				Stroke:	RR: 0.84; 95% CI: 0.67 to 1.05 p=0.12
				CV death:	RR: 0.94; 95% CI: 0.77 to 1.15 p=0.56
CHD, stroke, or thrombo-embolism	SNRI[b]	Archer 2012[328]; RCT	Phase 3, multicenter, one year followup; n=2,118	Ischemic cardiovascular events (rate per 1,000 woman-yrs):	Desvenlafaxine: 0.00; 90% CI: 0.00 to 2.56 Placebo: 1.07; 90% CI: 0.05 to 5.07 Excess risk with desvenlafaxine: -1.07; 90% CI: -2.86 to 0.72
				Cerebrovas-cular events (rate per 1,000 woman-yrs):	Desvenlafaxine: 1.11; 90% CI: 0.06 to 5.27 Placebo: 0.00; 90% CI: 0.00 to 2.46 Excess risk with desvenlafaxine: 1.11; 90% CI: -0.68 to 2.90

CHD: coronary heart disease; CI: confidence interval; CV: cardiovascular; MI: myocardial infarction; n=number; RCT: randomized controlled trial; RR: relative risk.

[a] Participants were women 40 year and older, at high risk for cardiovascular disease.

[b] Desvenlafaxine, 100 mg

Conclusions

The evidence comparing vitamin E with placebo and the risk for cardiovascular events, myocardial infarction, stroke, and cardiovascular death consists of two trials. The samples were large with mean followups of 9.4 and 10 years. Neither trial found a statistically significant benefit of vitamin E in the prevention of overall cardiovascular events, including myocardial infarction and stroke.[318, 324] The WHS report found a significant protective effect on cardiovascular death,[318] but the Women's Antioxidant Cardiovascular Study did not.[324]

Both trials were rated good quality (Table 83). Consistent results were reported for cardiovascular events overall, as well as for myocardial infarction and stroke when analyzed separately. The measures are direct and precise. The strength of evidence is rated high that vitamin E does not affect overall cardiovascular event risk, including myocardial infarction and stroke.

The WHS trial reported a statistically significant benefit of vitamin E in the prevention of cardiovascular death[318] whereas the Women's Antioxidant Cardiovascular Study did not.[324] There are uncertainties with the WHS result because it is inconsistent not only with the other trial, but with the WHS results which showed no difference in number of overall cardiovascular events. Additionally, there are well-described inaccuracies in the ascertainment of cardiovascular

deaths, as coded in death certificates.[330] Although the trial is of good quality, the outcome may have inaccuracies and be potentially biased. The strength of evidence is rated low that vitamin E decreases cardiovascular death risk.

The evidence for an association between desvenlafaxine and the risk for cardiovascular events consists of one phase 3 RCT.[328] Followup was one year, with one woman in the placebo group experiencing an acute myocardial infarction and one woman in the desvenlafaxine group experiencing a probable stroke and another woman in the desvenlafaxine group experiencing a probable transient ischemic attack. The trial was rated fair quality. Consistency is unknown with one trial. The measures are direct, but imprecise with small numbers of events resulting in large confidence intervals. The strength of evidence is rated insufficient that desvenlafaxine affects cardiovascular event risk.

Endometrial Cancer

Summary

No studies meeting inclusion criteria evaluating the effect of nonhormone agents on endometrial cancer were identified. However, we briefly note a report from a working group of 22 clinical and research experts in the field of women's health and botanicals convened by the North American Menopause Society.[331] The group evaluated current evidence on health effects of isoflavones in peri- and postmenopausal women, including both menopausal symptom relief and long-term benefits and harms. There was no description provided on how articles were chosen for inclusion in the report. The publication discusses several large population based studies on soy consumption and the risk of endometrial cancer, which are not applicable for this current review.[332-334] The Society paper also reviewed several RCTs on soy treatment and endometrial hyperplasia—an intermediate outcome.

Conclusions

The strength of evidence is rated insufficient that treatment with soy products affects endometrial cancer risk.

Osteoporotic Fractures

Summary

We identified three trials evaluating the effect of soy (isoflavones) on osteoporotic fractures[321-323] (which were incorporated in a meta-analysis[335]) and one observational study of the association between antidepressants and osteoporotic fractures.[320]

Spangler et al. (2008) analyzed data from participants of the Women's Health Initiative Observational Study, focusing on depressive symptoms, antidepressant use, and bone fractures.[320] After adjusting for depressive symptoms, as well as demographic, lifestyle, and reproductive factors, the investigators found SSRI use associated with an increased risk of fractures at any site. Analysis by fracture site found SSRI users with increased fracture risk in spine and other sites.

Bolaños et al. (2010) performed an indirect treatment comparison, comparing a meta-analysis of three isoflavones versus placebo trials with a meta-analysis of ten hormone replacement therapy versus placebo trials, for the reduction of vertebral fractures. A search through the trials register of Cochrane Osteoporosis Treatment Trial Group, Cochrane Controlled Trials,

MEDLINE®, EMBASE®, ProQuest, BIREME, Trip Database, LILACS, and Scielo through September 2009 was conducted. The Jadad scale[336] was used to assess the quality of the RCTs. The three isoflavones trials compared ipriflavone, at a dosage of 600 mg/day plus a calcium supplement versus a calcium supplement alone. The pooled estimate for isoflavones versus did not show a significant reduction in vertebral fractures. The authors concluded that isoflavones therapy was "similar" to menopausal hormone therapy for preventing vertebral fracture using a simple calculation of the indirect odds ratios, but did not apply methods necessary to appropriately obtain estimated indirect effects and assess consistency.[337] Because the appropriate statistical methods were not used, the meta-analysis is not included in our evidence table. The three RCTs[321-323] are included in our review (Table 89).

Table 89. Nonhormone therapies and osteoporotic fractures

Condition	Treatment	Source; Evidence Type	Trial Description	Results
Osteoporotic fractures	SSRI	Spangler 2007[320]; prospective cohort trial	WHI-OS SSRI users (n=7212) vs. non-SSRI users (n=86,463) average 7.4 year followup	HR (95% CI):[a] all sites: 1.30 (1.20 to 1.41) hip: 1.33 (0.95 to 1.86) spine: 1.25 (0.96 to 1.63) wrist: 1.29 (1.07 to 1.56) other: 1.32 (1.21 to 1.45)
	Soy (isoflavones, phytoestrogens, lignans)	Maugeri 1994[321]; RCT	n=84 600 mg/day ipriflavone (n=41) or placebo (n=43) ≥ 65 years old 2 year followup	Fracture incidence: Ipriflavone: 2 (4.9%) Placebo: 11 (25.6%)
		Passeri 1995[322]; RCT	n=40 600 mg/day ipriflavone (n=20) or placebo (n=20) 65-79 years of age 2 year followup	Fracture incidence: Ipriflavone: 4 (20.0%) Placebo: 9 (45.0%)
		Alexandersen 2001[323]; RCT	n=474 600 mg/day ipriflavone (n=234) or placebo (n=240) 45-75 years of age 3 year followup	Fracture incidence: Ipriflavone: 11 (4.7%) Placebo: 11 (4.6%) RR: 1.07 (95% CI: 0.53 to 2.16)

CI: confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; N: number; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SSRI: selective serotonin reuptake inhibitor; WHI-OS: Women's Health Initiative Observational Study.

[a] Adjusted for depressive symptoms.

Conclusions

The evidence for SSRI use and osteoporotic fractures consists of one large prospective cohort study (n=93,675) with 7212 SSRI users followed for a mean of 7.4 years.[320] Hazard ratios were consistent with an increased risk for fractures in all sites, but the risks were only significant for wrist, other, and all sites. The study was rated fair. Consistency is unknown with a single study. The measures were direct and precise. The strength of evidence is rated low that SSRIs increase osteoporotic fracture risk.

The evidence for soy (isoflavones) effect on osteoporotic fractures consists of three trials. Two trials enrolled samples fewer than 100 participants who were followed for two years,[321, 322] and one trial of 474 women had a followup of three years.[323] One trial was rated fair quality and two trials rated poor quality. The results were inconsistent, with the larger trial reporting no

effect and the two smaller trials showing a potential protective effect of isoflavones. The measures were direct, but imprecise due to the small sample sizes. The strength of evidence is rated insufficient that isoflavones affect osteoporotic fracture risk.

Ovarian Cancer

Summary

One trial (Table 90) examining the effect of vitamin E on ovarian cancer was identified.[319] The Women's Antioxidant Cardiovascular Study, a double blind placebo-controlled trial, administered 600 IU of vitamin E every other day to women aged 40 years or older and at risk for cardiovascular disease. The study found that vitamin E had no effect on ovarian cancer incidence.

Table 90. Nonhormone therapies and ovarian cancer

Condition	Treatment	Source; Evidence Type	Study Description		Results
Ovarian cancer	Vitamin E	Lin 2009[319]; RCT	Women's Antioxidant Cardiovascular Study 1995-2005 (n=8171)[a]	Placebo: Vitamin E:	14 cases 8 cases RR: 0.58; 95% CI: 0.24 to 1.37

CI: confidence interval; N: number; RCT: randomized controlled trial; RR: relative risk

Conclusions

The evidence for vitamin E and ovarian cancer consists of one RCT. The single trial, with a sample size of 8171, reports a protective, though insignificant, effect.[319] The trial is rated good quality. Consistency is unknown with one trial. The measure is direct, but imprecise due to the small number of cases resulting in a wide confidence interval. The strength of evidence is rated insufficient that vitamin E affects ovarian cancer risk.

Strength of Evidence—Nonhormone Other Benefits/Harms

Table 91 summarizes strength of evidence ratings for the effects of nonhormone menopausal therapies on breast, ovarian, endometrial, and colorectal cancers, cardiovascular disease, and gallbladder disease.

Table 91. Strength of evidence assessment for long-term effects of nonhormone therapies[a]

Outcome	Risk[b]	Treatment (vs. Placebo)	Risk of Bias	Consistency	Directness	Precision	Reporting Bias	SOE	Rationale for Downgrading
Breast Cancer	—	Vitamin E	L	C	D	P	U	High	
Breast Cancer		SSRI	H	C	D	I	U	Insuff	2 poor quality case control studies; 1 imprecise
Breast Cancer		Isoflavones	H	C	D	I	U	Insuff	3 obs studies (2 poor quality case control studies); 1 imprecise
Breast Cancer		Black cohosh	H	I	D	I	U	Insuff	3 obs studies with different results; wide CI
Breast Cancer		St. John's wort	H	C	D	I	U	Insuff	2 obs studies (1 poor quality); 2 imprecise
Breast Cancer		Dong quai	H	C	D	I	U	Insuff	2 obs studies (1 poor quality); 2 imprecise
Breast Cancer		Ginseng	H	U	D	I	U	Insuff	Only one study; wide CI
Colorectal Cancer	—	Vitamin E	L	C	D	P	U	High	
Cardiovascular Events	—	Vitamin E	L	C	D	P	U	High	
Cardiovascular Events		SNRI	L	U	D	I	U	Insuff	1 large trial; wide CI
Cardiovascular Death	↓	Vitamin E	L	I	U	I	U	Low	Inconsistent –2 trials with different results and small magnitude; uncertain directness as no effect on cardiovascular events; imprecise given CIs for effect magnitude
Osteoporotic Fractures	↑	SSRI	H	U	D	P	U	Low	Single observational study
Osteoporotic Fractures		Isoflavones	H	I	D	I	U	Insuff	1 fair and 2 poor quality trials; small sample sizes; directionality of risks differed
Ovarian Cancer		Vitamin E	L	U	D	I	U	Insuff	1 large trial; wide CI
Gallbladder Disease									No evidence identified
Endometrial Cancer									No evidence identified

[a] Risk of Bias: High (H), Medium (M), Low (L); Consistency: Inconsistent (I), Unknown (U), Consistent (C); Directness: Indirect (I), Direct (D); Precision: Imprecise (I), Unknown (U), Precise (P); Reporting Bias: Suspected (S), Undetected (U).
[b] Risk: ↑ increased, ↓ decrease, — no change, no direction posited for insufficient SOE
CI: confidence interval; Insuff: insufficient; Mod: moderate; obs: observational; SNRI: serotonin-norepinephrine reuptake inhibitor; SOE: strength of evidence; SSRI: selective serotonin reuptake inhibitor

Compounded Hormone Therapies

There is insufficient evidence regarding the safety and efficacy of compounded "bioidentical" hormone therapy for treatment of menopausal symptoms. We were unable to identify any clinical trials comparing compounded hormone therapy for menopausal symptoms that met our criteria for inclusion. One randomized trial compared the pharmacokinetics of

estrogen containing compounded "bioidentical" cream and a conventional "bioidentical" patch, but the outcome did not include a discussion of vasomotor symptoms or other harms/benefits, the study length was less than the 12-week duration for hormone trials and the number of participants was too low for inclusion in this review (NCT00864214).[338] Four evidence-based position statements from professional societies and special committee reports were reviewed and included in the report to illustrate the general consensus indicating that evidence-based research on compounded hormone therapy is lacking[19, 32, 33, 38-40] Due to growing interest and an increase in prescriptions of compounded hormones, the limitations in the evidence base regarding the safety and efficacy of these therapies emphasizes the priority that should be given to future research. Many claims regarding the safety, efficacy, and superiority of compounded hormones have not been supported and FDA has voiced concern over pharmacies misleading women and practitioners by unsupported claims of safety and greater efficacy than FDA-approved menopausal hormone therapies.

Adverse Events

Summary

Among KQ1 trials of nonhormone prescription therapies used to treat menopausal symptoms, 12 trials reported adverse events. Six trials reported adverse events for desvenlafaxine,[148, 166, 168, 171, 235, 339] three reported events for gabapentin,[200, 340] two reported events for escitalopram,[148, 167] and one reported events for clonidine.[106](Appendix M, Table M-1a and Table M-1b) The most common adverse events reported were in the following categories: nervous system (12 of 12 trials), gastrointestinal (11 of 12 trials), general disorders and administration site conditions (10 of 12 trials), and eye (6 of 12 trials). The highest incidence of reported events was from a trial with desvenlafaxine (47.8 percent gastrointestinal)[339] and from a trial with clonidine (52.4 percent nervous system).[106] (Appendix Table M-1a and Table M-1b)

Among KQ1 trials of nonprescription therapies to treat menopausal symptoms, 16 trials reported adverse events. Nine trials reported adverse events with the use of soy (isoflavones) treatments,[112, 201, 203, 205, 207, 208, 341-343] three with black cohosh,[128, 216, 344]three with plants or multibotanicals,[108, 134, 344] one with St. John's wort,[128] and one with DHEA.[150](Appendix M, Table M-2a and Table M-2b) One trial reported adverse events for both a nonhormone prescription therapy (fluoxetine) and a nonprescription therapy (black cohosh) and this trial's results were added to Appendix M, Tables M-1a and M-1b. The most common adverse events reported were in the following categories: gastrointestinal (15 of 16 trials), nervous system (11 of 16 trials), musculoskeletal (10 of 16 trials), reproductive system/breast (10 of 16 trials), and general disorders and administration site conditions (8 of 16 trials). The highest reported events were from a trial for soy (52.5 percent gastrointestinal)[342] and (25.4 percent reproductive system/breast).[342]

In addition to adverse events reported among KQ1 trials, a systematic review of black cohosh adverse events[345] and a meta-analysis of black cohosh and hepatotoxicity[346] were identified. The systematic review did not focus on postmenopausal women, but the authors discussed several case reports of potential liver problems, such as acute hepatitis and autoimmune hepatitis, related to the use of black cohosh when used to treat menopausal symptoms. Causal associations were difficult to discern because in some cases, herbal preparations were taken with black cohosh, and in one case, a relapse occurred after the black cohosh treatment had been stopped months earlier.[345] The meta-analysis included five RCTs with a total of 1,020 peri- and postmenopausal

women. There was no significant difference in liver function parameters (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltranspeptidase) among treatment groups and placebo groups.[346]

Key Question 4. Effectiveness of Treatments for Menopausal Symptoms in Selected Subgroups

This Key Question addresses the effectiveness of therapies for menopausal symptoms among subgroups of women. The evidence base consisted of the randomized controlled trials from that also included subgroup analyses. Subgroups of interest included age, BMI, race, severity of menopausal symptoms, time since menopause, and uterine status.

Twenty-seven trials reported relevant subgroup analyses.[93, 94, 114, 127, 144, 145, 167, 172, 175, 183, 199, 201, 216, 234, 244, 248-250, 266, 347-354] Results of the subgroup analyses are presented by outcome category: vasomotor symptoms, sexual function, psychological symptoms, quality of life, sleep disturbance, and urogenital symptoms. Within each outcome category, there is an evidence base table of trials by subgroup and type of treatment, trial quality assessments, and summaries. Detailed results tables are in Appendix N. Strength of evidence could not be assigned owing to the variety of treatments, outcome measures, and subgroup definitions.

Vasomotor Symptoms

Nineteen trials reported subgroup analyses for vasomotor outcomes: ten were hormone therapy trials,[175, 183, 234, 249, 250, 348-351, 353] one was an SSRI (escitalopram) trial,[167] and eight were nonprescription therapy trials.[114, 127, 201, 216, 266, 347, 352, 354] Results are summarized in Table 92.

Table 92. Summary of subgroup analyses reporting vasomotor outcomes

Subgroup	Trial	Comparators	Subgroup Categories	Improvement Over Comparator
Age	Hedrick 2010[348]	Estrogen (low dose) vs. placebo	<50 years 50 to 59 years ≥60 years	— Yes —
	Rigano 2001[349]	Estrogen (standard dose) vs. placebo	48 to 50 years 51 to 53 years 54 to 56 years	Yes Yes Yes
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	<55 years ≥55 years	Yes —
BMI	Tice 2003[201]	Isoflavones vs. placebo	<25 kg/m^2 ≥25 kg/m^2	— —
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	<25 kg/m^2 ≥25 kg/m^2	Yes —
Race	Freeman 2011[167]	SSRI (escitalopram, 10 to 20 mg) vs. placebo	African American White Other	— Yes Yes
Severity of symptoms	Maki 2007[234]	Estrogen/progestin (standard dose) vs. placebo	HF severity score: <1.2 ≥1.2	 — Yes
	Pitkin 2007[250]	Estrogen/progestin (three doses: two standard and one high)	HF/week: <30 ≥30	 Yes (all doses) Yes (all doses)
	Limpaphayom 2006[249]	Estrogen (three doses: ultralow, low, and standard)	HF/day <3 ≥3	 Yes (all doses) Yes (all doses)
	Crisafulli 2004[353]	Estrogen/progestin vs. isoflavones vs. placebo	HF score >5	Yes (both treatment groups)
	Aso 2012[347]	Equol vs. placebo	HF/day: <3 ≥3	 — Yes
	Lee 2010[266]	Isoflavones vs. placebo	Total KI score >20	Yes
	Frei-Kleiner 2005[352]	Black cohosh vs. placebo	Total KI score ≥20	Yes
	Verhoeven 2005[127]	Isoflavones/black cohosh vs. placebo	≥9 HF/day	—
	Burke 2003[354]	Isoflavones vs. placebo	≥4 HFNS/day	—
Time since menopause	Lobo 2009[351]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause <5 ≥5	 Yes (all doses) Yes (all doses)
	Utian 2009[183]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause <5 ≥5	 Yes (all doses) Yes (all doses)
	Simon 2001[350]	Estrogen (standard dose) vs. placebo	Months since menses 0 to ≤6 6 to ≤12 12 to ≤36 >36	 — — Yes Yes
	Baerug 1998[175]	Estrogen/progestin (two arms low dose) vs. placebo	Months amenorrhea: 3 to 12 ≥12	 Yes (all doses) Yes (all doses)
	Osmers 2005[216]	Black cohosh vs. placebo	Early climacteric Late climacteric	Yes Yes
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	Years amenorrhea: <4 ≥4	 Yes Yes
Uterine status	Hedrick 2010[348]	Estrogen (three low dose arms: 0.25 mg, 0.5 mg, 1.0 mg) vs. placebo	Uterus: Absent Present	 Yes (0.25 mg, 1.0 mg) Yes (0.5 mg, 1.0 mg)

HF: hot flushes; HFNS: hot flushes/night sweats; KI: Kupperman Index; SSRI: selective serotonin reuptake inhibitor

Vasomotor Symptoms by Age

Three trials included subgroup analyses on vasomotor symptoms by age (Appendix N, Table N-1). Two administered estrogens[348, 349] and one Chinese medicinal herbs.[114]

In a trial comparing three doses of estrogen skin gel (all low dose) with placebo, Hedrick et al. reported significant improvements in number of moderate to severe hot flushes and night sweats in all treatment arms. When analyzed by age (<50, 50 to 59, and ≥60), significant improvements were observed only in women aged 50 to 59 years. Significant improvements with the younger and the older age groups may not have been detected due to smaller sample sizes in those subgroups.[348]

Rigano et al. compared a standard dose estrogen patch with placebo on menopausal symptoms and reported significant improvements among women using the patch. Subgroup analyses by age (48 to 50, 51 to 53, and 54 to 56) found improvements in proportions with hot flushes in all groups.[349]

In a trial comparing Chinese medicinal herbs with placebo, Davis et al. reported improved vasomotor symptoms for both the treatment group and the placebo group, with no between-group difference. Analyses for women younger than 55 years and women 55 years of age or older, showed significant improvement in the MENQOL vasomotor score only among younger women treated with medicinal herbs.[114]

Vasomotor Symptoms by BMI

Two trials conducted subgroup analyses on vasomotor symptoms by BMI. Both interventions were nonprescription, one using two different doses of isoflavones[201] and one using Chinese medicinal herbs (Appendix N, Table N-2).[114]

In the isoflavones trial, Tice et al. reported equivalent improvements in vasomotor symptoms among the placebo and two isoflavones treatment groups. Subgroup analyses on women with a BMI <25 and ≥25 kg/m^2 found no effect modification by BMI. The numbers in each subgroup were not provided and significance tests were not performed.[201]

The trial with Chinese medicinal herbs reported that MENQOL vasomotor scores were similar between the treatment and placebo groups in the overall study population. Subgroup analyses on women with BMI ≤25 and >25 kg/m^2 found that women with BMI ≤25 kg/m^2 experienced significantly reduced vasomotor symptoms compared with placebo, while women with higher BMI did not.[114]

Vasomotor Symptoms by Race

One trial conducted a subgroup analysis on vasomotor symptoms by race (African-American, White, and other) (Appendix N, Table N-3).[167] The trial compared an SSRI (escitalopram, 10 to 20 mg) with placebo and reported significant improvements in vasomotor symptoms for the treatment group compared with the placebo. In the subgroup analysis, compared with placebo, daily total hot flushes and night sweats decreased among White, but not African-American women, in the SSRI group.

Vasomotor Symptoms by Severity of Symptoms

Nine trials included subgroup analyses on vasomotor symptoms according to severity of symptoms (Appendix N, Table N-4). Three trials administered estrogen/progestin — one included a placebo comparator[234] and two compared different estrogen/progestin doses.[249, 250]

Two trials compared isoflavones with placebo;[347, 354] a three-arm trial compared estrogen/progestin, isoflavones, and placebo;[353] one trial compared black cohosh with placebo;[352] one trial compared equol with placebo;[347] and one trial compared black cohosh plus isoflavones with placebo.[127]

In the trial comparing standard dose estrogen/progestin with placebo, Maki et al. presented mean change in total hot flushes for women with symptom severity scores over and below the overall mean at baseline. A significant decrease in vasomotor symptoms was observed only in the subgroup that was above the mean—possibly a floor effect in women with lesser symptoms.[234]

In a three arm trial with two standard doses of estrogen/progestin and one high dose of estrogen/progestin, Pitkin et al. measured weekly moderate to severe hot flushes for women and reported that all doses were accompanied by significant reductions. Subgroup analyses for women with 30 or more hot flushes per week at baseline and in those with fewer than 30 at baseline found significant hot flush reductions, regardless of estrogen dose or severity of symptoms at baseline.[250]

In a three-arm trial comparing three doses of estrogen (ultralow, low, and standard), mean daily total hot flushes decreased significantly among all treatment groups. Subgroup analysis on only women experiencing three or more hot flushes per day also showed that all estrogen doses were equally effective.[249]

The two isoflavones trials conducted analyses focusing only on women with more severe symptoms: a Kupperman Index score greater than 20[266] and women with 4 or more hot flushes and night sweats per day.[354] One trial reported a significant improvement in moderate to severe hot flushes among women treated with isoflavones compared with placebo,[266] but the other trial found equally significant improvements in total hot flushes and night sweats in both isoflavones and placebo groups.[354]

The three-arm trial of estrogen/progestin, isoflavones, and placebo reported significant reductions in daily total hot flushes in the two treatment groups compared with placebo for the whole trial population. A subgroup analysis limited to women with more severe symptoms (a hot flush score >5), also showed significant improvements in total hot flushes among both the treatment groups compared with placebo.[353]

One study compared black cohosh with placebo and reported similar reductions in total hot flushes among both the black cohosh and placebo groups in the larger study sample. However, in a subgroup analysis limited to women with more severe symptoms (Kupperman Index $\geq$20), women treated with black cohosh experienced significant improvements compared with placebo.[352]

In the equol trial, Aso et al. reported significant reductions in hot flushes in the treatment group compared with placebo.[347] Separate analyses on women with fewer than 3 hot flushes per day and women with 3 or more per day were performed. Both subgroups experienced decreases in daily hot flushes, but the difference was only significant in the subgroup with more severe symptoms.[347]

Verhoeven et al. conducted a trial comparing the effects of a supplement containing both isoflavones and black cohosh with placebo. Reductions in total hot flushes between the groups were similar in the whole trial sample, as well as in the subgroup with more severe symptoms ($\geq$9 hot flushes per day).[127]

Vasomotor Symptoms by Time Since Menopause

Six trials conducted subgroup analyses on vasomotor symptoms by time since menopause (Appendix N, Table N-5). Two trials compared estrogen plus bazedoxifene with placebo;[183, 351] one trial compared estrogen/progestin with placebo;[175] one trial compared estrogen with placebo;[350] and two trials compared nonprescription treatments (Chinese medicinal herbs[114] and black cohosh[216]) with placebo.

The two estrogen/bazedoxifene trials were part of the Selective Estrogens, Menopause, and Response to Therapy (SMART) trials. In these trials, low and standard dose estrogens, were combined with bazedoxifene, and compared with placebo. Women in both treatment groups experienced significant reductions in MENQOL vasomotor scores compared with women in the placebo group. When subgroup analyses were conducted on women less than 5 years and 5 years or more since menopause, the estrogen groups in both trials experienced significant reductions in vasomotor scores compared with placebo, regardless of time since menopause.[183, 351]

In the Baerug et al. (1998) trial, two low-dose estrogen/progestin groups were compared with placebo. All three groups experienced significant improvements in vasomotor symptoms, and the differences between the estrogen groups compared with the placebo group were also significant. Subgroup analysis comparing late perimenopausal and postmenopausal women show mean weekly hot flushes were similarly improved in both treatment groups compared with placebo.[175]

Simon et al. (2001) compared standard dose estrogen with placebo and found significant improvements in vasomotor symptoms over placebo. Subgroup analysis was conducted on four subgroups (0 to $\leq$6 months since last menses; 6 to $\leq$12 months since last menses; 12 to $\leq$36 months since last menses; and >36 months since last menses). Fewer daily moderate-to-severe hot flushes were observed in all subgroups with estrogen—significant only in the two later menopausal groups (12 to $\leq$36 months since last menses and >36 months since last menses). Significant improvements with the earlier menopausal groups may not have been detected due to smaller population sizes in those subgroups.[350]

Davis et al. (2001) compared Chinese medicinal herbs with placebo and reported improvements in vasomotor symptoms in both groups. Subgroup analysis for women experiencing less than 4 and 4 or more years of amenorrhea was performed. MENQOL vasomotor score and total daily hot flushes and night sweats were reported. There were no significant differences in vasomotor outcomes between the two subgroups.[114]

Osmers et al. (2005) compared black cohosh with placebo and noted significant improvements in vasomotor symptoms in the black cohosh group compared with placebo. A subgroup analysis on early and late climacteric women was performed. The difference in changes from placebo on the Menopause Rating Scale for hot flushes was significant in both early ($p<0.002$) and late ($p<0.006$) climacteric women.[216]

Vasomotor Symptoms by Uterus Status

One trial reported subgroup analyses by uterus status (absent or intact) and reported vasomotor outcomes (Appendix N, Table N-6). Three estrogen doses (all low dose: 0.25 mg, 0.50 mg, and 1.0 mg) of estrogen skin gel were compared with placebo.[348] No vasomotor outcomes for the study groups as a whole were reported. Among women with absent uteri, the number of moderate to severe hot flushes decreased significantly in women treated with 0.25 mg and 1.0 mg estrogen gel, and severity of flushes decreased significantly only in the 1.0 mg estrogen gel group. Among women with intact uteri, number of moderate to severe hot flushes

decreased significantly in the 0.50 mg and 1.0 mg treatment groups, and severity of hot flushes decreased significantly in all treatment groups.[348]

Sexual Function

Seven trials included subgroup analyses of sexual function outcomes (Table 93). Six were estrogen therapy trials[144, 145, 183, 244, 349, 351] and one was a nonprescription therapy trial.[114]

Table 93. Summary of subgroup analyses reporting sexual function outcomes

Subgroup	Trial	Comparators	Subgroup Categories	Improvement Over Comparator
Age	Brunner 2005[144]	Estrogen (standard dose) vs. placebo	50 to 54 years with moderate to severe vasomotor symptoms	—
	Hays 2003[145]	Estrogen/progestin (standard dose) vs. placebo	50 to 54 years with moderate to severe vasomotor symptoms	Yes
	Rigano 2001[349]	Estrogen (standard dose) vs. placebo	48 to 50 years 51 to 53 years 54 to 56 years	— — —
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	<55 years ≥55 years	— —
BMI	Davis 2001[114]	Chinese medicinal herbs vs. placebo	<25 kg/m^2 >25 kg/m^2	— —
Time since menopause	Lobo 2009[351]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 — Yes
	Utian 2009[183]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 — Yes
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	Years amenorrhea: <4 ≥4	 — —
Uterine status	Davis 2008[244]	Testosterone (two arms: 0.15 mg, 0.30 mg) vs. placebo	Uterus: Absent Present	 — Yes

BMI: body mass index; kg/m: kilogram/meter

Sexual Function by Age

Four trials conducted subgroup analyses on sexual function by age (Appendix N, Table N-7). Two trials compared estrogen alone treatment with placebo;[144, 349] one trial compared estrogen/progestin with placebo;[145] and one trial compared a nonprescription treatment with placebo.[114]

Two trials were part of the Women's Health Initiative. One trial examined standard dose estrogen with placebo[144] and one trial standard dose estrogen/progestin with placebo.[145] Both conducted subgroup analyses on women aged 50 to 54 years with moderate to severe vasomotor symptoms. There were significant improvements in sexual satisfaction scores compared with placebo in the estrogen/progestin, but not estrogen alone, groups.

Rigano et al. (2001) compared a standard dose estrogen patch with placebo and assessed sexual activity by age subgroups (48 to 50, 51 to 53, and 54 to 56). Estrogen treatment resulted in more women reporting decreased sexual activity compared with placebo, with the strongest effect in the oldest age group.[349]

Davis et al. (2001) compared Chinese medicinal herbs with placebo. There was no significant difference in MENQOL sexual score in the trial population as a whole. In subgroup analyses for women younger than 55 years and 55 years or older, improvement in MENQOL sexual score was seen in both age groups treated with herbs, but not statistically distinguishable compared with placebo.[114]

Sexual Function by BMI

Davis et al.[114] (Appendix N, Table N-8) compared Chinese medicinal herbs with placebo and found no difference in MENQOL sexual score. A subgroup analysis was conducted for women with BMI $\leq$25 and >25 kg/m^2. Neither BMI subgroup experienced a significant difference in MENQOL sexual score with treatment compared with placebo.[114]

Sexual Function by Time Since Menopause

Three trials reported subgroup analyses for sexual function according to time since menopause (Appendix N, Table N-9). Two compared estrogen plus bazedoxifene with placebo (SMART trials),[183, 351] and one Chinese medicinal herbs with placebo.[114]

In the estrogen/bazedoxifene trials, low or standard dose estrogens were combined with bazedoxifene and compared with placebo. MENQOL sexual scores were compared in analyses for women less than 5 and 5 or more years since menopause. In both trials, the estrogen/bazedoxifene treatment significantly improved sexual scores only in women menopausal for 5 years or more.[183, 351]

Davis et al. compared Chinese medicinal herbs with placebo and did not detect a difference in the study groups in MENQOL sexual score. Subgroup analyses of women who were amenorrheic for less than 4 or 4 or more years were performed. The difference in change over placebo in MENQOL sexual score was slightly lower in participants with more than 4 years amenorrhea, but the difference was not statistically significant.[114]

Sexual Function by Uterus Status

A single trial conducted subgroup analyses on sexual function by uterus status (Appendix N, Table N-10).[244] In this three arm trial of testosterone (0.15 mg and 0.30 mg) compared with placebo, number of satisfying sexual episodes per week did not differ among the three groups. Subgroup analyses were conducted among women with natural menopause and women with surgical menopause. Among women with natural menopause, significant improvements in number of satisfying sexual episodes per week were reported for both the 0.15 mg testosterone group ($p=0.02$) and the 0.30 mg testosterone group ($p<0.001$) compared with placebo. In women with surgical menopause, no significant differences from placebo were observed.[244]

Psychological Symptoms

Eight trials with subgroup analyses reported psychological outcomes (Table 94). Five were hormone therapy trials,[144, 145, 183, 199, 351] one was a desvenlafaxine trial,[172] one was a Chinese medicinal herb trial,[114] and one was a black cohosh trial.[216]

Table 94. Summary of subgroup analyses reporting psychological symptom outcomes

Subgroup	Trial	Comparators	Subgroup Categories	Improvement Over Comparator
Age	Brunner 2005[144]	Estrogen (standard dose) vs. placebo	50 to 54 years with moderate to severe vasomotor symptoms	—
	Hays 2003[145]	Estrogen/progestin (standard dose) vs. placebo	50 to 54 years with moderate to severe vasomotor symptoms	—
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	<55 years ≥55 years	— —
BMI	Davis 2001[114]	Chinese medicinal herbs vs. placebo	<25 kg/m^2 >25 kg/m^2	— —
Time since menopause	Lobo 2009[351]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 — —
	Utian 2009[183]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 — —
	Strickler 2000[199]	Estrogen (standard dose) vs. placebo	Years since menopause: <4 ≥4	 — —
	Kornstein 2010[172]	SNRI (10 mg desvenlafaxine) vs. placebo	Perimenopausal Postmenopausal	Yes Yes
	Osmers 2005[216]	Black cohosh vs. placebo	Early climacteric Late climacteric	Yes —
	Davis 2001[114]	Chinese medicinal herbs vs. placebo	Years amenorrhea: < 4 ≥ 4	 — —
Comorbidities	Strickler 2000[199]	Estrogen (standard dose) vs. placebo	Baseline anxiety score: <3.5 ≥3.5	 — Yes

BMI: body mass index; SNRI: serotonin-norepinephrine reuptake inhibitor

Psychological Symptoms by Age

Three trials conducted subgroup analyses on psychological symptoms by age.

Two of the trials were part of the Women's Health Initiative trials. One tested standard dose estrogen with placebo[144] and one tested standard dose estrogen/progestin with placebo.[145] Both trials conducted subgroup analyses on women aged 50 to 54 with moderate to severe vasomotor symptoms. The researchers combined the Center for Epidemiological Studies Depression Scale plus two items from the Diagnostic Interview Schedule as a psychological outcome measure. Neither of the trials found a significant difference in psychological measures in the treatment groups compared with placebo within this subgroup.

One trial compared Chinese medicinal herbs with placebo. A subgroup analysis was conducted on women younger than 55 years of age and women 55 years of age or older. Neither age group showed a statistically significant difference in MENQOL psychological score between the treatment and placebo groups.[114]

Psychological Symptoms by BMI

One trial conducted subgroup analyses on psychological symptoms by BMI (Appendix N, Table N-12).[114] Davis et al. compared Chinese medicinal herbs with placebo in women with a

BMI ≤25 and women with a BMI >25. Neither subgroup experienced significant differences in MENQOL psychological score between the treatment and placebo groups.

Psychological Symptoms by Time Since Menopause

Six trials conducted subgroup analyses on psychological symptoms by time since menopause (Appendix N, Table N-13). Two trials compared estrogen plus bazedoxifene with placebo;[183, 351] two trials compared nonprescription treatments (Chinese medicinal herbs[114] and black cohosh[216]) with placebo, one trial compared estrogen with placebo,[199] and one trial compared an SNRI (desvenlafaxine) with placebo.[172]

The two estrogen/bazedoxifene trials were part of the Selective Estrogens, Menopause, and Response to Therapy (SMART) trials. In these trials, low-dose and standard-dose estrogens were combined with bazedoxifene and compared with placebo. When subgroup analyses were conducted on women who were less than 5 years menopausal compared with women menopausal for 5 years or more, none of the treatment groups in either of the subgroups experienced significant reductions in MENQOL psychological scores compared with placebo.[183, 351]

Strickler et al. compared a standard dose of conjugated equine estrogen with placebo and reported no difference in WHQ anxiety scores among the two study groups. A subgroup analysis on women less than 4 years postmenopausal and women who were postmenopausal 4 years or more was conducted. The WHQ anxiety scores did not change significantly in either subgroup of the treatment groups compared with placebo.[199]

Kornstein et al. compared an SNRI (10 mg desvenlafaxine) with placebo and reported significant improvements in Hamilton depression scores in the treatment group compared with placebo. A subgroup analysis on perimenopausal and postmenopausal women found that both subgroups experienced significant improvements in depressive symptom scores following desvenlafaxine treatment compared with placebo.[172]

Davis et al. compared Chinese medicinal herbs with placebo among subgroups of women experiencing amenorrhea for less than 4 years and women experiencing amenorrhea for 4 years or more. The MENQOL psychological scores did not change significantly in either of the subgroups.[114]

Osmers et al. compared black cohosh (40 mg) with placebo and reported a significant improvement in Menopausal Rating Scale psychological scores for the black cohosh group compared with the placebo group. A subgroup analysis by time since menopause found a marginally significant improvement in psychological scores among the early climacteric women ($p=0.05$), but no significant change among the late climacteric women ($p=0.08$).[216]

Psychological Symptoms by Comorbidities

One trial conducted subgroup analyses on psychological symptoms by comorbidities. (Appendix N, Table N-14).[199] Strickler et al. (2000) reported no difference in WHQ anxiety scores among women treated with standard dose estrogen compared with placebo. Subgroup analyses were conducted on women with a baseline anxiety score of less than 3.5 and women with a baseline anxiety score 3.5 or more. A significant reduction in WHQ anxiety scores was observed only in the subgroup with higher baseline anxiety scores.[199]

Quality of Life

Nine trials conducting subgroup analyses reported quality-of-life outcomes (Table 95). Five were hormone therapy trials,[93, 94, 183, 234, 248, 351] two were black cohosh trials,[216, 352] and one was an isoflavones trial.[266]

Table 95. Summary of subgroup analyses reporting quality-of-life outcomes

Subgroup	Trial	Comparators	Subgroup Categories	Improvement Over Comparator
Severity of symptoms	Maki 2007[234]	Estrogen/progestin (standard dose) vs. placebo	HF severity score: <1.2 ≥1.2	 — Yes
	Lopes 2001[93]	Estrogen patch vs. estrogen spray (both standard doses)	> 7 HF/day	Yes (both routes)
	Mattsson 2000[94]	Estrogen oral (standard dose) vs. estrogen spray (standard dose)	> 7 HF/day	Yes (both routes)
	Lee 2010[266]	Isoflavones vs. placebo	Total KI score >20	Yes
	Frei-Kleiner 2005[352]	Black cohosh vs. placebo	Total KI score ≥20	Yes
Time since menopause	Lobo 2009[351]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 Yes (all doses) Yes (all doses)
	Utian 2009[183]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 Yes (all doses) Yes (all doses)
	Loh 2002[248]	Estrogen (two doses: standard and low)	Years since menopause: <3 ≥3	 Yes (all doses) Yes (all doses)
	Osmers 2005[216]	Black cohosh vs. placebo	Early climacteric Late climacteric	Yes Yes

HF: hot flushes; KI: Kupperman Index

Quality of Life by Severity of Symptoms

Five trials conducted subgroup analyses on quality of life by severity of symptoms (Appendix N, Table N-15). One trial compared estrogen/progestin with placebo;[234] one trial compared an estradiol spray with an estradiol patch;[93] one trial compared oral estradiol plus dydrogesterone with spray estradiol plus dydrogesterone;[94] one trial compared isoflavones with placebo;[266] and one trial compared black cohosh with placebo.[352]

Maki et al. compared standard dose estrogen/progestin with placebo and performed subgroup analyses on symptomatic women (hot flush severity score of ≥1.2 at baseline) and asymptomatic women (hot flush severity <1.2 at baseline). Two different quality-of-life scales were used as outcomes: total Greene Climacteric Scale (GCS), a menopause-specific quality of life scale, in which a lower score indicates a better quality of life and Utian Quality of Life (QOL) Scale, a general health quality-of-life scale, in which a higher score indicates a better quality of life. A significant improvement in quality of life was reported with the Utian QOL among symptomatic women in the treatment group compared with placebo. There was no difference using the GCS scale between the subgroups.[234]

Lopes et al. compared an estradiol patch with an estradiol spray and reported equivalent significant improvements in total Kupperman Index scores with both routes of administration in

the whole study population. A subgroup analysis on women with more severe symptoms, more than seven hot flushes per day, also found both routes of administration providing significant improvements in total Kupperman Index scores, with no difference between the routes.[93]

Mattsson et al. compared standard doses of oral estradiol with standard doses of estradiol spray and found equivalent significant improvements in total Kupperman Index scores with both routes of administration. A subgroup analysis on women with more severe symptoms, more than seven hot flushes per day, also found both routes of administration providing significant improvements in total Kupperman Index scores, with no difference between the routes.[94]

In a trial comparing isoflavones with placebo, Lee et al. report a significant improvement in total Kupperman Index score in the treatment group compared with placebo. A subgroup analysis on women with more severe symptoms, a greater than 20 Kupperman Index score at baseline, also found the isoflavones group with a significant improvement in quality of life compared with the placebo group.[266]

In a trial comparing black cohosh with placebo, Frei-Kleiner et al. report no difference in median Kupperman Index score among the study groups. When a separate analysis on the subgroup of women with a greater than 20 Kupperman Index score at baseline is conducted, the authors report a significant improvement in quality of life among those treated with black cohosh compared with placebo.[352]

Quality of Life by Time Since Menopause

Four trials conducted subgroup analyses on quality of life by time since menopause (Appendix N, Table N-16). Two trials compared estrogen plus bazedoxifene with placebo;[183, 351] one trial compared low dose and standard dose estrogen/progestin therapy;[248] and one trial compared black cohosh with placebo.[216]

The two estrogen/bazedoxifene trials were part of the Selective Estrogens, Menopause, and Response to Therapy (SMART) trials. In these trials, low dose and standard dose estrogens were combined with bazedoxifene and compared with placebo. Subgroup analyses were conducted on women who were less than 5 years menopausal compared with women menopausal for 5 years or more, all the treatment groups experienced significant reductions in total MENQOL scores compared to placebo, regardless of time since menopause.[183, 351]

Loh et al. (2002) compared low-dose estrogen/progestin with standard-dose estrogen/progestin and used Kupperman Index as an outcome. Both hormone treatments were efficacious in improving overall Kupperman Index scores in the whole study population. Subgroup analyses were performed on women whose time since menopause was less than 3 years and women whose time since menopause was 3 years or more. Total Kupperman Index scores were improved equally in both subgroups by both low-dose and standard-dose groups.[248]

In the Osmers et al. (2005) trial, black cohosh was compared with placebo and significant improvements in the black cohosh group in total Menopause Rating Scale (MRS) score was reported. Subgroup analyses were performed on early climacteric women and late climacteric women. For both early and late climacteric women, significant improvements in the black cohosh group compared with the placebo group were observed.[216]

Sleep Disturbance

Five trials conducting subgroup analyses reported sleep disturbance outcomes (Table 96). All five trials tested hormone therapies.[144, 145, 183, 349, 351]

Table 96. Summary of subgroup analyses reporting sleep disturbance outcomes

Subgroup	Trial	Comparators	Subgroup Categories	Improvement Over Comparator
Age	Brunner 2005[144]	Estrogen (standard dose) vs. placebo	50 to 54 years with moderate to severe vasomotor symptoms	—
	Hays 2003[145]	Estrogen/progestin (standard dose) vs. placebo	50 to 54 years with moderate to severe vasomotor symptoms	Yes
	Rigano 2001[349]	Estrogen (standard dose) vs. placebo	48 to 50 years 51 to 53 years 54 to 56 years	Yes Yes Yes
Time since menopause	Lobo 2009[351]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 — Yes
	Utian 2009[183]	Estrogen/bazedoxifene (standard and low dose) vs. placebo	Years since menopause: <5 ≥5	 Yes Yes

Sleep Disturbance by Age

Three trials conducted subgroup analyses on sleep disturbance by age categories (Appendix N - Table N-17). Two trials compared estrogen with placebo[144, 349] and one trial compared estrogen/progestin with placebo.[145]

Two of the trials were part of the Women's Health Initiative trials. One tested standard dose estrogen alone with placebo[144] and one tested standard dose estrogen/progestin with placebo.[145] Both trials conducted analyses on the subgroup of women aged 50 to 54 with moderate to severe vasomotor symptoms. The researchers used mean change in WHI sleep score as an outcome measure. Women treated with estrogen alone experienced significant improvements in sleep scores in the treatment group as a whole, but did not have significant improvements in sleep scores in the subgroup of younger women with more severe symptoms.[144] Women treated with estrogen/progestin experienced significant improvements in sleep scores in the treatment group as a whole, as well as in the subgroup of younger women with more severe symptoms.[145]

Rigano et al. compared a standard dose estrogen transdermal patch with placebo. Sleep disturbance measures were not provided for the population as a whole, only by age subgroups (48 to 50, 51 to 53, and 54 to 56). Women receiving hormone therapy in all age groups reported less insomnia compared to the women receiving placebo. Significance between subgroups was not calculated.[349]

Sleep Disturbance by Time Since Menopause

Two trials, comparing estrogen plus bazedoxifene with placebo, conducted subgroup analyses on sleep disturbance by time since menopause (Appendix N, Table N-19). The two estrogen/bazedoxifene trials were part of the Selective Estrogens, Menopause, and Response to Therapy (SMART) trials. In these trials, low dose and standard dose estrogens were combined with bazedoxifene and compared with placebo.[183, 351] Subgroup analyses were conducted in both trials on women who were less than 5 years menopausal and on women who were menopausal for 5 years or more. Lobo et al. measured mean difference in Quality of Sleep Score, and reported no significant improvements in sleep among women less than 5 years menopausal; however, significant improvements were found in women menopausal for 5 years or more who received the estrogen/bazedoxifene treatments.[351] Utian et al. reported significant improvements

in Medical Outcome Survey sleep scores among the treatment groups as a whole, and in both subgroups of early and late menopausal women.[183]

Urogenital Atrophy

One trial conducted subgroup analyses and reported urogenital atrophy outcomes (Table 97). The trial compared black cohosh with placebo[216]

Table 97. Summary of subgroup analyses reporting urogenital atrophy outcomes

Subgroup	Trial	Comparators	Subgroup Categories	Improvement Over Comparator
Time since menopause	Osmers 2005[216]	Black cohosh vs. placebo	Early climacteric	Yes
			Late climacteric	Yes

Urogenital Symptoms by Time Since Menopause

One trial conducted subgroup analyses on urogenital symptoms by time since menopause (Appendix N, Table N-19). The trial compared black cohosh with placebo and found improved Menopausal Rating Scale scores in the treatment group. When subgroup analysis was conducted on early and late climacteric women, Osmers et al. found that in both early and late climacteric women, black cohosh improved urogenital atrophy compared with placebo.[216]

Discussion

Introduction

For women experiencing menopausal symptoms considering any of the agents examined here, the choice of treatment is influenced by therapeutic efficacy while considering other potential benefits and harms—particularly over the long-term (Figure 1). The results and conclusions of this review offer an evidenced-based guide to comparative efficacy as well as other important benefits and harms. In this final section, we discuss what has been learned from evidence reviewed together with its limitations and gaps. But most importantly we place the evidence in the context of the analytic framework incorporating the four Key Questions considered not in isolation, but as a whole to inform decisions by women, health care providers, and policy makers.

Symptom Relief

Vasomotor Symptoms

A large body of evidence was identified comparing the efficacy of agents compared with placebo and other active treatments for the relief of vasomotor symptoms (Table 98). Trials were most numerous for estrogens, isoflavones, SSRI/SNRIs, gabapentin, ginseng, and black cohosh. Estrogens of any dose appeared more effective than other comparators without apparent meaningful differences between doses or routes of administration. Few differences were apparent in the network meta-analysis among isoflavones, SSRI/SNRIs, gabapentin, and black cohosh. Whether ginseng might have any effect is unclear. A host of other agents have been studied, but evidence is limited to single trials.

The efficacy of estrogens in treating vasomotor symptoms is well established. The comparative effectiveness of other agents relative to estrogens had been less clear. Albeit limited by trial quality, findings from the network analysis allow us to draw conclusions concerning comparative effectiveness. Although nonhormone agents can ameliorate vasomotor symptoms (SMDs ranging from -0.17 to -0.35), none have estrogen's effectiveness (SMDs ranging from -0.50 to -0.64).

Table 98. Magnitude and strength of evidence of treatments for vasomotor symptoms: standardized mean differences from pairwise comparisons[a]

Number of Comparisons	Comparators	Standardized Mean Difference (SMD) (95% CI)	Effect Size Category[b]	Strength of Evidence
9	Estrogen (high) vs. placebo	-0.50 (-0.61 to -0.39)	•••	High
39	Estrogen (standard) vs. placebo	-0.64 (-0.74 to -0.53)	••••	High
53	Estrogen (low/ultralow) vs. placebo	-0.55 (-0.61 to -0.48)	•••	High
13	SSRI/SNRI vs. placebo	-0.35 (-0.46 to -0.24)	••	High
35	Isoflavones vs. placebo	-0.31 (-0.41 to -0.22)	••	Low
5	Gabapentin vs. placebo	-0.28 (-0.38 to -0.19)	••	Moderate
4	Black Cohosh vs. placebo	-0.31 (-0.46 to -0.15)	••	Low
3	Ginseng vs. placebo	-0.17 (-0.43 to 0.09)	•	Low
11	Estrogen route a vs. route b	All SMDs close to 0; CrI included 0	—	High

[a] To enable easy comparisons in this and the following tables, effect size categories are displayed to provide an indication of comparative efficacy. The categories are not intended to confer other significance and do not correspond to so-called small, medium, and large suggested by Cohen for the purposes of sample size calculation.
[b] • (0 to > -0.2); •• (-0.2 to > -0.4) ; ••• (-0.4 to > -0.6) ; •••• (< -0.6); — (equivalent)
CI: confidence interval; SMD: standard mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Quality of Life

Trials evaluating numerous agents reported some quality-of-life metric, but the evidence base included more than a single trial for estrogens, isoflavones, SSRI/SNRIs, ginseng, and black cohosh. Compared with placebo, improved quality-of-life scores accompanied estrogens with standardized mean differences ranging from 0.36 to 0.76 with high strength of evidence; effect sizes for all other agents were lesser in magnitude or low SOE (Table 99). Similarly, estrogens ranked highest in the network comparison. For estrogens, there was no apparent meaningful difference in effect according to route of administration. Quality-of-life scores were reported from trials of many nonprescription agents, but results from single trials do not allow conclusions concerning effects.

We found improved global quality-of-life scores in women taking estrogens. Yet no effect was apparent in "Women's International Study of long Duration Oestrogen after The Menopause" (WISDOM)[35] or WHI.[144, 145] Results from these trials appeared somewhat discrepant in the analyses and is likely attributable to older age and lesser symptom severity of enrolled women. For the larger body of comparisons in women receiving estrogens, despite between-trial variability, results were more consistent. The general pattern of comparative efficacy seen with quality-of-life scores paralleled results for other vasomotor and other symptoms.

Table 99. Magnitude and strength of evidence of treatments for quality of life: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Standardized Mean Difference (SMD) (95% CI)	Effect Size Category[a]	Strength of Evidence
5	Estrogen (high) vs. placebo	0.76 (0.48 to 1.03)	••••	High
26	Estrogen (standard) vs. placebo	0.55 (0.41 to 0.69)	•••	High
17	Estrogen (low/ultralow) vs. placebo	0.36 (0.27 to 0.45)	••	High
6	SSRI/SNRI vs. placebo	0.28 (0.17 to 0.39)	••	High
24	Isoflavones vs. placebo	0.27 (0.17 to 0.37)	••	Low
4	Black cohosh vs. placebo	0.26 (-0.15 to 0.66)		Insufficient
3	Ginseng vs. placebo	0.19 (0.01 to 0.36)	•	Low
7	Estrogen route a vs. route b	SMDs close to 0	—	Moderate

[a] • (0 to < 0.2); •• (0.2 to < 0.4) ; ••• (0.4 to < 0.6) ; •••• (> 0.6); — (equivalent)
SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Psychological Symptoms

Just over one-third of trials examining symptom treatment reported a psychological outcome—depressive symptoms, anxiety symptoms, and global psychological well-being—and often more than one. Only half specified some psychological symptom as a primary outcome. Overall, the samples were not selected to represent populations with clinical depression or anxiety. Compared with placebo, standardized mean differences were in general not large (i.e., SMD between -0.5 and 0) for any of the agents studied for any psychological domain (Table

100). Compared with placebo, the strength of evidence was high for effects of SSRI/SNRIs and estrogens on all psychological measures.

An increased risk for depressive symptoms in the absence of prior depressive illness, during the menopausal transition has been described[355] and may be associated with vasomotor symptoms.[356] The evidence assessed here may provide guidance when menopausal women are experiencing psychological symptoms.

Table 100. Magnitude and strength of evidence of treatments for psychological symptoms: standardized mean differences from pairwise comparisons

Domain	Number of Comparisons	Comparators	Standardized Mean Difference (SMD) (95% CI)	Effect Size Category[a]	Strength of Evidence
Global	6	SSRI/SNRI vs. placebo	-0.42 (-0.60 to -0.24)	•••	High
Depressive symptoms	5	SSRI/SNRI vs. placebo	-0.43 (-0.60 to -0.26)	•••	High
Anxiety symptoms	3	SNRI vs. placebo	-0.31 (-0.50 to -0.12)	••	High
Global	14	Estrogen vs. placebo	-0.26 (-0.40 to -0.13)	••	High
Depressive symptoms	18	Estrogen vs. placebo	-0.36 (-0.53 to -0.20)	••	High
Anxiety symptoms	13	Estrogen vs. placebo	-0.34 (-0.50 to -0.18)	••	High
Global	2	Gabapentin vs. placebo	-0.23 (-0.48 to 0.02)		Insufficient
Global	7	Isoflavones vs. placebo	-0.11 (-0.22 to 0.01)	•	Low
Depressive symptoms	9	Isoflavones vs. placebo	-0.29 (-0.49 to -0.09)	••	Low
Anxiety symptoms	7	Isoflavones vs. placebo	-0.30 (-0.46 to -0.14)	••	Moderate

[a] • (0 to < 0.2); •• (0.2 to < 0.4) ; ••• (0.4 to < 0.6) ; •••• (> 0.6); — (equivalent)
SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Sexual Function

Some measure of sexual function was reported in about a third of trials; half of those trials specified the outcome as primary. Outcomes were reported in four domains: pain (dyspareunia), a global metric, activity, and interest (Table 101). Vaginal estrogens improved pain most convincingly compared with placebo (high strength of evidence), while improved pain scores with oral estrogens were less certain (moderate strength of evidence). There was an increase in global measures with estrogens and a modest improvement with SNRIs. Estrogens were the only agent enhancing measures of interest. Sexually satisfying episodes were more frequent in the comparison of testosterone with placebo—just over one extra episode reported every 4 weeks (strength of evidence moderate). Overall, these results are generally consistent with evidence-informed expert clinical opinion.[5]

The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE)[357] estimated approximately 15 percent of women aged 45 to 64 experienced some form of sexual distress. We identified one quantitative review by Myers. The study included literature published between 1972 and 1992.[358] In the analysis by Myers,

standardized effect representing any domain were combined from 108 studies of estrogen therapy yielding -0.67—somewhat larger in magnitude than obtained in this review.

Table 101. Magnitude and strength of evidence of treatments for sexual function: standardized mean differences from pairwise comparisons

Domain and Number of Comparisons	Comparators	Standardized Mean Difference (SMD) (95% CI)	Effect Size Category[a]	Strength of Evidence
Pain (lower is better)				
10	Vaginal estrogens vs. placebo	-0.54 (-0.73 to -0.34)	•••	High
4	Oral estrogens vs. placebo	-0.22 (-0.35 to -0.09)	••	Moderate
14	All estrogens vs. placebo	-0.45 (-0.61 to -0.29)	•••	High
Global (higher is better)				
15	All estrogens vs. placebo	0.27 (0.19 to 0.35)	••	High
2	SSRI/SNRI vs. placebo	0.27 (0.01 to 0.52)		Insufficient
4	Isoflavones vs. placebo	0.24 (-0.12 to 0.61)	••	Low
Interest (higher is better)				
7	All estrogens vs. placebo	0.18 (0.10 to 0.26)	•	Moderate
2	SNRI vs. placebo	0.16 (-0.07 to 0.39)		Insufficient
5	Isoflavones vs. placebo	0.26 (-0.001 to 0.52)		Insufficient
Pain, Interest, Global				
10	Estrogen route a vs. route b	SMDs close to 0	—	Moderate
Activity (higher is better)		**SSE/4 weeks**		
4	Testosterone, no women with intact uteri/ovaries	1.05 (0.64 to 1.45)[b]	NA	Moderate
4	Testosterone, women with/without uteri/ovaries	1.31 (0.89 to 1.72)	NA	
8	Testosterone, all trials	1.17 (0.88 to 1.46)	NA	

[a] For negative effect sizes • (0 to > -0.2); •• (-0.2 to > -0.4) ; ••• (-0.4 to > -0.6) ; •••• (< -0.6). For positive effect sizes • (0 to < 0.2); •• (0.2 to < 0.4) ; ••• (0.4 to < 0.6) ; •••• (> 0.6); — (equivalent).
[b] number of satisfying sexual episodes per four weeks
SSE: Satisfying sexual episodes; NA: not applicable; SMD: standard mean difference

Urogenital Atrophy

One-quarter of trials reported urogenital atrophy outcomes—a primary outcome in 60 percent. Ospemifene, an estrogen agonist/antagonist, was approved by the FDA in February 2013 to treat moderate to severe dyspareunia in postmenopausal women. Evidence from three clinical trials showed ospemifene improved vulvar and vaginal atrophy compared with placebo. Although vaginal estrogens showed a greater effect than oral estrogens (indirect comparison) in placebo comparisons, the strength of evidence was high that either oral or vaginal estrogens improved symptoms. The strength of evidence was low for isoflavones (Table 102).

The conclusions here are similar to those provided to clinicians[5] when considering treating symptoms that may be experienced by as many as 40 percent of postmenopausal women.[359] A 2006 Cochrane review including 19 trials concluded that vaginal or oral estrogens were equally effective for treating vaginal atrophy symptoms.[360] These results indicate, albeit indirectly based

on placebo comparisons, a greater magnitude of effect for vaginal compared with oral administration.

Table 102. Magnitude and strength of evidence of treatments for urogenital atrophy: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Standardized Mean Difference (SMD) (95% CI)	Effect Size Category[a]	Strength of Evidence
12	Vaginal estrogen vs. placebo	-0.44 (-0.65 to -0.23)	•••	High
15	Nonvaginal estrogen vs. placebo	-0.35 (-0.44 to -0.26)	••	High
5	Isoflavones vs. placebo	-0.48 (-0.77 to -0.18)	•••	Low
3	Ospemifene vs. placebo	-0.75 (-1.05 to -0.45)	••••	High

[a] • (0 to > -0.2); •• (-0.2 to > -0.4) ; ••• (-0.4 to > -0.6) ; •••• (< -0.6); — (equivalent)

Sleep

Many trials ascertained self-reported sleep outcomes, but only a single trial examined a drug FDA-approved for use in insomnia (eszopiclone). Compared with placebo, the standardized mean difference for improved sleep measures with eszopiclone was approximately three-fold greater than with estrogens or any other agent. This is consistent with modestly improved sleep accompanying other agents, including estrogens, used to treat menopausal symptoms (Table 103).

Although sleep disturbances during menopause are common,[361] how often they are secondary to menopausal symptoms is not well defined. Sedative hypnotic agents are not generally used to treat menopausal symptoms and so were not represented in the trials identified. Reported improvements in sleep evident with other agents such as estrogens is possibly due to treatment of vasomotor symptoms, but requires evidence not considered here.

Table 103. Magnitude and strength of evidence of treatments for sleep: standardized mean differences from pairwise comparisons

Number of Comparisons	Comparators	Standardized Mean Difference (SMD) (95% CI)	Effect Size Category[a]	Strength of Evidence
1	Eszopiclone vs. placebo	1.08 (0.53 to 1.62)	••••	Not Rated[b]
24	Estrogen vs. placebo	0.32 (0.24 to 0.46)	••	High
2	SSRI vs. placebo	0.46 (0.24 to 0.69)	•••	Low
2	Gabapentin vs. placebo	0.33 (0.18 to 0.49)	••	Low
6	Isoflavones vs. placebo	0.37 (0.10 to 0.64)	••	Low
2	Ginseng vs. placebo	0.13 (-0.05 to 0.32)		Insufficient

[a] • (0 to < 0.2); •• (0.2 to < 0.4) ; ••• (0.4 to < 0.6) ; •••• (> 0.6)
SSRI: selective serotonin reuptake inhibitor
[b] Eszopiclone, an oral sedative used to treat insomnia, was included as a referent. With only one trial comparing eszopiclone with placebo, a rating could not be made.

Limitations of the Evidence Base on Symptom Relief

The body of evidence synthesized for KQ1 was large but many trials were rated poor quality. However, the challenges of synthesizing this evidence extend beyond trial quality to limitations only partially incorporated in strength of evidence assessments. These include:

- Use of different outcome scales or metrics

- Necessity of calculating standardized mean differences and inherent difficulties estimating from publications
- Potential differences in populations represented by trial samples
- Potential for selective outcome reporting

Some two decades ago, in a review of sexuality and menopause, Myers foreshadowed the difficulties encountered here across all outcomes—variable scales, metrics, and definitions.[358] Even directionality of scales within the various outcomes often differed; authors did not always abide by conventions for a specific scale. The absence of standardized outcome reporting and common data elements limit the ability to quantify effects using metrics easily and transparently translated to quantities such as clinically meaningful improvement. Interpreting results when presented with continuous measures and multiple scales requiring the use of standardized mean differences is challenging. It is difficult to infer proportions of women achieving minimally clinically important improvements.[79, 80]

Given the well-described placebo effect, at least for vasomotor symptoms,[81] this limitation is important to consider interpreting results. One alternative approach to that adopted here would be to limit trials synthesized to those reporting similar outcome scales or metrics. Although appealing in many respects, if studies reporting some identical outcome metric were not representative of all trials and symptomatic women, the potential for introducing bias exists. So while interpretive limitations accompany standardized mean differences, their use allows including and pooling evidence from multiple trials, which would not be feasible otherwise. In many instances here, it enabled at the very least providing examining comparative efficacy and rankings when subject to network meta-analysis

On the surface, calculating standardized mean differences might appear trivial—yet it is often not. As outlined in the methods, there are a number of ways to obtain effect sizes from the continuous measures reported; trials typically did not report a between group difference and variance (standard deviation) allowing the most straightforward calculating of standardized mean differences. To avoid excluding trial results, other calculations were required including the use of p-values that typically were sometimes not reported exactly. Additionally, other results were reported as simply nonsignificant. In the case where results were pooled, excluding nonsignificant results lacking a p-value would introduce bias. While imputation allowed including those results, it introduces uncertainty. Fortunately, the number of p-values requiring imputation was small. A separate issue was the occasional outlier encountered because trials sometimes reported unusually large effects. Potential outliers required performing analyses to be certain effects could not be attributed to them.

Another concern is that although trial populations included women experiencing menopause, there were differences in mean age, length of follow-up, and symptom severities. While the initial intent was to examine subgroups according to characteristics such as the presence of a uterus, lack of sufficient reporting did not allow doing so. Conclusions then apply to average women across all trials.

It is also difficult to evaluated potential selective outcome reporting from the included trials. Vasomotor symptoms were reported in about three quarters of trials but other outcomes in fewer than half. Some trials, such as those of reporting sexual function or vaginal atrophy symptoms, were clearly not designed to primarily assess all outcomes. However, insignificant results may have been unreported. For some of the outcomes, in only half of the trials was the outcome reported as primary.

The results do not allow assessing whether effects on different outcomes are independent and some may not be causal. It is conceivable that the consequence of fewer vasomotor symptoms is improved quality of life, sleep, or better psychological well-being. Causally, it may be that the focus of therapy need not consider treatment efficacy for all outcomes, but rather a few—most likely beginning with vasomotor symptoms.

The target population for this review did not encompass all women experiencing menopausal symptoms. We did not include studies examining effects among breast cancer survivors—women frequently affected by troublesome symptoms including hot flushes.[362] Although effects of nonhormonal agents on hot flushes may be similar regardless of breast cancer history[363] breast cancer survivors constitute a different population. Accordingly, these results are not intended to apply to those women.

Finally, compounded hormone therapies are commonly prescribed, often in combination with some testing for hormone levels, with effectively no direct evidence examining comparative efficacy. We identified a single randomized, controlled trial comparing solely the pharmacokinetics of a compounded preparation with a conventional estradiol patch in 40 women followed for 16 days. Outcomes did not include safety or efficacy measurements.[364] No studies were identified examining the safety of the compounding practices for hormone therapies.

Other Benefits and Harms

Menopausal Hormone Therapy Preparations

In 1979, the National Institutes of Health convened their first consensus conference on estrogen use in postmenopausal women.[365] While breast and endometrial cancer were prominent in the summary, there was no mention of heart disease. Some three decades later there is now a robust evidence base allowing many conclusions regarding both beneficial and harmful outcomes.

Trials included in the recent review by Nelson[28] were assessed here with concordant conclusions. Because a majority of evidence derived from WHI trials, representing a target population overlapping the one for this review, assessing applicability of findings required considering observational study results. Still, a picture of long-term effects emerges with some clarity as summarized in Table 104. The USPSTF review reported differences in event rates with estrogen/progestin or estrogen compared with placebo. Extrapolating absolute rates from the WHI samples to the target population of this review is problematic. In broad absolute terms gallbladder disease is the most frequent occurrence with thromboembolic events, stroke, and breast cancer less frequent. Although less common they are not insignificant. For example, menopausal hormone therapy in women aged 50 to 74 years has been estimated responsible for 9 percent of all strokes in women in 2012.[366]

Table 104. Summary of long-term effects of menopausal hormone therapy preparations

Outcome	Risk	Treatment vs. Placebo	Strength of Evidence	Comment
Breast cancer	↑	Estrogen/progestin	High	
	↓	Estrogen	Low	Inconsistent
Gallbladder disease	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	↑	Estrogen	Moderate	Consistency unknown with 1 trial
Venous thromboembolic events	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	↑	Estrogen	High	
Stroke	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	↑	Estrogen	High	
Ovarian cancer	↑	Estrogen/progestin	Low	Consistency unknown with 1 trial; imprecise with few cases
Colorectal cancer	↓	Estrogen/progestin	Low	Consistency unknown with 1 trial
	—	Estrogen	Moderate	Consistency unknown with 1 trial
CHD	↑	Estrogen/progestin	Moderate	Consistency unknown with 1 trial
	—	Estrogen	Moderate	Consistency unknown
Endometrial cancer	—	Estrogen/progestin	Moderate	Imprecise
Osteoporotic fractures	↓	Estrogen/progestin	Moderate	Inconsistency between 2 trials
	↓	Estrogen	Moderate	Consistency unknown with 1 trial

Risk: ↑ increased, ↓ decreased, — no change
CHD: coronary heart disease

One limitation of the evidence base concerning long-term outcomes derives from necessity to rely on results of randomized controlled trials enrolling an overlapping, but not identical, target population that is the focus of this review. There are well described discrepant conclusions concerning these associations between observational studies and randomized controlled trials.[43] The discrepancies have been attributed to two primary reasons—selection bias and time-varying confounding.[44-46] Furthermore, although debate persists concerning the increased CHD risk, with some hypothesizing a protective effect from hormone therapy initiated soon after menopause,[367-369] post-hoc but detailed WHI analyses do not provide support for this "timing hypothesis." Moreover, the Kronos Early Estrogen Prevention Study, designed to examine the hypothesized cardiovascular benefit with early hormone therapy initiation, recently reported results.[370] From a sample of 727 women within three years of menopause, randomized to hormone therapy or placebo, over four years, there was no significant decrease in progression of carotid artery intimal thickness (the primary endpoint) or coronary artery calcium score (a secondary endpoint). Although the association with cardiovascular outcomes has been most scrutinized, difficulties assessing causal effects of menopausal hormone therapy from observational data appear to extend to other outcomes including hip fractures[44] and colorectal cancer.[46] As noted throughout, trials have been conducted from a target population overlapping with the one for this review creating some challenges for assessing applicability. Still, there is considerable certainty in the effects assessed—a remarkable body of evidence accrued since the 1979 NIH consensus conference. Finally, although evidence concerning potential long-term benefits was considered this review did not address use of therapies for prevention of chronic conditions.

Nonhormone Therapy Preparations

The evidence base informing other potential benefits and harms of nonhormone therapies is limited, but does not suggest harmful long-term effects are likely for those agents where studies were identified (Table 105). We included large trials examining vitamin E, small trials of isoflavones, and observational studies evaluating antidepressants that did not always distinguish risks for the classes of agents used to treat symptoms (SSRI/SNRI). While no salient benefits were identified, neither were safety signals apparent. However, given the large numbers of women potentially taking these agents some caution is advised particularly for nonprescription agents. For example, the possibility of increased mortality with high dose vitamin E has been raised.[371] Additionally, case reports of hepatotoxicity with black cohosh have been published.[372] This association has been debated,[373] but surveillance for adverse effects of nonprescription agents is generally inadequate. Safety data are also needed for the broad array of herbs and botanicals used to treat menopausal symptoms.

There are several further limitations to this evidence to consider. Many studies included women of all ages and therefore were excluded unless subgroup analyses on older women or menopausal women were specified. Much of the research available on the long-term effects of isoflavones and vitamin E consisted of population-based dietary studies and therefore did not meet inclusion criteria. Intermediate outcomes were reported in many of the studies. For example, bone density rather than osteoporotic fractures, and cholesterol rather than cardiovascular events. Finally, in studies that included all women rather than focusing on menopausal women, it was difficult to discern if exposure (to SSRI/SNRIs, isoflavones) occurred during menopausal years.

Table 105. Summary of long-term effects of nonhormone therapy preparations

Outcome	Risk	Treatment vs. Placebo	Strength of Evidence
Breast cancer	—	Vitamin E	High
Breast cancer		SSRI	Insufficient
Colorectal cancer	—	Vitamin E	High
Cardiovascular events	—	Vitamin E	High
Cardiovascular death	↓	Vitamin E	Low
Osteoporotic fractures	↑	SSRI	Low
Osteoporotic fractures		Isoflavones	Insufficient
Ovarian cancer		Vitamin E	Insufficient

Risk: ↑ increased, ↓ decreased, — no change
SSRI: selective serotonin reuptake inhibitor

Symptom Relief in Subgroups

A small subset of trials identified for Key Question 1 reported subgroup analyses on symptom relief: 10 for hormone therapies, two nonhormone prescription therapies, and four nonprescription therapies. Trials with hormone therapies included analyses by age, severity of symptoms, time since menopause, and uterine status. One trial of a nonhormone prescription therapy (escitalopram) provided a subgroup analysis by race. Trials with nonprescription therapies reported outcomes by age, BMI, severity of symptoms, and time since menopause. For example, age group subpopulations were defined as younger than 50, 50-59, and 60 years and

older in one trial and younger than 55 and 55 years or older in another trial. None of the subgroup analyses could be pooled, as no two trials had the same comparators, definitions of subgroups, and outcomes. The limited evidence did not allow rating strength of evidence.

Research Gaps

The principal gaps in the evidence on symptom relief include the following: lack of common validated instruments and assessing meaningful clinical improvement, safety data on nonprescription agents, lack of evidence on compounded hormone therapies, potential for predicting treatment response, and independence of outcomes:

- The trials comprising the body of evidence included in this review had in common the evaluation of outcomes on continuous scales using multiple instruments. A standard set of common data elements using validated instruments would facilitate evidence synthesis and interpreting results across trials. In place of, or in addition to, summary continuous effect measures, reporting differences in proportions of women achieving defined clinically meaningful improvements would be more informative for decisionmaking. Reporting only summaries of continuous effect measures challenges interpretation for patients and providers.
- A large number of nonprescription agents were studied. The Dietary Supplement Health and Education Act requires manufacturers of these agents to determine their products' safety and efficacy, but the manufacturers are not required to submit the safety or efficacy data to the FDA. As women may elect to use these agents, the data need to become available.
- Millions of women use compounded hormone treatments. Yet there is a stark absence of evidence concerning compounded hormone therapies, and the methods used to determine the personalized dosages. Although the gap is most concerning regarding safety, efficacy issues are important as well.
- For nonhormonal interventions where there is moderate evidence of efficacy, identifying predictors of response would likely be helpful.
- As noted previously, although we considered six categories of symptom relief outcomes, the extent of correlated response (not symptom presence) among them was unclear in the evidence. Although not an objective of this review, the evidence would provide little opportunity to examine that question.

Many important previous gaps in the evidence concerning long-term effects of hormone therapies have been filled. For some nonhormone therapies (Table 105), with reasonable certainty (i.e., moderate or greater strength of evidence) significant safety issues have not been apparent; the same cannot be said for the entirety of the nonprescription agents.

Finally, estrogen therapy has efficacy relieving many symptoms but is accompanied by other potentially important harms (varying according to whether combined with progestogen). Given the number of outcomes to consider with different exposure effects (e.g., duration of use); the overall risk-benefit calculus is not simple. Juxtaposing evidence concerning symptom relief (as obtained here) with models for the long-term harms and effect on osteoporosis[374] according to patient characteristics (e.g., lower risk of hip fracture in blacks) could facilitate informed decisions by women and health-care providers.

Implications for Clinical and Policy Decisionmaking

The implications of this review for clinical decision-making follow from better defining evidence supporting the multiple treatment options, each having different potential harms, for different yet overlapping menopausal symptoms. The results provide a guide to comparative efficacy alongside potential long-term benefits and harms; all are weighed in clinical decisions. Possibly most useful, for vasomotor symptoms and quality of life, the review provides clinicians with a simple ranked efficacy comparison for the most commonly used treatments. Although evidence concerning potential long-term benefits are included as they are part of the decision-making process, this review did not address use of therapies for those purposes.

From the policy perspective, there are two salient issues to consider. First, a 2007 Senate hearing concluded that there is a lack of evidence from well-designed scientific trials on the safety and efficacy of compounded hormone therapies. Yet no evidence on compounded hormones has appeared since the hearing. Efforts to address that absence are important. Second, is to clearly define and communicate, and translate when necessary, the net clinical benefits of hormone treatments according to duration of therapy when initiated for symptom relief (as many organizations have worked towards). Effective tools disseminating evidence to facilitate shared decision making in the most decision-informative could be considered.

Limitations of the Comparative Effectiveness Review Process

This review was a large undertaking. The variable manner in which trials reported results, multiple trial arms, multiple treatments, along with the goal of not excluding results for any a priori potentially arbitrary reason (e.g., reporting outcomes using a particular metric, or reported mean change and standard deviation) required abstracting, verifying, and managing a large amount of data for KQ1. Obtaining standardized effects is challenging.[57] A number of steps is required to calculate effect magnitudes often for more than one trial arm. There are multiple ways to obtain an effect measure and standard deviation for each trial arm. Unbiased ANCOVA effect estimates[77, 375] were rarely reported requiring the use of other comparisons. Furthermore, given multiple trial arms and multiple outcomes, the number of calculations required was substantial. We stipulated an approach to perform those calculations, but judgment was still required. Confidence intervals and strength of evidence ratings do not incorporate this analytical uncertainty. Whether type I error rates imposed should be higher is difficult to ascertain. What is clear, however, is that pooled estimates should be interpreted with this understanding. Finally, the analyses included network and many standard pairwise meta-analyses. Network meta-analyses are not trivial undertakings.

Analyses of the multiple treatments required some classification scheme that has limitations. For example, the estrogen dose categorization scheme did not consider progestin, or distinguish between combined and sequential progestin administration. Progestin use was problematic to separate because trials may have not given to women without a uterus, yet reported an effect for the entire sample.

Interpreting network and pairwise meta-analyses deserves comment. In the pairwise meta-analyses, only direct randomized comparisons are included; the network analyses incorporate both direct and indirect evidence. Underlying the network of comparisons is assumed similarity of study characteristics and patients (transitivity) as well consistency of effects throughout the network. All enrolled women were menopausal or perimenopausal, but there were some

differences in studies and samples as noted in the review. However, across all studies the assumption was likely satisfied. The closeness of most network and pairwise estimates shows that discrepancies or inconsistencies are likely small.

Finally, breast cancer patients were excluded from this review. There were two primary reasons to exclude women with breast cancer: (1) issues of comparability and exchangeability (estrogens being contraindicated), and (2) scope and quantity of literature.

Conclusions

Women experiencing symptoms of menopause can consider a number of potential treatments of varying efficacy. From a large body of evidence, there is considerable certainty that estrogens are the most effective relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. For other common symptoms—psychological, urogenital, and sleep disturbance—although estrogens are effective, some nonhormonal agents compare favorably. Estrogens are accompanied by potential long-term harms that require considering. There is limited evidence on the potential consequences of long-term use of nonhormonal agents when those agents are used to treat menopausal symptoms.

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Abbreviations

Acronym	Definition
AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CAM	complementary and alternative medicine
CE	conjugated estrogen
CEE	conjugated equine estrogen
CER	comparative effectiveness review
CES-D	Center for Epidemiologic Studies Depression Scale
CHD	coronary heart disease
CI	confidence interval
CV	Cardiovascular
DHEA	Dehydroepiandrosterone
EPC	evidence-based practice center
E2V	estradiol valerate
FDA	Food and Drug Administration
GCS	Greene Climacteric Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HF	hot flushes
HFNS	hot flushes and night sweats
HOPE	Health Outcomes Prevention Evaluation trial
HOPE-TOO	Health Outcomes Prevention Evaluation- The Ongoing Outcomes trial
HR	hazards ratio
HRT	hormone replacement therapy
IMS	International Menopause Society
IU	international unit
KI	Kupperman Index
MARIE	Mamma carcinoma Risk factor Investigation
MENQOL	Menopause-specific Quality of Life
MI	myocardial infarction
MPA	medroxyprogesterone acetate
MRS	Menopause Rating Scale
MSHF	moderate-to-severe hot flushes
MSHFNS	moderate-to-severe hot flushes and night sweats
MSVS	moderate-to-severe vasomotor symptoms
N	number
NAMS	North American Menopause Society
NETA	norethindrone acetate
NPNH	nonprescription nonhormone
NR	not reported
PICOTS	Population(s), Interventions, Comparators, Outcomes, Timing, and Setting
PMS	premenstrual syndrome
PND	postnatal depression
QOL	quality of life
RCT	randomized controlled trial

Acronym	Definition
RR	relative risk
SD	standard deviation
SNRI	serotonin-norepinephrine reuptake inhibitor
SRC	Scientific Resource Center
SSRI	selective serotonin reuptake inhibitor
STRAW	Stages of Reproductive Aging Workshop
TEP	Technical Expert Panel
THF	total hot flushes
THFNS	total hot flushes and night sweats
TOO	task order officer
USPSTF	United States Preventive Services Task Force
VAS	Visual Analog Scale
WHI	Women's Health Initiative
WHQ	Women's Health Questionnaire
WHS	Women's Health Study
WISDOM	Women's International Study of Long Duration Oestrogen after Menopause

Appendix A. Literature Search Strategies

Last search date: 1/17/2014

Search Strategy: PubMed

1. "Menopause"[Mesh] OR menopause OR menopausal OR "post-menopause" OR postmenopause OR "post-menopausal" OR postmenopausal OR climacteri* OR perimenopause OR "peri-menopause" OR "peri-menopausal" OR perimenopausal

2. "therapy" [Subheading] OR "Therapeutics"[Mesh] OR "Estrogen Replacement Therapy"[Mesh] OR "Drug Therapy"[Mesh] OR "drug therapy" [Subheading] OR "therapeutic use" [Subheading] OR "Hormone Replacement Therapy"[Mesh] OR "Complementary Therapies"[Mesh] OR "Estrogens"[Mesh] OR "Progestins"[Mesh] OR estrogen* OR progestin* OR "hormone replacement" OR antidepressant* OR eszopiclone OR clonidine OR methyldopa OR bellergal OR gabapentin OR pregabalin OR isoflavone* OR "red clover" OR "black cohosh" OR cimicifuga OR "st. johns wort" OR ginseng OR flaxseed OR "vitamin E" OR "dong quai" OR "Dehydroepiandrosterone"[Mesh] OR "Androgens"[Mesh] OR DHEA OR dehydroepiandrosterone OR "androgenic agents" OR "androgenic compounds" OR androgen*

3. Subset: Systematic Review OR Publication Type: Meta-analysis OR ("meta-analysis" OR metaanalysis OR "systematic review")

4. Limits: English, Human
Added - (1 AND 2) AND ("meta-analysis" OR metaanalysis OR "systematic review") NOT in previous set and in English and relevant = 31 additional nonindexed records

Vasomotor symptoms
("Hyperhidrosis"[Mesh]) OR "Hot Flashes"[Mesh] OR "vasomotor symptoms" OR "hot flashes" OR "night sweats" OR sweats OR flushes - + (1 AND 2) AND RCT(pt)/Eng/Human

Sleep disturbance
("Dyssomnias"[Mesh]) OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR insomnia OR sleeplessness OR "early awakening" OR "somatic complaints" - +(1 AND 2) AND RCT(pt)/Eng/Human

Psychological symptoms
("Behavioral Symptoms"[Mesh]) OR "Mood Disorders"[Mesh] OR irritability OR depression OR despair OR anxiety OR "difficulty concentrating" OR "over-reacting" OR forgetfulness OR "reminiscence lapses" OR "mood swings" OR "temper swings" OR "emotional flare-ups" OR weepiness - +(1 AND 2) AND RCT(pt)/Eng/Human

Urogenital atrophy
"Female Urogenital Diseases"[Mesh] OR "Urogenital System/pathology"[Mesh] OR "urogenital disorders" OR ((vulva* OR vagina* OR vulvovaginal OR urinary OR genital OR urogenital) AND atrophy) OR "atrophic vaginitis" +(1 AND 2) AND RCT(pt)/Eng/Human

Sexual function
"Sexual Dysfunction, Physiological"[Mesh] OR "Sexual Dysfunctions, Psychological"[Mesh] OR "Libido"[Mesh] OR "female sexual dysfunction" OR "female sexual dysfunctions" OR "hypoactive sexual desire disorder" OR "sexual function" OR "sexual desire" OR "sexual satisfaction" +(1 AND 2) AND RCT(pt)/Eng/Human

Quality of Life
"Quality of Life"[Mesh] OR "quality of life" OR "well-being" +(1 AND 2) AND RCT(pt)/Eng/Human

Harms Search

1. "Menopause"[Mesh] OR menopause OR menopausal OR "post-menopause" OR postmenopause OR "post-menopausal" OR postmenopausal OR climacteri* OR perimenopause OR "peri-menopause" OR "peri-menopausal" OR perimenopausal

2. ((((("adverse effects" [Subheading]) OR "complications" [Subheading]) OR ("poisoning" [Subheading] OR "Poisoning"[Mesh])) OR "drug effects" [Subheading]) OR "Drug Toxicity"[Mesh]

3. "Estrogen Replacement Therapy"[Mesh] OR "Hormone Replacement Therapy"[Mesh] OR "Estrogens"[Mesh] OR "Progestins"[Mesh] OR estrogen* OR progestin* OR "hormone replacement" OR antidepressant* OR eszopiclone OR clonidine OR methyldopa OR bellergal OR gabapentin OR pregabalin OR isoflavone* OR "red clover" OR "black cohosh" OR cimicifuga OR "st. johns wort" OR ginseng OR flaxseed OR "vitamin E" OR "dong quai" OR ("Dehydroepiandrosterone"[Mesh]) OR "Androgens"[Mesh] OR DHEA OR dehydroepiandrosterone OR "androgenic agents" OR "androgenic compounds" OR androgen*)

4. Subset: Systematic Review OR Publication Type: Randomized controlled trial OR ("placebo-controlled" OR (placebo AND (control OR controlled))) OR (observational OR cohort OR "case-control" OR "cross-sectional")

5. Limits: English, Human
(((1 AND 2) AND 3) AND 4)/English/Human

EMBASE

1. 'menopause'/exp OR menopausal OR 'post-menopause'/exp OR 'postmenopause'/exp OR 'post-menopausal' OR postmenopausal OR climacteri* OR 'perimenopause'/exp OR 'peri-menopause' OR 'peri-menopausal' OR perimenopausal AND [humans]/lim AND [english]/lim AND [embase]/lim =60511

2. 'estrogen replacement therapy'/exp OR 'drug therapy'/exp OR 'hormone replacement therapy'/exp OR estrogen* OR progestin* OR 'hormone replacement'/exp OR antidepressant* OR 'eszopiclone'/exp OR 'clonidine'/exp OR 'methyldopa'/exp OR 'bellergal'/exp OR 'gabapentin'/exp OR 'pregabalin'/exp OR isoflavone* OR 'red clover'/exp OR 'black cohosh'/exp OR 'cimicifuga'/exp OR 'st johns wort'/exp OR 'ginseng'/exp OR 'flaxseed'/exp OR 'vitamin e'/exp OR 'dong quai'/exp OR (DHEA OR dehydroepiandrosterone OR "androgenic agents" OR "androgenic compounds" OR androgen*)
(1 AND 2) AND [humans]/lim AND [english]/lim AND [embase]/lim

Cochrane searches were also performed for menopause/post-menopausal/climacteric to detect new references since the main search.

Appendix B. List of Excluded Studies

Abbreviations
DES: date earlier than systematic review
DUP: duplicate patient population or duplicate article
NCT: not clinical trial, MA, or SR
NOP: number of patients (too few)
NRC: not relevant comparator
NRD: not relevant design
NRF: not relevant followup
NRO: not relevant outcome
NRP: not relevant population
NRQ: not relevant question
PTU: prior to USPSTF report

H. O. Adami, I. Persson, R. Hoover, C. Schairer and L. Bergkvist. Risk of cancer in women receiving hormone replacement therapy. Int J Cancer 1989 44(5): 833-9. DES

P. Aidelsburger, S. Schauer, K. Grabein and J. Wasem. Alternative methods for the treatment of post-menopausal troubles. GMS Health Technol Assess 2012 8: Doc03. NRD

Y. AinMelk. Comparison of two continuous combined estrogen progestogen regimens in postmenopausal women: a randomized trial. Fertil Steril 1996 66(6): 962-8. NRO

S. Akhavan, F. Zandvakili, M. Arab, H. Karimi and F. Gharibi. Comparison of the therapeutic effects of fluoxetine, citalopram, estrogen and progesterone and placebo in the treatment of hot flushes in perimenopausal women. Scientific Journal of Kurdistan University of Medical Sciences 2011 16(3): . NCT

F. Al-Azzawi and H. M. Buckler. Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms. Climacteric 2003 6(2): 118-27. DUP

F. Al-Azzawi, M. Wahab, J. Thompson, M. Whitehead and W. Thompson. Acceptability and patterns of uterine bleeding in sequential trimegestone-based hormone replacement therapy: a dose-ranging study. Hum Reprod 1999 14(3): 636-41. NRO

P. Albertazzi, S. A. Steel and M. Bottazzi. Effect of pure genistein on bone markers and hot flushes. Climacteric 2005 8(4): 371-9. NRF

I. M. Alexander and A. Moore. Treating vasomotor symptoms of menopause: the nurse practitioner's perspective. J Am Acad Nurse Pract 2007 19(3): 152-63. NRD

J. L. Alexander, K. Kotz, L. Dennerstein, S. J. Kutner, K. Wallen and M. Notelovitz. The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. Menopause 2004 11(6 Pt 2): 749-65. NRD

J. L. Alexander, L. Dennerstein, H. Burger and A. Graziottin. Testosterone and libido in surgically and naturally menopausal women. Women's Health 2006 2(3): 459-477. NRD

K. P. Alexander, L. K. Newby, A. S. Hellkamp, R. A. Harrington, E. D. Peterson, S. Kopecky, A. Langer, P. O'Gara, C. M. O'Connor, R. N. Daly, R. M. Califf, S. Khan and V. Fuster. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. J Am Coll Cardiol 2001 38(1): 1-7. DES

P. Alexandersen, L. B. Tanko, Y. Z. Bagger, G. Qin and C. Christiansen. The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women. Climacteric 2006 9(2): 108-18. DES

M. A. Allison and J. E. Manson. Age, hormone therapy use, coronary heart disease, and mortality. Menopause 2011 18(3): 243-245. NRD

D. G. Altman. A meta-analysis of hormone replacement therapy for fracture prevention. JAMA 2001 286(17): 2096-7. NCT

S. M. van Anders, A. B. Chernick, B. A. Chernick, E. Hampson and W. A. Fisher. Preliminary clinical experience with androgen administration for pre- and postmenopausal women with hypoactive sexual desire. J Sex Marital Ther 2005 31(3): 173-85. NOP

G. L. Anderson, H. L. Judd, A. M. Kaunitz, D. H. Barad, S. A. Beresford, M. Pettinger, J. Liu, S. G. McNeeley and A. M. Lopez. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003 290(13): 1739-48. DES

G. L. Anderson, P. Autier, V. Beral, M. C. Bosland, E. Fernandez, S. Z. Haslam, D. G. Kaufman, C. La Vecchia, A. A. Molinolo, P. A. Newcomb, F. F. Parl, J. Peto, G. Rosano, D. Roy, F. Z. Stanczyk, D. B. Thomas, L. Vatten, T. Junghans, S. Olin, S. Shapiro, R. S. Stafford, C. W. Jameson, J. U. Meyer, R. Baan, J. Berthiller, V. J. Cogliano, C. Dresler, F. El Ghissassi, S. Franceschi, M. A. G. Goncalves, Y. Grosse, N. Guha, M. Marron, J. Mitchell, N. Napalkov, B. Secretan, K. Straif, A. Ullrich, S. Egraz, B. Kajo, M. Lezere and H. Lorenzen-Augros. Combined estrogen-progestogen menopausal therapy. 2007 91: 205-372. NCT

G. L. Anderson, R. T. Chlebowski, J. E. Rossouw, R. J. Rodabough, A. McTiernan, K. L. Margolis, A. Aggerwal, J. David Curb, S. L. Hendrix, F. Allan Hubbell, J. Khandekar, D. S. Lane, N. Lasser, A. M. Lopez, J. Potter and C. Ritenbaugh. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 2006 55(2): 103-15. DES

R. D'Anna, M. L. Cannata, M. Atteritano, F. Cancellieri, F. Corrado, G. Baviera, O. Triolo, F. Antico, A. Gaudio, N. Frisina, A. Bitto, F. Polito, L. Minutoli, D. Altavilla, H. Marini and F. Squadrito. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause 2007 14(4): 648-55. DUP

C. M. Antunes, P. D. Strolley, N. B. Rosenshein, J. L. Davies, J. A. Tonascia, C. Brown, L. Burnett, A. Rutledge, M. Pokempner and R. Garcia. Endometrial cancer and estrogen use. Report of a large case-control study. N Engl J Med 1979 300(1): 9-13. DES

A. Arana, C. Varas, A. Gonzalez-Perez, L. Gutierrez, L. Bjerrum and L. A. Garcia Rodriguez. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause 2006 13(5): 730-6. DES

D. F. Archer. Drospirenone and estradiol: a new option for the postmenopausal woman. Climacteric 2007 10 Suppl 1: 3-10. NRD

D. F. Archer. The effect of the duration of progestin use on the occurrence of endometrial cancer in postmenopausal women. Menopause 2001 8(4): 245-51. NCT

D. F. Archer, D. W. Sturdee, R. Baber, T. J. De Villiers, A. Pines, R. R. Freedman, A. Gompel, M. Hickey, M. S. Hunter, R. A. Lobo, M. A. Lumsden, A. H. MacLennan, P. Maki, S. Palacios, D. Shah, P. Villaseca and M. Warren. Menopausal hot flushes and night sweats: Where are we now?. Climacteric 2011 14(5): 515-528. NRD

D. F. Archer, D. W. Sturdee, R. Baber, T. J. de Villiers, A. Pines, R. R. Freedman, A. Gompel, M. Hickey, M. S. Hunter, R. A. Lobo, M. A. Lumsden, A. H. MacLennan, P. Maki, S. Palacios, D. Shah, P. Villaseca and M. Warren. Menopausal hot flushes and night sweats: where are we now?. Climacteric 2011 14(5): 515-28. NRQ

D. F. Archer, I. H. Thorneycroft, M. Foegh, V. Hanes, M. D. Glant, P. Bitterman and R. L. Kempson. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. Menopause 2005 12(6): 716-27. NRO

D. F. Archer, J. L. Shifren, R. F. J. Cheng, W. Bao and C. J. Guico-Pabia. Tolerability of desvenlafaxine 100 mg in women with vasomotor symptoms (VMS) associated with menopause: A pooled analysis of 5 trials. Fertility and Sterility 2011 96(3): S4-S5. NRD

D. F. Archer, K. Furst, D. Tipping, M. P. Dain and C. Vandepol. A randomized comparison of continuous combined transdermal delivery of estradiol-norethindrone acetate and estradiol alone for menopause. CombiPatch Study Group. Obstet Gynecol 1999 94(4): 498-503. NRC

D. F. Archer, L. A. Fischer, D. Rich, G. H. Schade, S. Schwartz, H. Wittcoff, C. S. Clark Sr, K. Maloney and F. O. Smith. Estrace(registered trademark) vs Premarin(registered trademark) for treatment of menopausal symptoms: Dosage comparison study. Advances in Therapy 1992 9(1): 21-31. NOP

B. H. Ascott-Evans, E. W. W. Sonnendecker and T. de Villiers. Hormone therapy in postmenopausal osteoporosis: 2008. Journal of Endocrinology, Metabolism and Diabetes of South Africa 2008 13(1): 8-12. DES

T. Aso, S. Uchiyama, Y. Matsumura, M. Taguchi, M. Nozaki, K. Takamatsu, B. Ishizuka, T. Kubota, H. Mizunuma and H. Ohta. A natural S-equol supplement alleviates hot flushes and other menopausal symptoms in equol nonproducing postmenopausal Japanese women. J Womens Health (Larchmt) 2012 21(1): 92-100. DUP

F. Atsma, M. L. Bartelink, D. E. Grobbee and Y. T. van der Schouw. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause 2006 13(2): 265-79. NRO

M. Atteritano, S. Mazzaferro, A. Bitto, M. L. Cannata, R. D'Anna, F. Squadrito, I. Macri, A. Frisina, N. Frisina, G. Bagnato. Genistein effects on quality of life and depression symptoms in osteopenic postmenopausal women: a 2-year randomized, double-blind, controlled study. Osteoporos Int 2013. NRP

G. K. Au. Evaluation of the benefits and risks of hormone replacement therapy. Hong Kong Med J 2000 6(4): 381-9. PTU

L. Auerbach, J. Rakus, C. Bauer, C. Gerner, R. Ullmann, H. Wimmer and J. Huber. Pomegranate seed oil in women with menopausal symptoms: a prospective randomized, placebo-controlled, double-blinded trial. Menopause 2012 19(4): 426-32. DUP

M. Aylward, F. Holly and R. J. Parker. An evaluation of clinical response to piperazine oestrone sulphate ('Harmogen') in menopause patients. Curr Med Res Opin 1974 2(7): 417-23. NOP

F. al-Azzawi, M. Wahab, J. Thompson, B. Pornel, E. Hirvonen, O. Ylikorkala, M. J. van der Mooren, J. Dillon and C. Magaril. Acceptability and patterns of endometrial bleeding in estradiol-based HRT regimens: a comparative study of cyclical sequential combinations of trimegestone or norethisterone acetate. Climacteric 2001 4(4): 343-54. NRC

G. A. Bachmann. Menopausal vasomotor symptoms: a review of causes, effects and evidence-based treatment options. J Reprod Med 2005 50(3): 155-65. NRD

G. A. Bachmann and J. O. Komi. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 2010 17(3): 480-6. NRO

Y. Z. Bagger, L. B. Tanko, P. Alexandersen, H. B. Hansen, A. Mollgaard, P. Ravn, P. Qvist, J. A. Kanis and C. Christiansen. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. Bone 2004 34(4): 728-35. DES

W. Bai, H. H. Henneicke-von Zepelin, S. Wang, S. Zheng, J. Liu, Z. Zhang, L. Geng, L. Hu, C. Jiao and E. Liske. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas 2007 58(1): 31-41. NRC

K. Bakken, A. Fournier, E. Lund, M. Waaseth, V. Dumeaux, F. Clavel-Chapelon, A. Fabre, B. Hemon, S. Rinaldi, V. Chajes, N. Slimani, N. E. Allen, G. K. Reeves, S. Bingham, K. T. Khaw, A. Olsen, A. Tjonneland, L. Rodriguez, M. J. Sanchez, P. A. Etxezarreta, E. Ardanaz, M. J. Tormo, P. H. Peeters, C. H. van Gils, A. Steffen, M. Schulz, J. Chang-Claude, R. Kaaks, R. Tumino, V. Gallo, T. Norat, E. Riboli, S. Panico, G. Masala, C. A. Gonzalez and F. Berrino. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2011 128(1): 144-56. DES

E. Balk, M. Chung, P. Chew, S. Ip, G. Raman, B. Kupelnick, A. Tatsioni, Y. Sun, B. Wolk, D. DeVine and J. Lau. Effects of soy on health outcomes. Evid Rep Technol Assess (Summ) 2005 (126): 1-8. NRD

D. Barad, C. Kooperberg, J. Wactawski-Wende, J. Liu, S. L. Hendrix and N. B. Watts. Prior oral contraception and postmenopausal fracture: a Women's Health Initiative observational cohort study. Fertil Steril 2005 84(2): 374-83. DES

D. H. Barlow. Menopause and HRT--the state of the art in Europe. Maturitas 2005 51(1): 40-7. NCT

D. H. Barlow. HRT and the risk of deep vein thrombosis. Int J Gynaecol Obstet 1997 59 Suppl 1: S29-33. NCT

V. M. Barnabei, B. B. Cochrane, A. K. Aragaki, I. Nygaard, R. S. Williams, P. G. McGovern, R. L. Young, E. C. Wells, M. J. O'Sullivan, B. Chen, R. Schenken and S. R. Johnson. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. Obstet Gynecol 2005 105(5 Pt 1): 1063-73. DUP

V. M. Barnabei, D. Grady, D. W. Stovall, J. A. Cauley, F. Lin, C. A. Stuenkel, M. L. Stefanick and J. H. Pickar. Menopausal symptoms in older women and the effects of treatment with hormone therapy. Obstet Gynecol 2002 100(6): 1209-18. NRP

E. Barrett-Connor. The menopause, hormone replacement, and cardiovascular disease: the epidemiologic evidence. Maturitas 1996 23(2): 227-34. NCT

E. Barrett-Connor and D. Grady. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health 1998 19: 55-72. NCT

E. Barrett-Connor, R. Young, M. Notelovitz, J. Sullivan, B. Wiita, H. M. Yang and J. Nolan. 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. NRO

D. Barton and C. L. Loprinzi. Making sense of the evidence regarding nonhormonal treatments for hot flashes. Clin J Oncol Nurs 2004 8(1): 39-42. NCT

A. Barzi, A. M. Lenz, M. J. Labonte, H. J. Lenz. Molecular pathways: Estrogen pathway in colorectal cancer. Clin Cancer Res 2013 19: 5842-8. NCT

S. Basaria and A. S. Dobs. Clinical review: Controversies regarding transdermal androgen therapy in postmenopausal women. J Clin Endocrinol Metab 2006 91(12): 4743-52. NRD

E. Basch, S. Bent, J. Collins, C. Dacey, P. Hammerness, M. Harrison, M. Smith, P. Szapary, C. Ulbricht, M. Vora and W. Weissner. Flax and flaxseed oil (Linum usitatissimum): a review by the Natural Standard Research Collaboration. J Soc Integr Oncol 2007 5(3): 92-105. NCT

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Appendix C. Abstraction Forms

Table C-1. Key Question 1, Form 1: study characteristics

Variable Name	Variable Type	Answer Code	Answer Code Label
RefID	Text		
Author	Text		
Author followed by (d)			Refid contains a duplicate pop.
Author followed by (m)			Refid contains multiple public.
Author followed by (a)			Refid is a conference abstract
Author followed by (c)			Refid is from clinical registry
Year	Text		
Country	Text		
Number of sites	Text		
Country/Center Comments	Text		
Treatment	Checkbox	1	Hormone
		2	Non-hormone prescription
		3	Non-hormone non-prescription
KQ1	Radio	1	Yes
		2	No
KQ2	Radio	1	Yes
		2	No
KQ3	Radio	1	Yes
		2	No
Study design	Radio	1	RCT with placebo comparator
		2	RCT with active comparator
		3	Crossover with placebo comparator
		4	Crossover with active comparator
Follow-up in wks	Text		
Women with intact uterus?	Radio	1	Yes, whole study sample
		2	No, whole study sample
		3	Both included in study sample
		4	Unknown
Percentage with intact uterus	Text		
Presence of vaso symptoms required for inclusion?	Radio	1	Yes, only women with vaso symptoms included in study.
		2	No, women with and without vaso symptoms included in study.
		3	Uncertain
Subgroup analysis?	Radio	1	Yes
		2	No
Describe subgrp analysis	Text		
Vasomotor symptoms	Radio	1	Yes
		2	No
Sleep disturbance	Radio	1	Yes
		2	No
Psychological symptoms	Radio	1	Yes
		2	No
Urogenital atrophy	Radio	1	Yes
		2	No
Sexual function	Radio	1	Yes
		2	No
Quality of life	Radio	1	Yes
		2	No

Variable Name	Variable Type	Answer Code	Answer Code Label
Osteoporotic fractures	Radio	1	Yes
		2	No
Coronary heart disease	Radio	1	Yes
		2	No
Stroke	Radio	1	Yes
		2	No
Thromboembolism	Radio	1	Yes
		2	No
Breast cancer	Radio	1	Yes
		2	No
Endometrial cancer	Radio	1	Yes
		2	No
Ovarian cancer	Radio	1	Yes
		2	No
Colorectal cancer	Radio	1	Yes
		2	No
Cholecystitis	Radio	1	Yes
		2	No
Adverse events	Radio	1	Yes
		2	No
Potential Industry Involvement:			
Funding source	Checkbox	1	Manufacture-related
		2	Public source
		3	Not stated
Any authors with industry funding?	Radio	1	Yes
		2	No
		3	Not stated
Any mention of editorial service?	Radio	1	Yes
		2	No
Pooling Data:	Text	1	Mixtures
		2	black cohosh + St John's wort
		3	Single ingredient supplements
		4	Pueraria mirifica
		5	Combinations with isoflavones
	Radio	1	Total
		2	Moderate-to-Severe
	Radio	1	Hot flashes
		2	Vasomotor symptoms
		3	Climacteric symptoms
	Text		Min #/#days
	Text		Comment box

Table C-2. Key Question 1, Form 2: study arm characteristics

Variable Name	Variable Type	Answer Code	Answer Code Label
Sample size, arm 1	Text		
Treatment, arm 1	Radio	1	Placebo
		2	Estrogen alone
		3	Estrogen and progestin combined
		4	Estrogen and progestin sequential
		5	Progestin alone
		6	Testosterone alone
		7	Testosterone and Estrogen combined

Variable Name	Variable Type	Answer Code	Answer Code Label
		8	Antidepressant
		9	Eszopiclone
		10	Clonidine
		11	Methyldopa
		12	Gabapentin, pregabalin
		13	Isoflavones, inc red clover, genistein, daidzein, equol
		14	Black cohosh (Cimicifuga racemosa)
		15	St John's wort (Hypericum perforatum)
		16	Ginseng
		17	Flax seed
		18	Vitamin E
		19	Dong quai (angelica sinensis)
		20	Dehydroepiandosterone (DHEA)
		21	Other
Other treatment description	Text		
Generic Drug name, arm 1	Text		
Trade Drug name, arm 1	Text		
Dose, arm 1	Text		
Dose category, arm 1	Radio	1	High
		2	Standard
		3	Low
		4	Ultra low
		5	Unknown
Mode of admin, arm 1	Radio	1	Oral
		2	Transdermal patch
		3	Vaginal cream
		4	Injection
		5	Dietary supplement
		6	Vaginal ring
		7	Intranasal spray
		8	Skin spray
		9	Vaginal ovule
		10	Vaginal gel
		11	Skin cream
		12	Skin gel
		13	Vaginal pessary/suppository
		14	Vaginal tablet
Mean age, arm 1	Text		
Age stand dev, arm 1	Text		
Lowest age, arm 1	Text		
Highest age, arm 1	Text		
Percent white, arm 1	Text		
Percent black, arm 1	Text		
Percent Hispanic, arm 1	Text		
Percent asian, arm 1	Text		
Percent other race, arm 1	Text		
Mean years since menopause, arm 1	Text		
Stand dev since menopause, arm 1	Text		
Mean months since last menstrual period, arm 1	Text		
Stand dev since last menstrual period, arm 1	Text		
Mean age at menopause, arm 1	Text		
Stand dev of age at menopause, arm 1	Text		
Percent previously using HRT	Text		

Variable Name	Variable Type	Answer Code	Answer Code Label
Mean BMI, arm 1	Text		
BMI stand dev, arm 1	Text		
Percent current smokers, arm 1	Text		
Percent former smokers, arm 1	Text		
Percent never smokers, arm 1	Text		
Comments (any characteristics sig different?)	Text		

Table C-3. Key Question 1, Form 3: vasomotor outcomes (estimating up to 3 different vasomotor outcomes reported in a single study)

Variable Name	Variable Type	Answer Code	Answer Code Label
Vasomotor scale, arm 1a	Radio	1	Greene vasomotor
		2	MENQOL vasomotor
		3	WHQ vasomotor
		4	Kupperman vasomotor
		5	Hot flashes
		6	Night sweats
		7	Hot flashes and night sweats
		8	Hot flash severity score
		9	Other
Vaso other scale description	Text		
Vaso frequency of measurements	Radio	1	Daily
		2	Weekly
		3	Monthly
Vaso symptom category	Radio	1	Total hot flashes
		2	Only moderate-severe hot flashes
Vaso baseline mean, arm 1a	Text		
Vaso baseline sd, arm 1a	Text		
Vaso baseline CI lower bound, arm 1a	Text		
Vaso baseline CI upper bound, arm 1a	Text		
Vaso 12-wk mean, arm 1a	Text		
Vaso 12-wk sd, arm 1a	Text		
Vaso 12-wk CI lower bound, arm 1a	Text		
Vaso 12-wk CI upper bound, arm 1a	Text		
Vaso 12-wk pre-post p-value, arm 1a	Text		
Vase 12-wk between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso last mean, arm 1a	Text		
Vaso last sd, arm 1a	Text		
Vaso last CI lower bound, arm 1a	Text		
Vaso last CI upper bound, arm 1a	Text		
Vaso last pre-post p-value, arm 1a	Text		
Vaso last between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	*Difference in post-test from placebo (Not present for arm 1, but is for arm 2-6)*
		2	*Difference between changes (delta)*
Vaso difference from placebo, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff CI lower bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff CI upper bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff p-value, arm 1a	*Text*		*(Not present for arm 1, but is for*

Variable Name	Variable Type	Answer Code	Answer Code Label
			arm 2-6)
Vaso mean change score, arm 1a	Text		
Vaso mean change std dev, arm 1a	Text		
Vaso other outcome, arm 1a	Text		
Vaso comments, arm 1a	Text		
Vasomotor scale, arm 1b	Radio	1	Greene vasomotor
		2	MENQOL vasomotor
		3	WHQ vasomotor
		4	Kupperman vasomotor
		5	Hot flashes
		6	Night sweats
		7	Hot flashes and night sweats
		8	Hot flash severity score
		9	Other
Vaso other scale description, arm 1b	Text		
Vaso frequency of measurements	Radio	1	Daily
		2	Weekly
		3	Monthly
Vaso symptom category	Radio	1	Total hot flashes
		2	Only moderate-severe hot flashes
Vaso baseline mean, arm 1b	Text		
Vaso baseline sd, arm 1b	Text		
Vaso baseline CI lower bound, arm 1b	Text		
Vaso baseline CI upper bound, arm 1b	Text		
Vaso 12-wk mean, arm 1b	Text		
Vaso 12-wk sd, arm 1b	Text		
Vaso 12-wk pre-post p-value, arm 1b	Text		
Vaso 12-wk CI lower bound, arm 1b	Text		
Vaso 12-wk CI upper bound, arm 1b	Text		
Vaso 12-wk pre-post p-value, arm 1b	Text		
Vaso 12-wk between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso last mean, arm 1b	Text		
Vaso last sd, arm 1b	Text		
Vaso last CI lower bound, arm 1b	Text		
Vaso last CI upper bound, arm 1b	Text		
Vaso last pre-post p-value, arm 1b	Text		
Vaso last between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	*Difference in post-test from placebo (Not present for arm 1, but is for arm 2-6)*
		2	*Difference between changes (delta)*
Vaso difference from placebo, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff CI lower bound, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff CI upper bound, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso mean change score, arm 1b	Text		
Vaso mean change std dev, arm 1b	Text		
Vaso other outcome, arm 1b	Text		
Vaso comments, arm 1b	Text		

Variable Name	Variable Type	Answer Code	Answer Code Label
Vasomotor scale, arm 1c	Radio	1	Greene vasomotor
		2	MENQOL vasomotor
		3	WHQ vasomotor
		4	Kupperman vasomotor
		5	Hot flashes
		6	Night sweats
		7	Hot flashes and night sweats
		8	Hot flash severity score
		9	Other
Vaso other scale description, arm 1c	Text		
Vaso frequency of measurements	Radio	1	Daily
		2	Weekly
		3	Monthly
Vaso symptom category	Radio	1	Total hot flashes
		2	Only moderate-severe hot flashes
Vaso baseline mean, arm 1c	Text		
Vaso baseline sd, arm 1c	Text		
Vaso baseline CI lower bound, arm 1c	Text		
Vaso baseline CI upper bound, arm 1c	Text		
Vaso 12-wk mean, arm 1c	Text		
Vaso 12-wk sd, arm 1c	Text		
Vaso 12-wk CI lower bound, arm 1c	Text		
Vaso 12-wk CI upper bound, arm 1c	Text		
Vaso 12-wk pre-post p-value, arm 1c	Text		
Vaso 12-wk between grp p-value, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso last mean, arm 1c	Text		
Vaso last sd, arm 1c	Text		
Vaso last CI lower bound, arm 1c	Text		
Vaso last CI upper bound, arm 1c	Text		
Vaso last pre-post p-value, arm 1c	Text		
Vaso last between grp p-value, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	*Difference in post-test from placebo (Not present for arm 1, but is for arm 2-6)*
		2	*Difference between changes (delta)*
Vaso difference from placebo, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff CI lower bound, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff CI upper bound, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso diff p-value, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Vaso mean change score, arm 1c	Text		
Vaso mean change p-value, arm 1c	Text		
Vaso other outcome, arm 1c	Text		
Vaso comments, arm 1c	Text		

Table C-4. Key Question 1, Form 4: sleep disturbance outcomes (estimating up to 2 different sleep outcomes reported in a single study)

Variable Name	Variable Type	Answer Code	Answer Code Label

Variable Name	Variable Type	Answer Code	Answer Code Label
Sleep scale, arm 1a	Radio	1	WHI
		2	Other
		3	WHQ
Sleep other scale description, arm 1a	Text		
Sleep baseline mean, arm 1a	Text		
Sleep baseline sd, arm 1a	Text		
Sleep baseline CI lower bound, arm 1a	Text		
Sleep baseline CI upper bound, arm 1a	Text		
Sleep 12-wk mean, arm 1a	Text		
Sleep 12-wk sd, arm 1a	Text		
Sleep 12-wk CI lower bound, arm 1a	Text		
Sleep 12-wk CI upper bound, arm 1a	Text		
Sleep 12-wk pre-post p-value, arm 1a	Text		
Sleep 12-wk between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep last mean, arm 1a	Text		
Sleep last sd, arm 1a	Text		
Sleep last CI lower bound, arm 1a	Text		
Sleep last CI upper bound, arm 1a	Text		
Sleep last pre-post p-value, arm 1a	Text		
Sleep last between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	*Difference in post-test from placebo (Not present for arm 1, but is for arm 2-6)*
		2	*Difference between changes (delta)*
Sleep difference from placebo, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep diff CI lower bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep diff CI upper bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep diff p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep mean change score, arm 1a	Text		
Sleep mean change std dev, arm 1a	Text		
Sleep other outcome, arm 1a	Text		
Sleep comments, arm 1a	Text		
Sleep scale, arm 1b	Radio	1	WHI
		2	Other
		3	WHQ
Sleep other scale description, arm 1b	Text		
Sleep baseline mean, arm 1b	Text		
Sleep baseline sd, arm 1b	Text		
Sleep baseline CI lower bound, arm 1b	Text		
Sleep baseline CI upper bound, arm 1b	Text		
Sleep 12-wk mean, arm 1b	Text		
Sleep 12-wk sd, arm 1b	Text		
Sleep 12-wk CI lower bound, arm 1b	Text		
Sleep 12-wk CI upper bound, arm 1b	Text		
Sleep 12-wk pre-post p-value, arm 1b	Text		
Sleep 12-wk between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep last mean, arm 1b	Text		
Sleep last sd, arm 1b	Text		

Variable Name	Variable Type	Answer Code	Answer Code Label
Sleep last CI lower bound, arm 1b	Text		
Sleep last CI upper bound, arm 1b	Text		
Sleep last pre-post p-value, arm 1b	Text		
Sleep last between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	*Difference in post-test from placebo (Not present for arm 1, but is for arm 2-6)*
		2	*Difference between changes (delta)*
Sleep difference from placebo, arm 1b	*Text*		
Sleep diff CI lower bound, arm 1b	*Text*		
Sleep diff CI upper bound, arm 1b	*Text*		
Sleep diff p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sleep mean change score, arm 1b	Text		
Sleep mean change std dev, arm 1b	Text		
Sleep other outcome, arm 1b	Text		
Sleep comments, arm 1b	Text		

Table C-5. Key Question 1, Form 5: psychological outcomes (estimating up to 3 different psychological outcomes reported in a single study)

Variable Name	Variable Type	Answer Code	Answer Code Label
Psych scale, arm 1a	Radio	1	Greene psychological score
		2	Greene anxiety score
		3	Greene depression score
		4	WHQ anxiety score
		5	WHQ depression score
		6	Beck anxiety score
		7	Beck depression score
		8	MENQOL psychosocial score
		9	MQOL emotional score
		10	Hamilton anxiety score
		11	Hamilton depression score
		12	SF-36 mental health score
		13	CES-D depression score
		14	Other
Psych other scale description, arm 1a	Text		
Psych baseline mean, arm 1a	Text		
Psych baseline sd, arm 1a	Text		
Psych baseline CI lower bound, arm 1a	Text		
Psych baseline CI upper bound, arm 1a	Text		
Psych 12-wk mean, arm 1a	Text		
Psych 12-wk sd, arm 1a	Text		
Psych 12-wk CI lower bound, arm 1a	Text		
Psych 12-wk CI upper bound, arm 1a	Text		
Psych 12-wk pre-post p-value, arm 1a	Text		
Psych 12-wk between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych last mean, arm 1a	Text		
Psych last sd, arm 1a	Text		
Psych last CI lower bound, arm 1a	Text		
Psych last CI upper bound, arm 1a	Text		
Psych last pre-post p-value, arm 1a	Text		
Psych last between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for*

Variable Name	Variable Type	Answer Code	Answer Code Label
			arm 2-6)
Specify difference	*Radio*	*1*	*Difference in post-test from placebo (Not present for arm 1, but is for arm 2-6)*
		2	*Difference between changes (delta)*
Psych difference from placebo, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff CI lower bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff CI upper bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych mean change score, arm 1a	Text		
Psych other outcome, arm 1a	Text		
Psych comments, arm 1a	Text		
Psych mean change std dev, arm 1a	Text		
Psych scale, arm 1b	Radio	1	Greene psychological score
		2	Greene anxiety score
		3	Greene depression score
		4	WHQ anxiety score
		5	WHQ depression score
		6	Beck anxiety score
		7	Beck depression score
		8	MENQOL psychosocial score
		9	MQOL emotional score
		10	Hamilton anxiety score
		11	Hamilton depression score
		12	SF-36 mental health score
		13	CES-D depression score
		14	Other
Psych other scale description, arm 1b	Text		
Psych baseline mean, arm 1b	Text		
Psych baseline sd, arm 1b	Text		
Psych baseline CI lower bound, arm 1b	Text		
Psych baseline CI upper bound, arm 1b	Text		
Psych 12-wk mean, arm 1b	Text		
Psych 12-wk sd, arm 1b	Text		
Psych 12-wk CI lower bound, arm 1b	Text		
Psych 12-wk CI upper bound, arm 1b	Text		
Psych 12-wk pre-post p-value, arm 1b	Text		
Psych 12-wk between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych last mean, arm 1b	Text		
Psych last sd, arm 1b	Text		
Psych last CI lower bound, arm 1b	Text		
Psych last CI upper bound, arm 1b	Text		
Psych last pre-post p-value, arm 1b	Text		
Psych last between grp p-value, arm 1b	Text		
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)

Variable Name	Variable Type	Answer Code	Answer Code Label
Psych difference from placebo, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff CI lower bound, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff CI upper bound, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych mean change score, arm 1b	Text		
Psych mean change std dev, arm 1b	Text		
Psych other outcome, arm 1b	Text		
Psych comments, arm 1b	Text		
Psych scale, arm 1c	Radio	1	Greene psychological score
		2	Greene anxiety score
		3	Greene depression score
		4	WHQ anxiety score
		5	WHQ depression score
		6	Beck anxiety score
		7	Beck depression score
		8	MENQOL psychosocial score
		9	MQOL emotional score
		10	Hamilton anxiety score
		11	Hamilton depression score
		12	SF-36 mental health score
		13	CES-D depression score
		14	Other
Psych other scale description, arm 1c	Text		
Psych baseline mean, arm 1c	Text		
Psych baseline sd, arm 1c	Text		
Psych baseline CI lower bound, arm 1c	Text		
Psych baseline CI upper bound, arm 1c	Text		
Psych 12-wk mean, arm 1c	Text		
Psych 12-wk sd, arm 1c	Text		
Psych 12-wk CI lower bound, arm 1c	Text		
Psych 12-wk CI upper bound, arm 1c	Text		
Psych 12-wk pre-post p-value, arm 1c	Text		
Psych 12-wk between grp p-value, arm 1c	*Text*		
Psych last mean, arm 1c	Text		
Psych last sd, arm 1c	Text		
Psych last CI lower bound, arm 1c	Text		
Psych last CI upper bound, arm 1c	Text		
Psych last pre-post p-value, arm 1c	Text		
Psych last between grp p-value, arm 1c	Text		
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
Psych difference from placebo, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff CI lower bound, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff CI upper bound, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Psych diff p-value, arm 1c	*Text*		*(Not present for arm 1, but is for arm 2-6)*

Variable Name	Variable Type	Answer Code	Answer Code Label
Psych mean change score, arm 1c	Text		
Psych mean change std dev, arm 1c	Text		
Psych other outcome, arm 1c	Text		
Psych comments, arm 1c	Text		

Table C-6. Key Question 1, Form 6: urogenital atrophy (estimating up to 2 QOL measures reported in a single study)

Variable Name	Variable Type	Answer Code	Answer Code Label
Urogenital atrophy scale, arm 1a	Radio	1	Vaginal dryness
		2	Vaginal atrophy
		3	Other
Urogen atrophy scale description, arm 1a	Text		
Urogen atrophy baseline percent, arm 1a	Text		
Urogen atrophy 12-wk percent, arm 1a	Text		
Urogen atrophy 12-wk CI lower bound, arm 1a	Text		
Urogen atrophy 12-wk CI upper bound, arm 1a	Text		
Urogen atrophy 12-wk pre-post p-value, arm 1a	Text		
Urogen atrophy 12-wk between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy last percent, arm 1a	Text		
Urogen atrophy last CI lower bound, arm 1a	Text		
Urogen atrophy last CI upper bound, arm 1a	Text		
Urogen atrophy last pre-post p-value, arm 1a	Text		
Urogen atrophy last between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
Urogen atrophy difference from placebo, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy diff CI lower bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy diff CI upper bound, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy diff p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy mean change score, arm 1a	Text		
Urogen atrophy mean change std dev, arm 1a	Text		
Urogen atrophy other outcome, arm 1a	Text		
Urogen atrophy comments, arm 1a	Text		
Urogenital atrophy scale, arm 1b	Radio	1	Vaginal dryness
		2	Vaginal atrophy
		3	Other
Urogen atrophy scale description, arm 1b	Text		
Urogen atrophy baseline percent, arm 1b	Text		
Urogen atrophy 12-wk percent, arm 1b	Text		
Urogen atrophy 12-wk CI lower bound, arm 1b	Text		
Urogen atrophy 12-wk CI upper bound, arm 1b	Text		
Urogen atrophy 12-wk pre-post p-value, arm 1b	Text		
Urogen atrophy 12-wk between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy last percent, arm 1b	Text		

Variable Name	Variable Type	Answer Code	Answer Code Label
Urogen atrophy last CI lower bound, arm 1b	Text		
Urogen atrophy last CI upper bound, arm 1b	Text		
Urogen atrophy last pre-post p-value, arm 1b	Text		
Urogen atrophy last between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
Urogen atrophy difference from placebo, arm 1b	*Text*		
Urogen atrophy diff CI lower bound, arm 1b	*Text*		
Urogen atrophy diff CI upper bound, arm 1b	*Text*		
Urogen atrophy diff p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Urogen atrophy mean change score, arm 1b	Text		
Urogen atrophy mean change std dev, arm 1b	Text		
Urogen atrophy other outcome, arm 1b	Text		
Urogen atrophy comments, arm 1b	Text		

Table C-7. Key Question 1, Form 7: quality of life outcomes (estimating up to 2 QOL measures reported in a single study)

Variable Name	Variable Type	Answer Code	Answer Code Label
Quality of life scale, arm 1a	Radio	1	Greene total score
		2	MENQOL total score
		3	Kupperman total score
		4	MQOL overall qol
		5	WHQ total score
		6	SF-36 total score
		7	Other
QOL other scale description, arm 1a	Text		
QOL baseline mean, arm 1a	Text		
QOL baseline sd, arm 1a	Text		
QOL baseline CI lower bound, arm 1a	Text		
QOL baseline CI upper bound, arm 1a	Text		
QOL 12-wk mean, arm 1a	Text		
QOL 12-wk sd, arm 1a	Text		
QOL 12-wk CI lower bound, arm 1a	Text		
QOL 12-wk CI upper bound, arm 1a	Text		
QOL 12-wk pre-post p-value, arm 1a	Text		
QOL 12-wk between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
QOL last mean, arm 1a	Text		
QOL last sd, arm 1a	Text		
QOL last CI lower bound, arm 1a	Text		
QOL last CI upper bound, arm 1a	Text		
QOL last pre-post p-value, arm 1a	Text		
QOL last between grp p-value, arm 1a	Text		
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
QOL difference from placebo, arm 1a	*Text*		
QOL diff CI lower bound, arm 1a	*Text*		

Variable Name	Variable Type	Answer Code	Answer Code Label
QOL diff CI upper bound, arm 1a	*Text*		
QOL diff p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
QOL mean change score, arm 1a	Text		
QOL mean change std dev, arm 1a	Text		
QOL other outcome, arm 1a	Text		
QOL comments, arm 1a	Text		
Quality of life scale, arm 1b	Radio	1	Greene total score
		2	MENQOL total score
		3	Kupperman total score
		4	MQOL overall qol
		5	WHQ total score
		6	SF-36 total score
		7	Other
QOL other scale description, arm 1b	Text		
QOL baseline mean, arm 1b	Text		
QOL baseline sd, arm 1b	Text		
QOL baseline CI lower bound, arm 1b	Text		
QOL baseline CI upper bound, arm 1b	Text		
QOL 12-wk mean, arm 1b	Text		
QOL 12-wk sd, arm 1b	Text		
QOL 12-wk CI lower bound, arm 1b	Text		
QOL 12-wk CI upper bound, arm 1b	Text		
QOL 12-wk pre-post p-value, arm 1b	Text		
QOL 12-wk between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
QOL last mean, arm 1b	Text		
QOL last sd, arm 1b	Text		
QOL last CI lower bound, arm 1b	Text		
QOL last CI upper bound, arm 1b	Text		
QOL last pre-post p-value, arm 1b	Text		
QOL last between grp p-value, arm 1b	Text		
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
QOL difference from placebo, arm 1b	Text		
QOL diff CI lower bound, arm 1b	Text		
QOL diff CI upper bound, arm 1b	Text		
QOL diff p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
QOL mean change score, arm 1b	Text		
QOL mean change std dev, arm 1b	Text		
QOL other outcome, arm 1b	Text		
QOL comments, arm 1b	Text		

Table C-8. Key Question 1, Form 8: sexual function outcomes (estimating up to 2 different sexual outcomes reported in a single study)

Variable Name	Variable Type	Answer Code	Answer Code Label
Sexual function scale, arm 1a	Radio	1	Greene sexual component score
		2	MENQOL sexual score
		3	MQOL sexual score

Variable Name	Variable Type	Answer Code	Answer Code Label
		4	WHQ sexual score
		5	McCoy sex scale
		6	Other
		7	Dyspareunia (pain during intercourse)
		8	Satisfying sexual episodes per week
		9	Total sexual episodes per week
Sexual function other scale description, arm 1a	Text		
Sexual function baseline mean, arm 1a	Text		
Sexual function baseline sd, arm 1a	Text		
Sexual function baseline CI lower bound, arm 1a	Text		
Sexual function baseline CI upper bound, arm 1a	Text		
Sexual function 12-wk mean, arm 1a	Text		
Sexual function 12-wk sd, arm 1a	Text		
Sexual function 12-wk CI lower bound, arm 1a	Text		
Sexual function 12-wk CI upper bound, arm 1a	Text		
Sexual function 12-wk pre-post p-value, arm 1a	Text		
Sexual function 12-wk between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function last mean, arm 1a	Text		
Sexual function last sd, arm 1a	Text		
Sexual function last CI lower bound, arm 1a	Text		
Sexual function last CI upper bound, arm 1a	Text		
Sexual function last pre-post p-value, arm 1a	Text		
Sexual function last between grp p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
Sexual function difference from placebo, arm 1a	*Text*		
Sexual function diff CI lower bound, arm 1a	*Text*		
Sexual function diff CI upper bound, arm 1a	*Text*		
Sexual function diff p-value, arm 1a	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function mean change score, arm 1a	Text		
Sexual function mean change std dev, arm 1a	Text		
Sexual function other outcome, arm 1a	Text		
Sexual function comments, arm 1a	Text		
Sexual function scale, arm 1b	Radio	1	Greene sexual component score
		2	MENQOL sexual score
		3	MQOL sexual score
		4	WHQ sexual score
		5	McCoy sex scale
		6	Other
		7	Dyspareunia (pain during intercourse)
		8	Satisfying sexual episodes per week
		9	Total sexual episodes per week
Sexual function other scale description, arm 1b	Text		
Sexual function baseline mean, arm 1b	Text		
Sexual function baseline sd, arm 1b	Text		

Variable Name	Variable Type	Answer Code	Answer Code Label
Sexual function baseline CI lower bound, arm 1b	Text		
Sexual function baseline CI upper bound, arm 1b	Text		
Sexual function 12-wk mean, arm 1b	Text		
Sexual function 12-wk sd, arm 1b	Text		
Sexual function 12-wk CI lower bound, arm 1b	Text		
Sexual function 12-wk CI upper bound, arm 1b	Text		
Sexual function 12-wk pre-post p-value, arm 1b	Text		
Sexual function 12-wk between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function last mean, arm 1b	Text		
Sexual function last sd, arm 1b	Text		
Sexual function last CI lower bound, arm 1b	Text		
Sexual function last CI upper bound, arm 1b	Text		
Sexual function last pre-post p-value, arm 1b	Text		
Sexual function last between grp p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Specify difference	*Radio*	*1*	Difference in post-test from placebo *(Not present for arm 1, but is for arm 2-6)*
		2	Difference between changes (delta)
Sexual function difference from placebo, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function diff CI lower bound, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function diff CI upper bound, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function diff p-value, arm 1b	*Text*		*(Not present for arm 1, but is for arm 2-6)*
Sexual function mean change score, arm 1b	Text		
Sexual function mean change std dev, arm 1b	Text		
Sexual function other outcome, arm 1b	Text		
Sexual function comments, arm 1b	Text		

Table C-9. Key Question 1, Form 9: study quality

Variable Name	Variable Type	Answer Code	Answer Code Label
Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?	Radio	1	Yes
		2	No
		3	Uncertain
Were the researchers and subjects blinded to the study group assignment?	Radio	1	Yes
		2	No
		3	Uncertain
Was there adequate concealment of the study group assignments?	Radio	1	Yes
		2	No
		3	Uncertain
Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?	Radio	1	Yes
		2	No
		3	Uncertain
Was there important differential loss to follow-up or overall high loss to follow-up?	Radio	1	Yes
		2	No
		3	Uncertain
Were measurements equal, reliable and valid (includes masking of outcome assessment)?	Radio	1	Yes
		2	No
		3	Uncertain
Were definitions of interventions clear?	Radio	1	Yes

Variable Name	Variable Type	Answer Code	Answer Code Label
		2	No
		3	Uncertain
Were all important outcomes considered and defined?	Radio	1	Yes
		2	No
		3	Uncertain
At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?	Radio	1	Yes
		2	No
		3	Uncertain
Overall Quality Assessment	Radio	1	Good
		2	Fair
		3	Poor

Appendix D. Estrogen Dosing Categories

Table D-1. Estrogen dosing categories

Mode of administration	Dose Category	17B-estradiol	Conjugated equine estrogen	Estradiol valerate	Estrone sulphate (estropipate or estrone piperazine)	Esterified estrogen	Ethinyl estradiol	Estradiol acetate
Oral	Ultra low	0.5mg	0.15mg 0.3mg	--	0.3mg	--	--	--
	Low	1.0mg	0.4mg	0.5mg	0.625mg	0.3mg	<0.010mg	--
	Standard	1.5mg 2mg	0.625mg	1mg	1.25mg 1.5mg	0.625mg	0.010mg	--
	High	4mg	1.25mg	2mg	2.5mg	1.25mg	>0.010mg	--
Transdermal Patch	Ultra low	0.025mg	--	--	--	--	--	--
	Low	0.0375mg	--	--	--	--	--	--
	Standard	0.05mg	--	--	--	--	--	--
	High	0.075mg 0.1mg	--	--	--	--	--	--
Vaginal Cream	Ultra low		--	--	--	--	--	--
	Low	0.1 mg	--	--	--	--	--	--
	Standard		0.625 mg	--	--	1.0 mg	--	--
	High	--	--	--	--	--	--	--
Vaginal Ring	Ultra low	--	--	--	--	--	--	--
	Low	0.0075mg	--	--	--	--	--	--
	Standard	--	--	--	--	--	--	--
	High	--	--	--	--	--	--	0.05 mg 0.10 mg
Topical (cream, spray, gel)	Ultra low	0.01% (gel) 0.03% (gel)	--	--	--	--	--	--
	Low	1.5 mg (spray) 0.04% (gel) 0.06% (gel) 0.10% (gel)	--	--	--	--	--	--
	Standard	0.05 mg (cream)	--	--	--	--	--	--
	High	--	--	--	--	--	--	--
Vaginal (pessary/suppository, tablet)	Ultra low	--	--	--	--	--	--	--
	Low	0.01 mg 0.0258 mg	--	--	--	--	--	--
	Standard	--	--	--	--	--	--	--
	High	--	--	--	--	--	--	--

Appendix E. Evidence Base for Key Question 1

Table E-1. Study characteristics for trials comparing hormone with placebo

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Martin 1971	United States	2	165	RCT Plac Compare	3	12		No/NR
Campbell 1977	United Kingdom	1	136	Crossover	2	52		No/NR
Baumgardner 1978	United States	8	156	RCT Plac Compare	4	24		No/NR
Coope 1981	United Kingdom	1	55	Crossover	2	26		No/NR
Jensen 1983	Denmark	1	131	RCT Plac Compare	2	104		No/NR
Foidart 1991	Belgium	2	109	RCT Plac Compare	2	26		No/NR
Eriksen 1992	Denmark	NR	154	RCT Plac Compare	2	12		No/NR
Wiklund 1993	Sweden	15	223	RCT Plac Compare	2	12		No/NR
Derman 1995	United States	3	82	RCT Plac Compare	2	16	Yes	No/NR
Saletu 1995	Austria	1	64	RCT Plac Compare	2	12		No/NR
Good 1996	United States	NR	273	RCT Plac Compare	3	12		No/NR
Speroff (Study 1) 1996	United States	17	108	RCT Plac Compare	2	12	Yes	No/NR
Chung 1996	Hong Kong	1	83	Crossover	2	26		No/NR
Speroff (Study 2) 1996	United States	17	111	RCT Plac Compare	3	12	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Speroff (Study 3) 1996	United States	17	106	RCT Plac Compare	2	12	Yes	No/NR
Bacchi-Modena 1997	Italy	11	109	RCT Plac Compare	2	12		No/NR
Baerug 1998	Norway	5	119	RCT Plac Compare	3	12	Yes	No/NR
Bech 1998	Denmark	1	151	RCT Plac Compare	3	52		No/NR
de Vrijer 1999	Netherlands	16	254	RCT Plac Compare	3	12		No/NR
Leonetti 1999	United States	1	90	RCT Plac Compare	2	52	Yes	No/NR
Studd 1999	Multinational	63	355	RCT Plac Compare	5	12		No/NR
Polo-Kantola 1999	Finland	1	62	Crossover	2	12	Yes	No/NR
Casper 1999	Germany		67	RCT Plac Compare	2	24		No/NR
Cohen 1999	United States	Multi	259	RCT Plac Compare	2	12	Yes	No/NR
Rebar 2000	United States	25	204	RCT Plac Compare	2	104	Yes	No/NR
Speroff (Study 1) 2000	United States	11	219	RCT Plac Compare	5	16	Yes	No/NR
Rovati 2000	Italy	15	311	RCT Plac Compare	4	12	Yes	No/NR
Notelovitz 2000	United States	23	145	RCT Plac Compare	3	12		No/NR
Strickler 2000	United States	32	201	RCT Plac Compare	2	52	Yes	No/NR
Notelovitz 2000	United	15	333	RCT Plac	5	12	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
	States			Compare				
DeAloysio 2000	Italy	1	156	RCT Plac Compare	3	12	Yes	No/NR
von Holst 2000	Germany	34	186	RCT Plac Compare	2	12		No/NR
Notelovitz 2000	United States	26	219	RCT Plac Compare	4	12	Yes	No/NR
Alexandersen 2000	Denmark	1	200	RCT Plac Compare	4	104	Yes	No/NR
Speroff (Study 2) 2000	United States	24	266	RCT Plac Compare	4	12	Yes	No/NR
Rigano 2001	Italy	1	362	RCT Plac Compare	2	26		No/NR
Utian (CEE alone arms) 2001	United States	57	117	RCT Plac Compare	4	52	Yes	No/NR
Simon 2001	United States	4	120	RCT Plac Compare	2	12	Yes	No/NR
Soares 2001	Brazil	2	50	RCT Plac Compare	2	12	Yes	No/NR
Utian (CEE/MPA arms) 2001	United States	57	152	RCT Plac Compare	5	52	Yes	No/NR
Rozenbaum 2002	France	21	165	RCT Plac Compare	3	12		No/NR
Shulman (Study 1) 2002	United States	32	293	RCT Plac Compare	3	12	Yes	No/NR
von Holst 2002	Germany	Multi	172	RCT Plac Compare	2	12		No/NR
Archer 2003	United States	11	221	RCT Plac Compare	3	12	Yes	No/NR
Vestergaard 2003	Denmark	Mult	1006	RCT Plac	2	260		No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
		i		Compare				
Speroff 2003	United States	35	333	RCT Plac Compare	3	13	Yes	No/NR
Jirapinyo 2003	Thailand	1	120	RCT Plac Compare	2	52	Yes	No/NR
Haines 2003	Hong Kong	1	152	RCT Plac Compare	3	52	Yes	No/NR
Hays 2003	United States		16608	RCT Plac Compare	2	52		No/NR
Gambacciani 2003	Italy	1	50	RCT Plac Compare	2	12		No/NR
Gelfand 2003	Canada	18	119	RCT Plac Compare	2	12	Yes	No/NR
Wren 2003	Australia	1	80	RCT Plac Compare	2	12	Yes	No/NR
Simunic 2003	Croatia	15	1612	RCT Plac Compare	2	52		No/NR
Parsons 2003	United States	16	94	RCT Plac Compare	2	13	Yes	No/NR
Berlex (SIP) 2003	United States	NR	180	RCT Plac Compare	2	12		No/NR
Rudolph 2004	Germany	2	129	RCT Plac Compare	2	24	Yes	No/NR
Yang 2004	Taiwan	1	51	RCT Plac Compare	2	24		No/NR
Schurmann 2004	Multinational	19	225	RCT Plac Compare	4	16		No/NR
Utian 2004	United States	Multi	281	RCT Plac Compare	4	12	Yes	No/NR
Dessole 2004	Italy	NR	88	RCT Plac	2	26		No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Duramed (SIP) 2004	United States	NR	104	RCT Plac Compare	2	12		
Brunner 2005	United States		10739	RCT Plac Compare	2	52		No/NR
Onalan 2005	Turkey	1	210	RCT Plac Compare	3	52		No/NR
Bayer Healthcare (SIP) 2005	United States	NR	351	RCT Plac Compare	2	12		
Novartis (SIP) 2005	United States	NR	160	RCT Plac Compare	3	12		No/NR
Speroff (Study 1) 2006	United States	41	289	RCT Plac Compare	3	12	Yes	No/NR
Simon 2006	United States	37	200	RCT Plac Compare	2	12	Yes	No/NR
Nielsen 2006	Denmark	2	335	RCT Active Compare	3	104		No/NR
Osmanagaoglu 2006	Turkey	1	104	RCT Plac Compare	2	26		No/NR
Speroff (Study 2) 2006	United States	36	221	RCT Plac Compare	2	12	Yes	No/NR
Bachmann (d) 2007	United States	48	425	RCT Plac Compare	3	12	Yes	No/NR
Maki 2007	United States	19	180	RCT Plac Compare	2	17	Yes	No/NR
Endrikat 2007	Germany	31	324	RCT Plac Compare	2	12	Yes	No/NR
Lee 2007	South Korea	6	72	RCT Plac Compare	2	16	Yes	No/NR
Panay 2007	Multinational	Mult	575	RCT Plac	3	24	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
		i		Compare				
Simon 2007	Multinational	28	484	RCT Plac Compare	4	12	Yes	Yes
Pefanco 2007	United States	1	57	RCT Plac Compare	2	156	Yes	No/NR
Bayer Healthcare (SIP) 2007	United States	NR	165	RCT Plac Compare	2	12		No/NR
Buster (Study 1) 2008	United States	43	151	RCT Plac Compare	2	12	Yes	No/NR
Veerus 2008	Estonia	3	796	RCT Plac Compare	2	187	Yes	No/NR
Davis 2008	Multinational	65	811	RCT Plac Compare	3	52	Yes	No/NR
Bachmann 2008	United States	9	230	RCT Plac Compare	3	12	Yes	No/NR
Welton 2008	Multinational	2	2130	RCT Plac Compare	2	52		No/NR
Buster (Study 2) 2008	United States	43	150	RCT Plac Compare	2	12	Yes	No/NR
Buster (Study 3) 2008	United States	43	153	RCT Plac Compare	2	12	Yes	No/NR
Simon (SIP) 2008	United States	42	248	RCT Plac Compare	2	12	Yes	No/NR
Benster 2009	United Kingdom	2	221	RCT Plac Compare	5	24	Yes	No/NR
Utian 2009	United States	43	318	RCT Plac Compare	3	12	Yes	Yes
Lobo 2009	Multinational	94	2974	RCT Plac Compare	3	104	Yes	No/NR
Haines 2009	Multinational	Mult	160	RCT Plac	2	12	Yes	Yes

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
		i		Compare				
Bachmann (d) 2009	United States	48	121	RCT Plac Compare	3	12	Yes	No/NR
Hedrick 2009	Multinational	48	495	RCT Plac Compare	4	12	Yes	No/NR
Baksu 2009	Turkey	1	132	RCT Plac Compare	4	52		No/NR
Bachmann (Study 1) 2009	Multinational	Multi	215	RCT Plac Compare	2	12	Yes	No/NR
Freedman 2009	United States	88	275	RCT Plac Compare	2	12	Yes	No/NR
Gast 2009	Multinational	25	285	RCT Plac Compare	2	24	Yes	Yes
Bachmann (Study 2) 2009		Multi	208	RCT Plac Compare	2	12	Yes	No/NR
Hassa 2010	Turkey	1	247	RCT Plac Compare	3	26		No/NR
Stevenson 2010	Multinational	15	313	RCT Plac Compare	3	13	Yes	No/NR
Bachmann 2010	United States	66	542	RCT Plac Compare	3	12	Yes	Yes
Raghunandan 2010	India	1	75	RCT Plac Compare	3	12		No/NR
Hedrick 2010	Multinational	48	488	RCT Plac Compare	4	12	Yes	No/NR
Liu 2011	Multinational	Multi	1029	RCT Plac Compare	6	12		No/NR
Lin 2011	China	9	244	RCT Plac Compare	2	16	Yes	Yes
Demetrio 2011	Brazil	1	66	RCT Plac	2	24		No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Liu 2012	United States	19	157	RCT Plac Compare	3	12	Yes	No/NR
Archer 2012	United States	78	351	RCT Plac Compare	3	12	Yes	Yes
Archer 2012	United States	78	344	RCT Plac Compare	3	12	Yes	No/NR
Cano 2012	Spain	12	167	RCT Plac Compare	2	12	Yes	No/NR
Polisseni 2013	Brazil	1	88	RCT Plac Compare	2	12	Yes	No/NR
Raz 2013	United States	8	59	RCT Plac Compare	2	192		No/NR
Archer 2013	United States	79	710	RCT Plac Compare	4	12	Yes	Yes
Pinkerton 2013	United States		410	RCT Plac Compare	4	52	Yes	No/NR

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial; (SIP); data came from a package insert

Table E-2. Study characteristics for trials comparing antidepressant with placebo

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Suvanto-Luukkonen 2005	Finland	2	149	RCT Plac Compare	3	39	Yes	No/NR
Evans 2005	United States	1	80	RCT Plac Compare	2	12	Yes	No/NR
Kerwin 2007	United States	NR	87	Crossover	2	4	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Kalay 2007	Turkey	NR	50	RCT Plac Compare	2	8		No/NR
Speroff 2008	United States	37	620	RCT Plac Compare	5	12	Yes	No/NR
Soares 2008	Canada	NR	56	RCT Plac Compare	2	6	Yes	No/NR
Archer 2009	United States	32	541	RCT Plac Compare	3	26	Yes	Yes
Archer 2009	United States	34	452	RCT Plac Compare	3	12	Yes	Yes
Kornstein 2010	United States	37	372	RCT Plac Compare	2	8	Yes	Yes
Soares 2010	Multinational	72	461	RCT Active Compare	2	8	Yes	No/NR
Freeman 2011	United States	4	205	RCT Plac Compare	2	8		No/NR
Bouchard 2012	Multinational	38	287	RCT Plac Compare	2	12	Yes	Yes
Pinkerton 2012	United States	122	365	RCT Plac Compare	2	52	Yes	Yes
Simon (Study 2) 2013	United States	Multi	568	RCT Plac Compare	2	24	Yes	Yes
Pinkerton 2013	United States	122	2118	RCT Plac Compare	2	52	Yes	Yes
Simon (Study 1) 2013	United States	Multi	606	RCT Plac Compare	2	12	Yes	Yes

(c): data came from posted results on the clinical trial registry; F/U: followup NR: not reported; Plac: placebo; RCT: randomized controlled trial

Table E-3. Study characteristics for trials comparing other prescriptions with placebo

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Clayden 1974	United Kingdom	18	85	Crossover	2	4		No/NR
Guttuso 2003	United States	1	59	RCT Plac Compare	2	12		No/NR
Butt 2008	Canada	NR	197	RCT Plac Compare	2	4	Yes	No/NR
Joffe 2010	United States	NR	59	Crossover	2	4	Yes	No/NR
Depomed (c) 2012	United States	45	532	RCT Plac Compare	3	12	Yes	No/NR
Depomed (c) 2012	United States	45	559	RCT Plac Compare	3	12	Yes	No/NR
Pinkerton 2013	United States	67	593	RCT Plac Compare	2	24	Yes	No/NR

(c): data came from posted results on the clinical trial registry; F/U: followup; NR: not reported; Plac: placebo; RCT: randomized controlled trial;

Table E-4. Study characteristics for trials comparing nonprescription nonhormone with placebo

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Chenoy 1994	United Kingdom	2	56	RCT Plac Compare	2	26		No/NR
Murkies 1995	Australia	1	58	RCT Active Compare	2	12		No/NR
Hirata 1997	United States	1	71	RCT Plac Compare	2	24		No/NR
Albertazzi 1998	Italy	2	104	RCT Plac Compare	2	12	Yes	No/NR
Baber 1999	Australia	1	51	Crossover	2	12	Yes	No/NR
Wiklund 1999	Multinational	Multi	384	RCT Plac	2	16	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Barnhart 1999	United States	1	60	RCT Plac Compare	2	12	Yes	No/NR
Upmalis 2000	United States	15	175	RCT Plac Compare	2	12	Yes	No/NR
Kotsopoulos 2000	Australia	NR	94	RCT Plac Compare	2	13		No/NR
Davis 2001	Australia	NR	55	RCT Plac Compare	2	12		No/NR
Faure 2002	France	1	75	RCT Plac Compare	2	16	Yes	No/NR
Han 2002	Brazil	1	80	RCT Plac Compare	2	22		No/NR
Tice 2003	United States	3	252	RCT Plac Compare	3	12	Yes	No/NR
Penotti 2003	Italy	1	62	RCT Plac Compare	2	26		No/NR
Burke 2003	United States	1	211	RCT Plac Compare	3	104	Yes	No/NR
Sammartino 2003	Italy	1	63	RCT Plac Compare	2	52		No/NR
Nahas 2004	Brazil	1	50	RCT Plac Compare	2	26	Yes	No/NR
Atkinson 2004	United Kingdom	1	205	RCT Plac Compare	2	52	Yes	No/NR
Hartley 2004	United Kingdom	1	57	RCT Plac Compare	2	12	Yes	No/NR
Winther 2005	Denmark	1	64	RCT Plac Compare	2	13	Yes	No/NR
Frei-Kleiner 2005	Switzerland	14	122	RCT Plac	2	12	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Verhoeven 2005	Netherlands	11	124	RCT Plac Compare	2	12	Yes	No/NR
Kok 2005	Netherlands	NR	202	RCT Plac Compare	2	52	Yes	No/NR
Hidalgo 2005	Ecuador	2	106	Crossover	2	26		No/NR
Dodin 2005	Canada	1	179	RCT Plac Compare	2	52		No/NR
Osmers 2005	Germany	24	286	RCT Plac Compare	2	12		No/NR
Mucci 2006	Italy	Multi	89	RCT Plac Compare	2	24		No/NR
Heger (m) 2006	Ukraine	9	109	RCT Plac Compare	2	12	Yes	No/NR
Lewis 2006	Canada	1	99	RCT Plac Compare	3	16		No/NR
Uebelhack 2006	Germany	NR	301	RCT Plac Compare	2	16	Yes	No/NR
Sammartino 2006	Italy	1	75	RCT Plac Compare	2	12		No/NR
Casini 2006	Italy	3	154	Crossover	2	26		No/NR
Nahas 2007	Brazil	1	76	RCT Plac Compare	2	39	Yes	No/NR
Yang 2007	Taiwan	1	155	RCT Plac Compare	2	24	Yes	No/NR
Chung 2007	South Korea	Multi	77	RCT Plac Compare	2	12	Yes	No/NR
Cheng 2007	Sweden	NR	51	RCT Plac Compare	2	12		No/NR
Ho 2007	Hong Kong	1	176	RCT Plac	2	26	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Cancellieri 2007	Italy	9	125	RCT Plac Compare	2	26		No/NR
Haines 2008	Hong Kong	1	84	RCT Plac Compare	2	26		No/NR
Jou 2008	Taiwan	2	96	RCT Plac Compare	3	26		No/NR
Khaodhiar 2008	United States	1	142	RCT Plac Compare	3	12	Yes	No/NR
Ferrari 2009	Italy	Multi	176	RCT Plac Compare	2	12		Yes
van der Sluijs 2009	Australia	5	92	RCT Plac Compare	2	16	Yes	No/NR
D'Anna (m) 2009	Italy	1	236	RCT Plac Compare	2	104		No/NR
van Die 2009	Australia	NR	100	RCT Plac Compare	2	16	Yes	No/NR
de Sousa-Munoz 2009	Brazil	1	84	RCT Plac Compare	2	16		No/NR
Labrie 2009	Multinational	Multi	216	RCT Plac Compare	4	12	Yes	No/NR
Panjari 2009	Australia	1	89	RCT Plac Compare	2	26		No/NR
Basaria 2009	United States	1	84	RCT Plac Compare	2	12		No/NR
Radhakrishnan 2009	India	1	85	RCT Plac Compare	2	26	Yes	No/NR
Lee 2010	South Korea	1	87	RCT Plac Compare	2	12	Yes	No/NR
Garcia 2010	Multinational	Multi	131	RCT Plac	2	12	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Lipovac 2010	Austria	2	109	Crossover	2	12	Yes	No/NR
Shen 2010	United States	1	91	RCT Plac Compare	2	24		No/NR
Jassi 2010	India	NR	75	RCT Plac Compare	3	12		No/NR
Evans 2011	Canada	5	83	RCT Plac Compare	2	12	Yes	No/NR
Hsu 2011	Taiwan	2	50	RCT Plac Compare	2	52		No/NR
Andrikoula 2011	United Kingdom	1	70	RCT Plac Compare	2	12	Yes	No/NR
Levis 2011	United States	1	248	RCT Plac Compare	2	104		No/NR
Plotnikoff 2011	United States	1	178	RCT Plac Compare	3	13	Yes	No/NR
Chang 2011	United States	NR	64	RCT Plac Compare	2	12		No/NR
Auerbach 2012	Austria	NR	81	RCT Plac Compare	2	12	Yes	No/NR
Cianci 2012	Italy	Multi	120	RCT Plac Compare	2	12		No/NR
Kim 2012	South Korea	1	72	RCT Plac Compare	2	12	Yes	No/NR
Xia 2012	China	1	72	RCT Plac Compare	2	12		No/NR
Ye 2012	China	1	90	RCT Plac Compare	3	24	Yes	No/NR
Aso 2012	Japan	4	126	RCT Plac Compare	2	12	Yes	

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Amato 2012	United States	4	403	RCT Plac Compare	3	24		No/NR
Colau 2012	France	35	101	RCT Plac Compare	2	12	Yes	Yes
Lima 2012	Brazil	1	55	RCT Plac Compare	2	12		No/NR
Pandit 2012	India	1	54	RCT Plac Compare	2	12		No/NR
Schellenberg 2012	Germany	4	166	RCT Plac Compare	3	12	Yes	No/NR
von Hagens 2012	Germany	1	94	Crossover	2	12	Yes	No/NR
Yang 2012	China	7	215	RCT Plac Compare	2	24		No/NR
Colacurci 2013	Italy	unspecified	124	RCT Plac Compare	2	52		No/NR
Crawford 2013	United States	1	130	RCT Plac Compare	3	12		No/NR
Kohama 2013	Japan	1	156	RCT Plac Compare	2	12		No/NR
Zhong 2013	Hong Kong	12	108	RCT Plac Compare	2	12		No/NR
Chi 2013	China	3	70	RCT Plac Compare	2	26		No/NR
Mainini 2013	Italy	1	150	RCT Plac Compare	2	12		No/NR
Constantine 2014	United States	1	919	RCT Plac Compare	2	12	Yes	No/NR
Constantine 2014	Multinational	23	426	RCT Plac Compare	2	52	Yes	No/NR
Constantine 2014	United	76	544	RCT Plac	2	12	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
	States			Compare				

F/U: followup; (m): trial contains data from multiple publications; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial

Table E-5. Study characteristics for trials comparing hormone and nonprescription nonhormone with placebo

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Crisafulli 2004	Italy	1	90	RCT Plac Compare	3	52		No/NR
Newton 2006	United States	1	351	RCT Plac Compare	5	52		No/NR
Yalamanchili 2012	United States	3	489	RCT Plac Compare	4	36	Yes	No/NR
Gupta 2013	India	1	75	RCT Plac Compare	3	52		No/NR

F/U: followup; (m): trial contains data from multiple publications; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial

Table E-6. Study characteristics for trials comparing hormone with hormone

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Polvani 1991	Italy	17	373	RCT Active Compare	2	26		No/NR
Henriksson 1994	Multinational	9	157	RCT Active Compare	2	12		No/NR
Studd 1995	Multinational	19	204	RCT Active Compare	2	12		No/NR
Ayton 1996	Australia	3	194	RCT Active Compare	2	12	Yes	No/NR
Hilditch 1996	Canada	NR	74	RCT Active	2	14	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
				Compare				
Egarter 1996	Austria	Multi	101	RCT Active Compare	2	26	Yes	No/NR
Hirvonen 1997	Finland	1	120	RCT Active Compare	2	52		No/NR
Hirvonen 1997	Finland	1	173	RCT Active Compare	3	104	Yes	No/NR
Rozenberg 1997	Multinational	35	774	RCT Active Compare	5	52	Yes	No/NR
Al-Azzawi 1997	Netherlands	Multi	394	RCT Active Compare	3	28		No/NR
Lubbert 1997	Germany	469	2459	RCT Active Compare	2	12		No/NR
Barentsen 1997	Netherlands	12	165	RCT Active Compare	2	12		Yes
Bachmann 1997	United States		196	RCT Active Compare	2	15	Yes	No/NR
Good 1999	United States	NR	321	RCT Active Compare	4	12	Yes	No/NR
Mattsson 2000	Multinational	Multi	659	RCT Active Compare	2	24	Yes	No/NR
Saure 2000	Denmark	Multi	376	RCT Active Compare	2	26		No/NR
Graser 2000	Multinational	49	581	RCT Active Compare	3	52	Yes	No/NR
Rioux 2000	Canada	6	159	RCT Active Compare	2	24	Yes	No/NR
Dugal 2000	Norway	Multi	96	RCT Active Compare	2	24		No/NR
Parsey 2000	United	19	193	RCT Active	2	12	Yes	No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
	States			Compare				
Meuwissen 2001	Netherlands	56	634	RCT Active Compare	2	52	Yes	No/NR
Lopes 2001	France	51	361	Crossover	2	12		No/NR
Ozsoy 2002	Turkey	1	201	RCT Active Compare	2	24		No/NR
Loh 2002	Singapore	3	96	RCT Active Compare	2	26		No/NR
Buckler (d) 2003	United Kingdom	21	159	RCT Active Compare	2	24	Yes	No/NR
Lobo 2003	United States		218	RCT Active Compare	2	16	Yes	No/NR
Pornel 2005	Multinational	98	764	RCT Active Compare	2	52		No/NR
Gambacciani 2005	Multinational	4	850	RCT Active Compare	3	104		No/NR
Utian 2005	United States	33	248	RCT Active Compare	3	12	Yes	No/NR
Davis 2005	Multinational	2	120	RCT Active Compare	2	16		No/NR
Raynaud 2005	France	Multi	405	RCT Active Compare	3	24		No/NR
Braunstein 2005	United States	39	446	RCT Plac Compare	4	24	Yes	No/NR
Simon 2005	Multinational	52	562	RCT Plac Compare	2	24	Yes	Yes
Weisberg 2005	Australia	4	185	RCT Active Compare	2	48	Yes	No/NR
Buster 2005	Multinational	53	532	RCT Plac Compare	2	24	Yes	Yes

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Akhila 2006	India	1	88	RCT Active Compare	3	52		No/NR
Serrano 2006	Italy	4	114	RCT Active Compare	2	52		No/NR
Cieraad 2006	United Kingdom	29	189	RCT Active Compare	2	24		No/NR
Davis 2006	Multinational	15	76	RCT Plac Compare	2	24	Yes	No/NR
Long 2006	Taiwan	1	73	RCT Active Compare	2	12		No/NR
Shifren 2006	Multinational	58	549	RCT Active Compare	2	24	Yes	No/NR
Limpaphayom (m) 2006	Multinational	22	1028	RCT Active Compare	3	24	Yes	No/NR
Odabasi 2007	Turkey	1	61	RCT Active Compare	2	12		No/NR
Pitkin (d) 2007	Multinational	45	459	RCT Active Compare	3	52	Yes	No/NR
Penteado 2008	Brazil	1	56	RCT Plac Compare	2	52	Yes	No/NR
Panay 2010	Multinational	17	272	RCT Plac Compare	2	24	Yes	No/NR

(d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial

Table E-7. Study characteristics for trials comparing hormone with nonprescription nonhormone

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Nappi 2005	Italy	2	64	RCT Active Compare	2	13		No/NR

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Nathorst-Boos 2006	Sweden	1	106	Crossover	2	26	Yes	No/NR
Kaari 2006	Brazil	1	68	RCT Active Compare	2	26	Yes	No/NR
Chandeying 2007	Thailand	1	60	RCT Active Compare	2	24		No/NR
Menati 2013	Iran, Islamic Republic of	1	52	RCT Active Compare	2	12		No/NR
Zhang 2013	China	1	89	RCT Active Compare	3	12		No/NR

F/U: followup; NR: not reported; Plac: placebo; RCT: randomized controlled trial

Table E-8. Study characteristics for trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Liske 2002	Poland	4	149	RCT Active Compare	2	12		No/NR
Hidalgo 2006	Spain	Multi	925	RCT Active Compare	2	26		No/NR
Zervoudis (a) 2008	Greece	Multi	62	RCT Active Compare	2	52		No/NR
Agosta 2011	Italy	91	636	RCT Active Compare	2	12		No/NR
Le Donne 2011	Italy	1	62	RCT Active Compare	2	13		No/NR
Virojchaiwong 2011	Thailand	1	52	RCT Active Compare	2	26		No/NR
Yang 2012	Taiwan	4	130	RCT Active Compare	2	24		No/NR

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial; (SIP); data came from a

Table E-9. Study characteristics for trials comparing nonprescription nonhormone with antidepressant

Study	Country	Sites	Analyzed	Design	Study Arms	F/U (weeks)	Industry Funding	Editorial Assistance
Oktem 2007	Turkey	1	80	RCT Active Compare	2	26		No/NR

(a): data came from a conference abstract; F/U: followup; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial

Table E-10. Age, BMI, and smoking status for trials comparing hormone with placebo

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Martin 1971						
Campbell 1977						
Baumgardner 1978						
Coope 1981	48.3					
Jensen 1983	49.2	44 to 54				
Foidart 1991	54.4	32 to 66				
Eriksen 1992	58.4 (6.0)		23.8			
Wiklund 1993	52.6 (4.2)		24.6	29.1		
Derman 1995						
Saletu 1995	51.2 (3.3)					
Good 1996	50.9 (7.0)		25.6			
Speroff (Study 1) 1996						
Chung 1996	43.8 (4.9)					
Speroff (Study 2) 1996						
Speroff (Study 3) 1996						
Bacchi-Modena 1997	51.9 (4.0)	39 to 61				
Baerug 1998	51.3 (3.7)	45 to 61				
Bech 1998						

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
de Vrijer 1999	52.0	40 to 64				
Leonetti 1999	52.5 (3.9)		26.2 (4.3)			
Studd 1999	52.2 (3.7)					
Polo-Kantola 1999	56.4 (4.4)	47 to 65	26.9 (4.0)			
Casper 1999						
Cohen 1999	50.0			24		
Rebar 2000	51.2 (4.0)		25.7 (3.5)			
Speroff (Study 1) 2000	51.6 (3.9)			22.9	26.9	49.8
Rovati 2000	53.0 (4.4)		24.8	14.2		
Notelovitz 2000	49.5	28 to 63	26.1	38		
Strickler 2000	54.7 (3.5)		25.5 (3.5)			
Notelovitz 2000	51.1 (4.1)					
DeAloysio 2000	53.3 (4.0)					
von Holst 2000	53.5					
Notelovitz 2000	53.3 (5.6)		26.7 (5.5)	28		
Alexandersen 2000	59.2 (3.1)		25.4 (3.8)			
Speroff (Study 2) 2000	51.0 (4.1)			27.3	22.2	50
Rigano 2001						
Utian (CEE alone arms) 2001	52.0 (4.7)		24.4 (2.6)			
Simon 2001	48.6 (5.2)	38 to 66		29.8		
Soares 2001	49.8 (3.6)					
Utian (CEE/MPA arms) 2001	52.5 (4.9)		24.3 (2.8)			
Rozenbaum 2002	52.4 (5.1)		23.9 (3.6)			
Shulman (Study 1) 2002	52.0	43 to 68			28	72
von Holst 2002	53.3 (5.1)					66.9
Archer 2003	50.9 (6.4)					
Vestergaard 2003	49.8 (2.8)		25.2 (4.4)	44		
Speroff 2003	51.7 (7.1)	29 to 85	28.3	19		
Jirapinyo 2003	54.3 (4.3)		24.1 (3.4)			
Haines 2003						

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Hays 2003	63.2 (7.1)		28.5 (5.8)			
Gambacciani 2003	54.3 (2.0)		24.3 (3.5)			
Gelfand 2003	52.6 (4.1)		25.4 (3.6)	5.9		
Wren 2003						
Simunic 2003	58.8 (7.0)					
Parsons 2003	59.1 (7.2)		27.8 (5.7)			
Berlex (SIP) 2003						
Rudolph 2004	56.1 (5.1)		25.4 (5.4)			
Yang 2004	53.2 (3.2)					
Schurmann 2004	53.6 (4.8)		26.2 (4.2)			
Utian 2004	51.1 (6.6)	26 to 65				
Dessole 2004	57.0 (4.5)		22.1 (4.7)			
Duramed (SIP) 2004						
Brunner 2005	63.6 (7.3)		30.1 (6.2)	10.5	38.4	51.1
Onalan 2005	52.1 (6.0)		25.5 (3.9)			
Bayer Healthcare (SIP) 2005						
Novartis (SIP) 2005						
Speroff (Study 1) 2006	53.4 (4.5)	41 to 68	28.1			
Simon 2006	51.9 (6.0)	36 to 73				
Nielsen 2006	52.7 (1.8)		25.2 (3.9)	28.8		
Osmanagaoglu 2006	50.5 (2.1)		25.0 (1.0)			
Speroff (Study 2) 2006	52.2 (7.0)	36 to 80	28.0			
Bachmann (d) 2007	52.7 (5.5)	40 to 71				
Maki 2007	52.2 (3.4)					
Endrikat 2007	56.2 (4.8)	40 to 68	26.6 (3.8)	11.4		
Lee 2007	52.0 (5.4)		23.6 (2.6)			
Panay 2007	55.5 (4.6)	44 to 65	25.2 (3.6)	18.2		
Simon 2007	54.4 (6.4)		26.2 (3.8)			
Pefanco 2007	75.6 (5.1)					
Bayer Healthcare (SIP) 2007						

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Buster (Study 1) 2008	52.2 (6.0)	38 to 69	27.1 (4.5)			
Veerus 2008						
Davis 2008	54.3 (5.9)		27.2 (5.4)			
Bachmann 2008	57.9 (6.5)	46 to 79				
Welton 2008						
Buster (Study 2) 2008	52.1 (6.9)	37 to 76	27.3 (4.5)			
Buster (Study 3) 2008	53.1 (6.9)	36 to 71	26.7 (4.0)			
Simon (SIP) 2008	58.7 (7.5)		27.1 (6.0)			
Benster 2009						
Utian 2009	53.4 (4.7)		26.2 (4.0)			
Lobo 2009	56.5 (5.8)		25.8 (3.4)			
Haines 2009	52.4 (4.3)		24.0 (3.7)			
Bachmann (d) 2009	53.0 (5.8)	40 to 68				
Hedrick 2009	54.5 (6.8)		27.0 (4.0)			
Baksu 2009	50.1 (4.8)		26.7 (2.9)			
Bachmann (Study 1) 2009	57.8 (5.8)					
Freedman 2009	59.9 (6.7)		26.9 (4.9)			
Gast 2009	54.5	42 to 68				
Bachmann (Study 2) 2009	57.8 (5.6)					
Hassa 2010	50.2 (5.1)		28.4 (4.2)			
Stevenson 2010	53.7 (4.2)	45 to 66	26.4 (7.0)			
Bachmann 2010	56.3 (4.5)		25.4 (3.9)			
Raghunandan 2010	51.7 (6.0)		23.7 (0.6)			
Hedrick 2010						
Liu 2011						
Lin 2011	52.0 (3.7)		23.5 (2.8)	1.2		98.3
Demetrio 2011	50.4 (2.9)	45 to 56				
Liu 2012	54.1 (5.9)	33 to 66	28.5 (5.7)			
Archer 2012	53.7 (4.7)		28.1 (4.9)			
Archer 2012	53.7 (4.7)		28.1 (4.9)			

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Cano 2012	56.7 (6.0)		26.0 (4.2)			
Polisseni 2013	53.1 (3.8)					
Raz 2013						
Archer 2013	53.5 (6.0)		28.6 (5.8)	19.7	23.1	57.2
Pinkerton 2013	53.5 (3.7)		26.2 (3.8)			

(a): data came from a conference abstract; BMI: body mass index; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; SD: standard deviation; (SIP); data came from a

Table E-11. Age, BMI, and smoking status for trials comparing antidepressant with placebo

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Suvanto-Luukkonen 2005	54.0	45 to 66		24.8		
Evans 2005	52.2 (5.5)			30.2		
Kerwin 2007	52.5 (5.1)			14.9		
Kalay 2007	52.6 (4.9)		28.0 (4.2)	22		
Speroff 2008	53.5 (4.8)	37 to 78	27.0 (4.6)			
Soares 2008	56.3 (2.7)					
Archer 2009	53.7 (5.0)		27.1 (4.6)			
Archer 2009	53.4 (4.8)	29 to 71	27.9 (5.0)			
Kornstein 2010	52.3 (6.3)	40 to 70				
Soares 2010	56.0 (6.0)					
Freeman 2011	53.9 (4.1)		29.1 (6.5)	22.9	28.8	48.3
Bouchard 2012	54.0 (4.5)	40 to 66	26.0 (4.0)			
Pinkerton 2012	54.0 (5.0)	45 to 71	26.5 (4.0)			
Simon (Study 2) 2013		40 to 74	27.5			
Pinkerton 2013	54.0 (5.0)	43 to 77	26.7 (4.0)			
Simon (Study 1) 2013		40 to 79	28.7			

BMI: body mass index; (c): data came from posted results on the clinical trial registry; SD: standard deviation

Table E-12. Age, BMI, and smoking status for trials comparing other prescriptions with placebo

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Clayden 1974						
Guttuso 2003	52.8 (3.4)					
Butt 2008	56.2 (4.6)		25.7 (4.5)	10.7		
Joffe 2010	52.2 (4.6)		27.6 (6.9)			
Depomed (c) 2012	52.9 (6.1)					
Depomed (c) 2012	53.2 (6.4)					
Pinkerton 2013	54.0 (6.1)	34 to 70				

BMI: body mass index; (c): data came from posted results on the clinical trial registry; SD: standard deviation

Table E-13. Age, BMI, and smoking status for trials comparing nonprescription nonhormone with placebo

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Chenoy 1994	54.0	45 to 67				
Murkies 1995	54.9 (5.5)		26.0 (3.8)			
Hirata 1997	52.4 (5.0)	44 to 69	24.4 (4.1)			
Albertazzi 1998	52.8 (3.3)	45 to 62	25.9 (3.8)			
Baber 1999						
Wiklund 1999	53.4 (4.0)					
Barnhart 1999	48.5 (2.5)					
Upmalis 2000	54.6 (4.5)					
Kotsopoulos 2000	59.5 (6.9)		25.5 (4.8)			
Davis 2001	55.2		25.9			
Faure 2002	53.4 (4.9)		24.9 (3.7)			
Han 2002	48.5 (7.6)			25		
Tice 2003	52.3 (3.1)		26.1 (4.9)	11.7		
Penotti 2003	52.5 (2.4)	49 to 58	23.2 (2.9)			
Burke 2003	50.8 (2.5)		27.0 (5.9)			
Sammartino 2003	51.8 (1.9)		25.3 (3.0)			
Nahas 2004	53.3 (5.2)		29.0 (5.2)			

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Atkinson 2004	55.2 (4.8)		25.3 (3.7)			
Hartley 2004	57.9 (4.7)		25.2 (3.8)			
Winther 2005	51.4 (3.6)		26.6 (5.2)	20.4		
Frei-Kleiner 2005	52.4 (3.6)		24.7			
Verhoeven 2005	53.8 (4.8)		25.5 (2.9)	18.6		
Kok 2005	66.8 (4.7)		26.2 (3.7)	15.8	33.2	
Hidalgo 2005						
Dodin 2005	54.7 (4.3)		26.2 (4.6)	6.9		
Osmers 2005	54.5 (6.0)		25.2 (2.9)			
Mucci 2006	53.9 (5.9)		24.2 (3.4)			
Heger (m) 2006	48.9 (3.1)		25.9 (2.8)			
Lewis 2006	53.1 (3.2)	45 to 60	17.3 (2.8)	9.1	23.2	67.7
Uebelhack 2006	52.2 (4.3)	44 to 60	25.0 (3.5)			
Sammartino 2006	50.7 (1.8)		25.1 (3.0)			
Casini 2006						
Nahas 2007	55.7 (6.8)		29.1 (5.0)			
Yang 2007	46.8 (4.7)		24.1 (3.0)	2.9		
Chung 2007	50.7 (3.2)		22.6 (2.0)			
Cheng 2007	57.7 (4.6)		24.9 (3.1)			
Ho 2007	63.5 (5.9)		24.5 (3.3)			96.5
Cancellieri 2007	54.3 (4.7)		24.9 (3.6)			
Haines 2008	52.1 (4.8)		22.9 (3.1)			
Jou 2008	53.9 (3.5)		22.6 (2.8)			
Khaodhiar 2008	53.1 (5.2)		28.6 (5.2)		18.3	81.7
Ferrari 2009	54.1 (4.5)		24.5 (4.2)			
van der Sluijs 2009	55.7 (4.2)		25.6 (3.9)			
D'Anna (m) 2009	53.1 (2.1)		23.8 (3.6)			
van Die 2009	52.2 (4.0)		26.5 (4.7)			
de Sousa-Munoz 2009						
Labrie 2009	58.0	42 to 74				

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Panjari 2009	54.5 (4.6)		25.6 (3.5)			
Basaria 2009	55.7 (8.8)	46 to 76	26.0 (5.2)	4.5		
Radhakrishnan 2009	48.9 (6.3)		25.5 (4.5)			
Lee 2010	53.0 (3.6)	45 to 60				
Garcia 2010	54.4 (3.6)	47 to 61	23.1 (3.7)			
Lipovac 2010	54.1 (7.1)		24.7 (3.9)			
Shen 2010	57.0 (6.5)		28.6 (5.2)			
Jassi 2010	51.1 (7.7)		23.4 (2.9)			
Evans 2011	53.5 (4.7)		26.0 (3.8)	21	22.2	56.8
Hsu 2011	52.5 (3.0)		23.8 (3.5)			
Andrikoula 2011	54.1 (7.1)		26.0 (7.1)			
Levis 2011	52.5 (3.3)		26.3 (3.3)			
Plotnikoff 2011	53.5 (3.2)					
Chang 2011	53.7 (5.8)	42 to 70	27.9 (5.0)			
Auerbach 2012	54.5 (7.5)		25.0 (3.8)			
Cianci 2012	55.0 (6.2)		25.6 (8.5)			
Kim 2012	54.0 (3.4)		22.1 (2.4)			
Xia 2012	50.5 (3.0)		25.2 (2.4)			
Ye 2012	52.3 (3.3)		22.6 (2.3)			
Aso 2012	53.5 (3.5)	45 to 60	21.5 (2.0)			
Amato 2012	54.8 (3.9)		25.2 (3.7)			
Colau 2012	54.5 (4.4)					84.2
Lima 2012	57.0		27.6			
Pandit 2012	48.9 (7.1)	40 to 60				
Schellenberg 2012	51.8 (6.4)		25.2 (4.4)	25.3		74.7
von Hagens 2012	53.5 (4.6)		26.0 (3.8)	11.7		88.3
Yang 2012	48.1 (2.9)		23.2 (2.8)			
Colacurci 2013	56.1 (7.7)		24.9 (2.9)			
Crawford 2013	54.5 (4.7)		27.9 (4.9)	3.9		
Kohama 2013	46.5 (3.2)		22.8 (3.4)	16		67.5

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Zhong 2013	50.5 (3.0)		22.3 (2.8)			
Chi 2013	49.1 (3.1)					
Mainini 2013	54.6 (5.0)		25.9 (1.7)			
Constantine 2014	58.6 (6.5)		26.2 (4.3)			
Constantine 2014	61.9 (6.2)		24.5 (2.9)			
Constantine 2014	58.7 (6.2)		26.0 (4.4)			

(a): data came from a conference abstract; BMI: body mass index; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; Multi: multicenter trial; NR: not reported; Plac: placebo; RCT: randomized controlled trial; SD: standard deviation; (SIP); data came from a

Table E-14. Age, BMI, and smoking status for trials comparing hormone and nonprescription nonhormone with placebo

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Crisafulli 2004	51.7 (4.0)		23.7 (2.7)			
Newton 2006	52.2 (2.4)		28.6 (6.0)			
Yalamanchili 2012	71.5 (3.7)					
Gupta 2013						

(a): data came from a conference abstract; BMI: body mass index; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; SD: standard deviation; (SIP); data came from a package insert

Table E-15. Age, BMI, and smoking status for trials comparing hormone with hormone

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Polvani 1991						
Henriksson 1994	59.4 (6.7)	45 to 80		12.7		
Studd 1995	52.0 (4.8)	38 to 65	25.8			
Ayton 1996	59.5 (7.3)	36 to 86		12.7		
Hilditch 1996	56.4 (3.4)		24.6 (3.4)			
Egarter 1996	49.0	41 to 55				
Hirvonen 1997	56.3 (4.2)	46 to 65				
Hirvonen 1997	54.2 (5.4)	41 to 70		26		
Rozenberg 1997	52.8 (4.9)		24.8 (3.0)			
Al-Azzawi 1997						

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Lubbert 1997	54.0 (7.0)					
Barentsen 1997						
Bachmann 1997	56.8	35 to 76				
Good 1999	50.4 (7.6)					
Mattsson 2000	51.1 (4.2)		25.2 (4.1)			
Saure 2000	49.0 (5.0)					
Graser 2000	54.1 (5.5)		25.3 (3.4)			
Rioux 2000	57.3 (7.4)					
Dugal 2000	58.8 (5.1)					
Parsey 2000	52.0 (4.9)					
Meuwissen 2001	52.9 (4.9)		25.2 (3.3)			
Lopes 2001	51.5 (4.5)		25.3 (4.3)			
Ozsoy 2002	50.6 (3.3)		23.3 (3.1)			
Loh 2002	53.7 (4.2)		23.0 (3.2)			
Buckler (d) 2003	51.5 (5.4)	31 to 63		25.6		
Lobo 2003	53.4 (5.7)	40 to 65	26.1 (5.0)			
Pornel 2005	52.7 (4.5)		25.1 (3.5)	24		
Gambacciani 2005	53.4 (4.4)		25.1 (3.4)	23.8		
Utian 2005	52.8 (6.6)	34 to 74	28.3			
Davis 2005	53.7 (4.0)	42 to 65		9.5		70
Raynaud 2005	52.5 (4.5)		24.3 (3.6)			
Braunstein 2005	49.3 (7.7)					
Simon 2005	49.1 (7.6)	26 to 70	27.9 (6.0)			
Weisberg 2005	57.9	46 to 81				
Buster 2005	48.9 (7.5)		27.6 (5.8)			
Akhila 2006						
Serrano 2006	52.2 (3.2)		25.0 (4.1)	19		
Cieraad 2006	49.1 (4.0)		26.1 (4.4)			
Davis 2006	50.1	30 to 66	24.4 (2.7)			
Long 2006	53.8 (6.7)					

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Shifren 2006	53.9 (4.9)		25.8 (4.7)			
Limpaphayom (m) 2006	53.4 (5.0)		23.7 (3.4)			
Odabasi 2007	49.5 (3.1)		29.3 (3.5)			
Pitkin (d) 2007	51.5 (4.1)		24.8 (3.0)			
Penteado 2008	52.1 (3.9)	42 to 60	27.3 (4.2)			
Panay 2010	56.6 (5.3)		26.5 (4.8)			

(a): data came from a conference abstract; BMI: body mass index; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; SD: standard deviation; (SIP); data came from a package insert

Table E-16. Age, BMI, and smoking status for trials comparing hormone with nonprescription nonhormone

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Nappi 2005	50.7 (2.0)		22.4 (2.2)			
Nathorst-Boos 2006						
Kaari 2006	53.8 (5.3)		25.6 (3.8)			
Chandeying 2007	48.4 (5.0)	40 to 59		1.6		
Menati 2013	50.7 (2.6)	45 to 57	27.5 (4.4)			
Zhang 2013	52.8 (3.3)					

BMI: body mass index; SD: standard deviation;

Table E-17. Age, BMI, and smoking status for trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Liske 2002	50.0 (4.5)	42 to 60				
Hidalgo 2006						
Zervoudis (a) 2008						
Agosta 2011	53.1 (5.0)		25.2 (3.6)			
Le Donne 2011	58.8 (4.0)					
Virojchaiwong 2011	46.5 (4.4)		23.9 (3.9)			
Yang 2012	51.9 (4.7)		22.6 (2.8)			

(a): data came from a conference abstract; BMI: body mass index; SD: standard deviation; (SIP); data came from a package insert

Table E-18. Age, BMI, and smoking status for trials comparing nonprescription nonhormone with antidepressant

Study	Age, Mean (SD)	Range	BMI, Mean (SD)	Current	Former	Never
Oktem 2007	52.9 (6.0)		27.1 (3.8)	41.2		

BMI: body mass index; SD: standard deviation;

Table E-19. Racial makeup for trials comparing hormone with placebo

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Martin 1971						
Campbell 1977						
Baumgardner 1978						
Coope 1981						
Jensen 1983						
Foidart 1991						
Eriksen 1992						
Wiklund 1993						
Derman 1995						
Saletu 1995						
Good 1996	87.5	10.3			2.2	
Speroff (Study 1) 1996						
Chung 1996						
Speroff (Study 2) 1996						
Speroff (Study 3) 1996						
Bacchi-Modena 1997						
Baerug 1998						
Bech 1998						
de Vrijer 1999						
Leonetti 1999	45.1					54.9
Studd 1999	100					
Polo-Kantola 1999						

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Casper 1999						
Cohen 1999	83.5	13			3.5	
Rebar 2000						
Speroff (Study 1) 2000						
Rovati 2000						
Notelovitz 2000	82.6	8.3		2	6.7	0.4
Strickler 2000						
Notelovitz 2000						
DeAloysio 2000						
von Holst 2000						
Notelovitz 2000	87.7	4.3			8	
Alexandersen 2000						
Speroff (Study 2) 2000						
Rigano 2001						
Utian (CEE alone arms) 2001						
Simon 2001	68.6	27.4		0.8	3.2	
Soares 2001						
Utian (CEE/MPA arms) 2001						
Rozenbaum 2002	100					
Shulman (Study 1) 2002	80.6	13.3	4.4	0.7	1	
von Holst 2002						
Archer 2003	81.4	15.9		1.8	0.9	
Vestergaard 2003						
Speroff 2003	77.3	12	9	0.6	0.9	0.2
Jirapinyo 2003						
Haines 2003				100		
Hays 2003	83.9	6.8	5.3	2.2	1.8	
Gambacciani 2003						
Gelfand 2003	96.6	0.8		1.7	0.9	
Wren 2003						

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Simunic 2003						
Parsons 2003	88.2	6.4	3.2	1.1	1.1	
Berlex (SIP) 2003						
Rudolph 2004						
Yang 2004						
Schurmann 2004	100					
Utian 2004	81.2	17.4			1.4	
Dessole 2004	98.5					1.5
Duramed (SIP) 2004						
Brunner 2005	75.3	15.1	6.1	1.5	2	
Onalan 2005						
Bayer Healthcare (SIP) 2005						
Novartis (SIP) 2005						
Speroff (Study 1) 2006	78.1	8.7	12.5		0.7	
Simon 2006	75.5	19.5			5	
Nielsen 2006						
Osmanagaoglu 2006						
Speroff (Study 2) 2006	80.1	13.6	4.5		1.8	
Bachmann (d) 2007						
Maki 2007	81.7	9.5	6.1	1.1		1.6
Endrikat 2007						
Lee 2007				100		
Panay 2007	95	0.3		1	0.7	3
Simon 2007	84.5	9.7			5.8	
Pefanco 2007						
Bayer Healthcare (SIP) 2007						
Buster (Study 1) 2008	64.9	29.8	2.7	0.6	1.3	0.7
Veerus 2008						
Davis 2008	88.8	7.6	1.8	0.5	1.2	0.1
Bachmann 2008	92.2				7.8	

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Welton 2008						
Buster (Study 2) 2008	74	22	2		2	
Buster (Study 3) 2008	71.2	21.6	4.6		2.6	
Simon (SIP) 2008	81.8	3.6	10.5	2.4	1.6	0.1
Benster 2009						
Utian 2009	80.5	10.7	5.7	1.2	1.9	
Lobo 2009	80.7	13.8	3.2		1.8	0.5
Haines 2009						
Bachmann (d) 2009						
Hedrick 2009	86.1	10.2		1.5	2.2	
Baksu 2009						
Bachmann (Study 1) 2009	91.6					8.4
Freedman 2009	86.6	5.5	6.5	0.7	0.7	
Gast 2009						
Bachmann (Study 2) 2009	92.8					7.2
Hassa 2010						
Stevenson 2010						
Bachmann 2010	91.5	3.5			5	
Raghunandan 2010						
Hedrick 2010						
Liu 2011						
Lin 2011						
Demetrio 2011	79.9	6.3		3.1	10.7	
Liu 2012	66.9	14.6	16.6	0.6	1.3	
Archer 2012	80.6	17.7			1.7	
Archer 2012	80.6	17.7			1.7	
Cano 2012	100					
Polisseni 2013	59				41	
Raz 2013						
Archer 2013	67.6	24.2	7	0.6	0.6	

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Pinkerton 2013	87.8	10.7			1.5	

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-20. Racial makeup for trials comparing antidepressant with placebo

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Suvanto-Luukkonen 2005						
Evans 2005	76.5	8.5		8.5	6.5	
Kerwin 2007	80.6		13.6		5.8	
Kalay 2007						
Speroff 2008	85.1	9.7			5.2	
Soares 2008	85.6	8.9	5.5			
Archer 2009	87.3	10.9			1.8	
Archer 2009	82.6	15.7			1.7	
Kornstein 2010	82.3	14.3			3.3	0.1
Soares 2010	80.5	7.9			11.5	0.1
Freeman 2011	49.8	46.3			3.9	
Bouchard 2012	92.5	0.5			7	
Pinkerton 2012	86.5	12			1.5	
Simon (Study 2) 2013	75.5	21.5		1.6	1.4	
Pinkerton 2013	83.5	14			2.5	
Simon (Study 1) 2013	64.7	32.8		0.3	2.2	

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-21. Racial makeup for trials comparing other prescriptions with placebo

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Clayden 1974						
Guttuso 2003	93.2	6.8				

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Butt 2008	76.7				23.3	
Joffe 2010	71.2					28.8
Depomed (c) 2012	67.1	23.6	7	0.6	1.7	
Depomed (c) 2012						
Pinkerton 2013	69.5	26.3	3		1.1	0.1

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-22. Racial makeup for trials comparing nonprescription nonhormone with placebo

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Chenoy 1994						
Murkies 1995						
Hirata 1997	69	15.5	4.2	8.4		2.9
Albertazzi 1998						
Baber 1999						
Wiklund 1999						
Barnhart 1999						
Upmalis 2000	75.3	13.2			11.5	
Kotsopoulos 2000						
Davis 2001						
Faure 2002						
Han 2002	33.7	58.8		7.5		
Tice 2003	84.3	10			5.7	
Penotti 2003						
Burke 2003						
Sammartino 2003						
Nahas 2004						
Atkinson 2004						
Hartley 2004						
Winther 2005						

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Frei-Kleiner 2005						
Verhoeven 2005						
Kok 2005						
Hidalgo 2005						
Dodin 2005						
Osmers 2005						
Mucci 2006						
Heger (m) 2006						
Lewis 2006						
Uebelhack 2006	100					
Sammartino 2006						
Casini 2006						
Nahas 2007						
Yang 2007				100		
Chung 2007				45.5		54.5
Cheng 2007						
Ho 2007				100		
Cancellieri 2007						
Haines 2008				100		
Jou 2008				100		
Khaodhiar 2008	61.9	30.1			8	
Ferrari 2009						
van der Sluijs 2009						
D'Anna (m) 2009						
van Die 2009						
de Sousa-Munoz 2009						
Labrie 2009						
Panjari 2009						
Basaria 2009	79.6	9.7			10.7	
Radhakrishnan 2009						

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Lee 2010						
Garcia 2010				21.4		78.6
Lipovac 2010						
Shen 2010						
Jassi 2010						
Evans 2011						
Hsu 2011						
Andrikoula 2011						
Levis 2011	22.6	9.6	66.1		1.6	0.1
Plotnikoff 2011	93.9					6.1
Chang 2011						
Auerbach 2012						
Cianci 2012						
Kim 2012						
Xia 2012						
Ye 2012						
Aso 2012				100		
Amato 2012						
Colau 2012						
Lima 2012						
Pandit 2012						
Schellenberg 2012						
von Hagens 2012						
Yang 2012						
Colacurci 2013						
Crawford 2013	91.7	4.1	2.5		1.7	
Kohama 2013						
Zhong 2013						
Chi 2013						
Mainini 2013						

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Constantine 2014	87.6					12.4
Constantine 2014	99.4	0.3		0.3		
Constantine 2014	90.2					9.8

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-23. Racial makeup for trials comparing hormone and nonprescription nonhormone with placebo

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Crisafulli 2004						
Newton 2006	93.2	2.5			4.3	
Yalamanchili 2012						
Gupta 2013						

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-24. Racial makeup for trials comparing hormone with hormone

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Polvani 1991						
Henriksson 1994						
Studd 1995	97.5				2.5	
Ayton 1996	66.5				1	32.5
Hilditch 1996						
Egarter 1996						
Hirvonen 1997						
Hirvonen 1997						
Rozenberg 1997						
Al-Azzawi 1997						
Lubbert 1997						
Barentsen 1997						

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Bachmann 1997	85.6	6.7	6.1		1.6	
Good 1999	87.5	11.8			0.6	0.1
Mattsson 2000						
Saure 2000						
Graser 2000						
Rioux 2000						
Dugal 2000						
Parsey 2000	84	10.5	4.5		1	
Meuwissen 2001						
Lopes 2001	100					
Ozsoy 2002						
Loh 2002				100		
Buckler (d) 2003						
Lobo 2003	91.7	4.6	2.3		1.4	
Pornel 2005	99.2	0.3			0.5	
Gambacciani 2005	99.5	0.2			0.3	
Utian 2005	73.4				26.6	
Davis 2005						
Raynaud 2005						
Braunstein 2005						
Simon 2005	88.6	8.5	2.5		0.4	
Weisberg 2005						
Buster 2005	90.3	5	3.5		1.2	
Akhila 2006						
Serrano 2006						
Cieraad 2006						
Davis 2006						
Long 2006						
Shifren 2006	93.8	3.5	2		0.7	
Limpaphayom (m) 2006				100		

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Odabasi 2007						
Pitkin (d) 2007	99.4	0.3		0.3		
Penteado 2008						
Panay 2010	98.6	0.7		0.7		

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-25. Racial makeup for trials comparing hormone with nonprescription nonhormone

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Nappi 2005						
Nathorst-Boos 2006						
Kaari 2006						
Chandeying 2007						
Menati 2013						
Zhang 2013						

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-26. Racial makeup for trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Liske 2002						
Hidalgo 2006						
Zervoudis (a) 2008						
Agosta 2011						
Le Donne 2011						
Virojchaiwong 2011						
Yang 2012						

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-27. Racial makeup for trials comparing nonprescription nonhormone with antidepressant

Study	White (%)	Black (%)	Hispanic (%)	Asian (%)	Other (%)	Not Classified (%)
Oktem 2007						

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; F/U: followup; (m): trial contains data from multiple publications; (SIP); data came from a package insert

Table E-28. Uterus status, age since menopause, and prior HRT use for trials comparing hormone with placebo

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Martin 1971	Mixed	56			
Campbell 1977	NR				
Baumgardner 1978	Mixed	63			
Coope 1981	Mixed	65.5			
Jensen 1983	NR			1.9	
Foidart 1991	Mixed	52.3			
Eriksen 1992	NR				
Wiklund 1993	All			3.1 (3.4)	31.8
Derman 1995	NR				
Saletu 1995	Mixed	71.9			
Good 1996	Mixed	43.6	43.0 (8.3)		
Speroff (Study 1) 1996	None				
Chung 1996	None		42.1 (8.0)	0.6 (1.5)	
Speroff (Study 2) 1996	None				
Speroff (Study 3) 1996	None				
Bacchi-Modena 1997	All			2.7	
Baerug 1998	NR		49.0 (3.3)	2.5 (2.9)	30.3
Bech 1998	NR				
de Vrijer 1999	Mixed	65		4.4	
Leonetti 1999	NR			3.2 (1.4)	
Studd 1999	NR			2.5 (1.8)	52.7

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Polo-Kantola 1999	None				
Casper 1999	Mixed				
Cohen 1999	Mixed	81.5			
Rebar 2000	Mixed	67.6			
Speroff (Study 1) 2000	All			2.0 (1.6)	
Rovati 2000	Mixed	71.1		3.5 (3.6)	
Notelovitz 2000	Mixed	30		5.9	49.7
Strickler 2000	NR			4.5 (1.9)	40.3
Notelovitz 2000	All			2.9 (2.8)	
DeAloysio 2000	Mixed	94.9		1.1 (1.1)	
von Holst 2000	None				
Notelovitz 2000	All			5.2 (4.9)	36.9
Alexandersen 2000	NR			9.3 (3.4)	
Speroff (Study 2) 2000	All			2.1 (1.2)	
Rigano 2001	All				
Utian (CEE alone arms) 2001	All		48.1 (4.7)	3.9 (3.5)	
Simon 2001	NR			7.2	
Soares 2001	NR			0.4 (0.4)	
Utian (CEE/MPA arms) 2001	All		48.2 (4.3)	4.2 (3.9)	
Rozenbaum 2002	Mixed	77.6	49.6 (3.9)	3.4 (3.1)	53.3
Shulman (Study 1) 2002	Mixed				
von Holst 2002	All				
Archer 2003	Mixed	76.9		10.2 (8.4)	62
Vestergaard 2003	Mixed	81		0.7 (0.6)	
Speroff 2003	Mixed	81			78.3
Jirapinyo 2003	All				
Haines 2003	None				
Hays 2003	All				26
Gambacciani 2003	NR			4.6 (3.0)	
Gelfand 2003	All			2.7 (3.0)	15.1

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Wren 2003	NR				
Simunic 2003	All		49.9 (4.6)	9.2 (3.6)	
Parsons 2003	All			9.3 (6.7)	
Berlex (SIP) 2003	NR				
Rudolph 2004	Mixed			9.7 (8.0)	
Yang 2004	All		49.8 (3.2)	4.1 (0.9)	
Schurmann 2004	All				
Utian 2004	Mixed				
Dessole 2004	NR			7.2 (5.0)	
Duramed (SIP) 2004	NR				
Brunner 2005	None				48.4
Onalan 2005	All			4.4 (3.7)	
Bayer Healthcare (SIP) 2005	NR				
Novartis (SIP) 2005	NR				
Speroff (Study 1) 2006	Mixed	57			
Simon 2006	Mixed	50.5			
Nielsen 2006	Mixed	94.3		2.2 (1.7)	6.6
Osmanagaoglu 2006	All				
Speroff (Study 2) 2006	Mixed	41			
Bachmann (d) 2007	Mixed	42.4	44.1 (8.0)	9.1 (8.2)	
Maki 2007	All			1.8 (0.8)	
Endrikat 2007	Mixed	67		4.6 (3.3)	
Lee 2007	Mixed				
Panay 2007	All				
Simon 2007	Mixed			8.7 (8.2)	81
Pefanco 2007	Mixed	68.4			
Bayer Healthcare (SIP) 2007	NR				
Buster (Study 1) 2008	Mixed	61.7			
Veerus 2008	NR				
Davis 2008	Mixed	55.9			

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Bachmann 2008	Mixed	52.6		14.0 (8.6)	
Welton 2008	Mixed				
Buster (Study 2) 2008	Mixed	61.7			
Buster (Study 3) 2008	Mixed	61.7			
Simon (SIP) 2008	Mixed	58.1		13.0 (9.3)	
Benster 2009	Mixed				
Utian 2009	All			4.5	
Lobo 2009	All			6.9 (4.9)	
Haines 2009	Mixed	62.5		5.1 (5.1)	
Bachmann (d) 2009	Mixed	44.6		9.8 (8.6)	
Hedrick 2009	Mixed	47			
Baksu 2009	None				
Bachmann (Study 1) 2009	All			9.2 (6.2)	
Freedman 2009	Mixed	62.6		13.0 (8.8)	
Gast 2009	All			5.3	52.6
Bachmann (Study 2) 2009	All			5.3	
Hassa 2010	None				
Stevenson 2010	All			5.5 (4.6)	
Bachmann 2010	All			7.4 (4.8)	
Raghunandan 2010	Mixed			7.0 (1.5)	
Hedrick 2010	Mixed	48.4			
Liu 2011	Mixed				
Lin 2011	All			2.8 (3.0)	
Demetrio 2011	None			3.7	
Liu 2012	Mixed				
Archer 2012	Mixed	65.4		8.5 (7.7)	
Archer 2012	Mixed	65.4		8.5 (7.7)	
Cano 2012	Mixed	86.2		9.9 (6.6)	
Polisseni 2013	All			4.7 (3.5)	
Raz 2013	All				

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Archer 2013	Mixed	45.6	44.7 (7.5)	9.4 (8.5)	
Pinkerton 2013	All			3.6 (3.1)	

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-29. Uterus status, age since menopause, and prior HRT use for trials comparing antidepressant with placebo

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Suvanto-Luukkonen 2005	All		50.0		35.5
Evans 2005	Mixed	79.2	47.5 (5.0)	4.5 (4.0)	
Kerwin 2007	NR				
Kalay 2007	Mixed			6.5 (4.2)	
Speroff 2008	Mixed	78.2		4.7 (4.5)	
Soares 2008	Mixed				
Archer 2009	Mixed	76.2			
Archer 2009	Mixed	79.9			
Kornstein 2010	Mixed				
Soares 2010	Mixed				
Freeman 2011	Mixed	75.6			
Bouchard 2012	All			5.5 (4.0)	
Pinkerton 2012	Mixed	59.5		8.3 (6.6)	
Simon (Study 2) 2013	Mixed	80.5			
Pinkerton 2013	Mixed	65.5		7.3 (6.3)	
Simon (Study 1) 2013	Mixed	81.7			

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-30. Uterus status, age since menopause, and prior HRT use for trials comparing other prescriptions with placebo

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Clayden 1974	NR				

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Guttuso 2003	Mixed	76.2		4.7 (5.0)	
Butt 2008	All			6.4 (6.1)	61.9
Joffe 2010	Mixed	86.2			
Depomed (c) 2012	Mixed				
Depomed (c) 2012	Mixed				
Pinkerton 2013	Mixed	74.7			

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-31. Uterus status, age since menopause, and prior HRT use for trials comparing nonprescription nonhormone with placebo

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Chenoy 1994	NR				19.6
Murkies 1995	NR			5.7 (6.4)	
Hirata 1997	All			3.7 (3.2)	42.2
Albertazzi 1998	NR			3.9 (3.9)	
Baber 1999	NR				
Wiklund 1999	NR				
Barnhart 1999	NR				
Upmalis 2000	All				
Kotsopoulos 2000	NR				
Davis 2001	NR			5.2	49.1
Faure 2002	Mixed				
Han 2002	All			1.9 (1.6)	
Tice 2003	Mixed	93.7	49.1 (4.9)	3.3 (4.5)	
Penotti 2003	All			2.4 (1.4)	
Burke 2003	Mixed	73.4			85.4
Sammartino 2003	All			1.5	

Nahas 2004	NR		48.1 (3.5)	13.2 (1.6)	
Atkinson 2004	NR				
Hartley 2004	NR			7.8 (1.0)	
Winther 2005	Mixed	96.9		1.5 (1.4)	
Frei-Kleiner 2005	Mixed	81.1		3.2 (4.2)	
Verhoeven 2005	Mixed			4.0	41.1
Kok 2005	NR		48.5 (5.0)	18.6 (6.7)	22.4
Hidalgo 2005	Mixed				
Dodin 2005	Mixed	87		5.3	
Osmers 2005	Mixed	64			
Mucci 2006	NR			4.7 (5.2)	
Heger (m) 2006	NR				
Lewis 2006	All		49.5 (3.5)	3.7 (2.7)	37.4
Uebelhack 2006	Mixed	84.7			
Sammartino 2006	NR			1.3	
Casini 2006	All				
Nahas 2007	All		48.0 (3.6)	6.8 (4.5)	
Yang 2007	All				
Chung 2007	All				
Cheng 2007	NR			7.7 (4.6)	
Ho 2007	NR			13.8 (6.7)	
Cancellieri 2007	NR			2.8	
Haines 2008	Mixed		46.6 (5.2)	5.5 (3.8)	
Jou 2008	NR		50.5 (5.5)		
Khaodhiar 2008	NR			5.1 (5.6)	
Ferrari 2009	Mixed			5.3 (5.2)	
van der Sluijs 2009	Mixed	81.5		5.8 (5.8)	54.4
D'Anna (m) 2009	Mixed	91.5		3.2 (1.7)	

van Die 2009	Mixed	83 (however all women experienced natural menopause)		4.1 (5.4)	32
de Sousa-Munoz 2009	Mixed				
Labrie 2009	NR				
Panjari 2009	Mixed	82	47.6 (6.3)	6.9 (6.5)	
Basaria 2009	Mixed	25		5.6 (6.0)	
Radhakrishnan 2009	Mixed	57		5.1 (4.8)	
Lee 2010	All		49.0 (2.8)		
Garcia 2010	All		49.2 (3.3)	5.1 (3.5)	
Lipovac 2010	Mixed	84.4			58.7
Shen 2010	NR			11.8 (8.3)	
Jassi 2010	Mixed			2.5 (1.2)	
Evans 2011	Mixed	66.3			
Hsu 2011	All			2.6 (1.4)	
Andrikoula 2011	NR		46.9 (4.8)		
Levis 2011	NR				
Plotnikoff 2011	Mixed	92.1			
Chang 2011	All			4.4	
Auerbach 2012	NR				
Cianci 2012	NR			5.3 (4.0)	
Kim 2012	NR		50.8 (3.1)		
Xia 2012	All				
Ye 2012	NR			2.6 (1.5)	
Aso 2012	All			3.7 (2.0)	
Amato 2012	Mixed		48.1 (5.6)	6.7 (5.7)	
Colau 2012	All				
Lima 2012	All		48.5	9.0	
Pandit 2012	NR				
Schellenberg 2012	NR				

von Hagens 2012	Mixed				
Yang 2012	All				
Colacurci 2013	NR				3.0 (2.7)
Crawford 2013	Mixed	83.8			
Kohama 2013	NR				
Zhong 2013	NR				6.1 (3.4)
Chi 2013	NR				
Mainini 2013	NR				5.5 (5.4)
Constantine 2014	Mixed	53			
Constantine 2014	All				
Constantine 2014	Mixed	45.9			

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-32. Uterus status, age since menopause, and prior HRT use for trials comparing hormone and nonprescription nonhormone with placebo

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Crisafulli 2004	All			6.7 (4.3)	
Newton 2006	Mixed	89			40.1
Yalamanchili 2012	Mixed	40.7			
Gupta 2013	None				

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-33. Uterus status, age since menopause, and prior HRT use for trials comparing hormone with hormone

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Polvani 1991	All				

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Henriksson 1994	Mixed	87.2		9.8 (6.8)	47.2
Studd 1995	Mixed	99		4.4 (3.5)	
Ayton 1996	All			9.3 (7.3)	50.6
Hilditch 1996	All		50.1 (3.0)	3.5 (1.5)	
Egarter 1996	All				
Hirvonen 1997	NR		49.4 (3.6)		86.7
Hirvonen 1997	Mixed	59	47.9 (4.4)		65.3
Rozenberg 1997	All			4.6 (4.1)	69.8
Al-Azzawi 1997	None				
Lubbert 1997	Mixed	47.7			
Barentsen 1997	Mixed				
Bachmann 1997	Mixed	54		10.3	57.6
Good 1999	Mixed	45.8	42.5 (9.0)		
Mattsson 2000	Mixed	70.8	48.5 (4.1)	3.1 (2.8)	42
Saure 2000	All				34
Graser 2000	NR			5.7 (4.4)	
Rioux 2000	All			7.8 (7.1)	37
Dugal 2000	NR		49.5 (3.8)		26
Parsey 2000	Mixed	28.5			
Meuwissen 2001	All				56.3
Lopes 2001	NR			2.9 (2.9)	33.5
Ozsoy 2002	All		48.0 (4.0)	2.9 (2.7)	32.5
Loh 2002	NR			3.9 (7.0)	
Buckler (d) 2003	Mixed	55			
Lobo 2003	Mixed			7.1 (6.0)	100
Pornel 2005	All			4.4 (4.0)	
Gambacciani 2005	All			1.2 (1.0)	
Utian 2005	Mixed	49.6			
Davis 2005	Mixed	73			58
Raynaud 2005	Mixed	22.5		3.8 (3.8)	

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Braunstein 2005	None				
Simon 2005	None				
Weisberg 2005	All			3.7	
Buster 2005	None				
Akhila 2006	Mixed	30.6			
Serrano 2006	All		50.1 (3.0)	1.9 (1.3)	
Cieraad 2006	All				
Davis 2006	None				100
Long 2006	None				
Shifren 2006	Mixed	68.5		6.2 (4.2)	100
Limpaphayom (m) 2006	All				
Odabasi 2007	All		46.8 (3.2)	2.7 (2.8)	
Pitkin (d) 2007	All		50.1 (4.1)	1.9 (0.6)	45.7
Penteado 2008	All			5.1 (4.6)	
Panay 2010	All				

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-34. Uterus status, age since menopause, and prior HRT use for trials comparing hormone with nonprescription nonhormone

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Nappi 2005	All			0.8 (0.2)	
Nathorst-Boos 2006	All				
Kaari 2006	All		47.7 (5.0)	6.0	
Chandeying 2007	Mixed				
Menati 2013	All			2.3 (1.2)	
Zhang 2013	NR			1.6 (0.9)	

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-35. Uterus status, age since menopause, and prior HRT use for trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Liske 2002	NR				
Hidalgo 2006	NR				
Zervoudis (a) 2008	NR				
Agosta 2011	Mixed	83.5			72
Le Donne 2011	NR		49.0 (2.8)		
Virojchaiwong 2011	None				
Yang 2012	All			3.6 (3.9)	

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-36. Uterus status, age since menopause, and prior HRT use for trials comparing nonprescription nonhormone with antidepressant

Study	Intact Uterus	(%)	Mean Age Menopause (SD)	Years Since Menopause (SD)	Prior HT (%)
Oktem 2007	Mixed	75	46.8 (4.7)		40

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; NR: not reported; SD: standard deviation; (SIP); data came from a package insert

Table E-37. Reported outcomes for trials comparing hormone with placebo

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Martin 1971	Yes	+					
Campbell 1977	No	+	+	+	+	+	
Baumgardner 1978	Yes	+					
Coope 1981	Uncertain	+		+			
Jensen 1983	Uncertain						+
Foidart 1991	Yes				+		+
Eriksen 1992	Uncertain				+	+	
Wiklund 1993	Uncertain	+	+	+		+	+
Derman 1995	Yes	+		+			+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Saletu 1995	Uncertain			+			+
Good 1996	Yes	+					
Speroff (Study 1) 1996	Yes	+					
Chung 1996	Uncertain	+	+		+		+
Speroff (Study 2) 1996	Yes	+					
Speroff (Study 3) 1996	Yes	+					
Bacchi-Modena 1997	Yes	+					+
Baerug 1998	Yes	+		+		+	+
Bech 1998	Uncertain	+	+	+	+		+
de Vrijer 1999	Yes	+					+
Leonetti 1999	No	+					
Studd 1999	Yes	+					+
Polo-Kantola 1999	Uncertain	+	+	+			
Casper 1999	Uncertain				+	+	
Cohen 1999	Yes	+					
Rebar 2000	Uncertain	+					+
Speroff (Study 1) 2000	Yes	+					
Rovati 2000	Yes	+					+
Notelovitz 2000	Yes	+					
Strickler 2000	Uncertain	+	+	+		+	+
Notelovitz 2000	Yes	+					
DeAloysio 2000	Yes	+					+
von Holst 2000	Yes	+			+		+
Notelovitz 2000	Yes	+					
Alexandersen 2000	Uncertain						+
Speroff (Study 2) 2000	Yes	+					
Rigano 2001	Yes						+
Utian (CEE alone arms) 2001	No	+					
Simon 2001	Yes	+					
Soares 2001	Uncertain			+			+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Utian (CEE/MPA arms) 2001	No	+					
Rozenbaum 2002	Yes	+		+	+		+
Shulman (Study 1) 2002	Yes	+			+		
von Holst 2002	Yes	+					+
Archer 2003	Yes	+					
Vestergaard 2003	No	+	+		+	+	
Speroff 2003	Yes	+		+	+	+	+
Jirapinyo 2003	No						+
Haines 2003	No			+			+
Hays 2003	No		+	+			+
Gambacciani 2003	Uncertain	+	+	+		+	
Gelfand 2003	Yes	+		+		+	+
Wren 2003	Yes	+		+		+	
Simunic 2003	Uncertain				+	+	
Parsons 2003	Uncertain				+	+	
Berlex (SIP) 2003	Uncertain	+					
Rudolph 2004	No			+			
Yang 2004	Uncertain	+		+		+	+
Schurmann 2004	Yes	+	+		+		
Utian 2004	Yes	+					
Dessole 2004	Uncertain				+	+	
Duramed (SIP) 2004	Uncertain	+					
Brunner 2005	No		+	+			+
Onalan 2005	No			+			
Bayer Healthcare (SIP) 2005	Yes	+					
Novartis (SIP) 2005	Uncertain	+					
Speroff (Study 1) 2006	Yes	+					
Simon 2006	Yes	+					
Nielsen 2006	Uncertain	+	+	+		+	
Osmanagaoglu 2006	Uncertain					+	

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Speroff (Study 2) 2006	Yes	+					
Bachmann (d) 2007	Yes	+					
Maki 2007	No						
Endrikat 2007	Yes	+					
Lee 2007	Yes	+	+		+		
Panay 2007	Yes	+	+				+
Simon 2007	Yes	+		+	+	+	+
Pefanco 2007	Uncertain			+			
Bayer Healthcare (SIP) 2007	Uncertain	+					
Buster (Study 1) 2008	Yes	+					
Veerus 2008	Uncertain	+	+				+
Davis 2008	Uncertain					+	
Bachmann 2008	Uncertain				+		
Welton 2008	No	+	+	+	+	+	+
Buster (Study 2) 2008	Yes	+					
Buster (Study 3) 2008	Yes	+					
Simon (SIP) 2008	Yes				+	+	
Benster 2009	Yes	+		+			
Utian 2009	Yes	+	+	+		+	+
Lobo 2009	Yes	+					
Haines 2009	Yes	+			+	+	+
Bachmann (d) 2009	Yes				+		
Hedrick 2009	Yes	+					
Baksu 2009	Uncertain	+	+	+			+
Bachmann (Study 1) 2009	Uncertain				+	+	
Freedman 2009	Uncertain				+	+	
Gast 2009	Uncertain	+				+	
Bachmann (Study 2) 2009	Uncertain				+	+	
Hassa 2010	Uncertain	+		+		+	+
Stevenson 2010	Yes	+					+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Bachmann 2010	No	+		+		+	+
Raghunandan 2010	Uncertain				+	+	
Hedrick 2010	Yes						
Liu 2011	Yes	+					
Lin 2011	Yes	+	+		+		
Demetrio 2011	Yes			+			
Liu 2012	Yes	+					
Archer 2012	Yes	+					
Archer 2012	Yes	+					
Cano 2012	Uncertain				+	+	
Polisseni 2013	Yes	+	+	+		+	+
Raz 2013	Uncertain			+			
Archer 2013	Yes	+					
Pinkerton 2013	Yes	+	+	+		+	+

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; QoL: quality of life; (SIP); data came from a package insert; VMS: vasomotor symptoms

Table E-38. Reported outcomes for trials comparing antidepressant with placebo

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Suvanto-Luukkonen 2005	Uncertain	+	+	+			+
Evans 2005	Yes	+		+		+	
Kerwin 2007	Yes	+					
Kalay 2007	Yes	+		+			
Speroff 2008	Yes	+					
Soares 2008	Yes	+		+			
Archer 2009	Yes	+					+
Archer 2009	Yes	+		+		+	+
Kornstein 2010	No			+			
Soares 2010	Uncertain			+		+	+
Freeman 2011	Yes	+	+	+		+	+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Bouchard 2012	Yes	+		+			+
Pinkerton 2012	Yes	+					
Simon (Study 2) 2013	Yes	+					
Pinkerton 2013	Yes			+		+	+
Simon (Study 1) 2013	Yes	+					

(c): data came from posted results on the clinical trial registry; QoL: quality of life; VMS: vasomotor symptoms

Table E-39. Reported outcomes for trials comparing other prescriptions with placebo

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Clayden 1974	Yes	+					
Guttuso 2003	Yes	+	+	+			
Butt 2008	Yes	+		+			
Joffe 2010	Uncertain	+	+	+			
Depomed (c) 2012	Yes	+					
Depomed (c) 2012	Yes	+					
Pinkerton 2013	Yes	+	+				

(c): data came from posted results on the clinical trial registry; QoL: quality of life; VMS: vasomotor symptoms

Table E-40. Reported outcomes for trials comparing nonprescription nonhormone with placebo

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Chenoy 1994	Yes	+					
Murkies 1995	Yes	+					+
Hirata 1997	Yes	+			+		+
Albertazzi 1998	Yes	+					
Baber 1999	Yes	+					+
Wiklund 1999	Yes	+	+	+		+	+
Barnhart 1999	No	+	+	+	+		+
Upmalis 2000	Yes	+					

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Kotsopoulos 2000	Uncertain	+	+	+	+	+	
Davis 2001	Yes	+				+	
Faure 2002	Yes	+					
Han 2002	Yes	+	+				+
Tice 2003	Yes	+		+		+	
Penotti 2003	Yes	+					
Burke 2003	Yes	+					
Sammartino 2003	Yes						+
Nahas 2004	Yes	+					+
Atkinson 2004	No	+					+
Hartley 2004	Uncertain	+	+	+		+	+
Winther 2005	Yes	+					+
Frei-Kleiner 2005	Yes	+					+
Verhoeven 2005	Yes	+					+
Kok 2005	No			+			+
Hidalgo 2005	Uncertain	+	+	+	+	+	+
Dodin 2005	No	+					+
Osmers 2005	Uncertain	+		+	+		+
Mucci 2006	Uncertain	+	+	+	+		
Heger (m) 2006	Yes	+	+	+	+	+	+
Lewis 2006	Uncertain	+		+		+	+
Uebelhack 2006	Yes	+		+	+		+
Sammartino 2006	Yes						+
Casini 2006	No			+			
Nahas 2007	Yes	+					
Yang 2007	Uncertain	+	+	+		+	
Chung 2007	Uncertain	+					+
Cheng 2007	Yes	+					
Ho 2007	No	+		+			
Cancellieri 2007	Uncertain						+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Haines 2008	Uncertain	+		+		+	
Jou 2008	Uncertain	+					+
Khaodhiar 2008	Yes	+					+
Ferrari 2009	Yes	+					+
van der Sluijs 2009	Yes	+		+		+	+
D'Anna (m) 2009	Yes	+					
van Die 2009	Yes	+	+	+		+	+
de Sousa-Munoz 2009	Yes			+			
Labrie 2009	Uncertain			+	+	+	+
Panjari 2009	Uncertain			+		+	+
Basaria 2009	Uncertain	+		+		+	
Radhakrishnan 2009	No	+					+
Lee 2010	Uncertain	+	+		+		+
Garcia 2010	Yes	+					
Lipovac 2010	Yes	+		+			+
Shen 2010	Uncertain			+			+
Jassi 2010	No	+	+	+			+
Evans 2011	Yes	+		+		+	+
Hsu 2011	Uncertain	+	+	+		+	+
Andrikoula 2011	Yes	+		+			+
Levis 2011	No						+
Plotnikoff 2011	Yes	+					
Chang 2011	Yes	+	+	+	+		+
Auerbach 2012	Yes	+	+	+	+		+
Cianci 2012	Uncertain	+			+	+	
Kim 2012	Yes	+					+
Xia 2012	Yes	+		+		+	
Ye 2012	Yes	+					+
Aso 2012	Yes	+					+
Amato 2012	Uncertain	+		+		+	

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Colau 2012	Yes	+					+
Lima 2012	Uncertain				+	+	
Pandit 2012	No	+	+	+			+
Schellenberg 2012	Yes	+	+	+			+
von Hagens 2012	Yes	+	+	+	+	+	+
Yang 2012	Yes	+		+		+	+
Colacurci 2013	Yes	+			+	+	
Crawford 2013	Yes	+					
Kohama 2013	Uncertain	+	+	+		+	+
Zhong 2013	Yes	+		+	+	+	+
Chi 2013	Yes	+	+	+		+	+
Mainini 2013	Yes	+					+
Constantine 2014	Uncertain				+	+	
Constantine 2014	Uncertain				+		
Constantine 2014	Uncertain				+		

(m): trial contains data from multiple publications; QoL: quality of life; VMS: vasomotor symptoms

Table E-41. Reported outcomes for trials comparing hormone and nonprescription nonhormone with placebo

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Crisafulli 2004	Uncertain	+					
Newton 2006	Yes	+					
Yalamanchili 2012	Uncertain			+			
Gupta 2013	No	+	+	+	+	+	

QoL: quality of life; VMS: vasomotor symptoms

Table E-42. Reported outcomes for trials comparing hormone with hormone

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Polvani 1991	Uncertain						+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Henriksson 1994	Uncertain				+	+	
Studd 1995	Yes	+					
Ayton 1996	Uncertain				+	+	
Hilditch 1996	Uncertain	+		+		+	
Egarter 1996	Yes						+
Hirvonen 1997	Uncertain	+					
Hirvonen 1997	No	+					
Rozenberg 1997	No	+					
Al-Azzawi 1997	Yes	+					
Lubbert 1997	Uncertain	+	+	+	+	+	+
Barentsen 1997	Uncertain				+	+	
Bachmann 1997	Uncertain				+		
Good 1999	Yes	+					
Mattsson 2000	Uncertain	+					+
Saure 2000	Yes	+		+			
Graser 2000	Yes						+
Rioux 2000	Uncertain				+		
Dugal 2000	Uncertain				+		
Parsey 2000	Yes	+					
Meuwissen 2001	Yes	+					+
Lopes 2001	Uncertain	+					+
Ozsoy 2002	Uncertain	+					+
Loh 2002	No	+		+		+	+
Buckler (d) 2003	Yes	+		+	+	+	+
Lobo 2003	Uncertain					+	
Pornel 2005	Yes	+	+				+
Gambacciani 2005	Yes	+		+			+
Utian 2005	Yes	+			+	+	
Davis 2005	Yes	+		+		+	+
Raynaud 2005	Yes	+					+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Braunstein 2005	Uncertain					+	
Simon 2005	Uncertain					+	
Weisberg 2005	Uncertain		+		+	+	
Buster 2005	Uncertain					+	
Akhila 2006	Uncertain	+		+	+		
Serrano 2006	No	+		+		+	
Cieraad 2006	Yes	+		+		+	
Davis 2006	No					+	
Long 2006	Uncertain				+	+	
Shifren 2006	Uncertain					+	
Limpaphayom (m) 2006	No	+	+	+	+	+	
Odabasi 2007	Uncertain	+		+	+		+
Pitkin (d) 2007	Yes	+	+	+	+	+	+
Penteado 2008	Uncertain				+	+	
Panay 2010	Uncertain					+	

(d): duplicate patient population with other included article; (m): trial contains data from multiple publications; QoL: quality of life; VMS: vasomotor symptoms

Table E-43. Reported outcomes for trials comparing hormone with nonprescription nonhormone

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Nappi 2005	Yes	+		+	+		
Nathorst-Boos 2006	Uncertain			+		+	
Kaari 2006	No	+					+
Chandeying 2007	Yes	+	+		+	+	+
Menati 2013	Uncertain	+					
Zhang 2013	Yes	+		+		+	+

QoL: quality of life; VMS: vasomotor symptoms

Table E-44. Reported outcomes for trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Liske 2002	Yes			+			+

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Hidalgo 2006	Yes	+	+				+
Zervoudis (a) 2008	Uncertain	+	+				
Agosta 2011	Yes	+	+	+	+		
Le Donne 2011	Uncertain				+		
Virojchaiwong 2011	Uncertain	+			+		+
Yang 2012	Uncertain	+		+	+		+

(a): data came from a conference abstract; QoL: quality of life; VMS: vasomotor symptoms

Table E-45. Reported outcomes for trials comparing nonprescription nonhormone with antidepressant

Study	VMS Required	VMS	Sleep	Psychological	Urogenital	Sexual	QoL
Oktem 2007	Yes	+		+			+

QoL: quality of life; VMS: vasomotor symptoms

Table E-46. Therapies used in trials comparing hormone with placebo

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Martin 1971	1	56	Plac		Oral			
	2	53	EP seq	0.025 mg E + 1 mg P	Oral	mestranol + norethindrone		Standard
	3	56	EP seq	0.05 mg E + 1 mg P	Oral	mestranol + norethindrone		High
Campbell 1977	1	68	Plac		Oral			
	2	68	Est	1.25 mg	Oral	conjugated equine estrogens	Premarin	High
Baumgardner 1978	1	42	Plac		Oral			
	2	42	Est	0.1 mg	Oral	quinestrol	Estrovis	Low
	3	35	Est	0.2 mg	Oral	quinestrol	Estrovis	Standard
	4	37	Est	1.25 mg	Oral	conjugated estrogen	Premarin	High

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Coope 1981	1	26	Plac		Oral			
	2	29	Est	0.3mg	Oral	piperazine estrone sulphate		UltraLow
Jensen 1983	1	90	Plac		Oral			
	2	41	EP seq	4 mg E + 1 mg P	Oral	estradiol + estriol + norethisterone acetate	Trisequens Forte	High
Foidart 1991	1	53	Plac		VagPes			
	2	56	Est	1 mg	VagPes	estriol	Ortho-Gynest-Depot	Low
Eriksen 1992	1	79	Plac		VagTab			
	2	75	Est	0.025 mg	VagTab	estradiol	Vagifem	Low
Wiklund 1993	1	111	Plac		Patch			
	2	112	Est	0.05 mg	Patch	estradiol		Standard
Derman 1995	1	42	Plac		Oral			
	2	40	EP seq	2 mg E + 1 mg P	Oral	estradiol + norethindrone acetate	Trisequens	Standard
Saletu 1995	1	32	Plac		Patch			
	2	32	Est	0.05 mg	Patch	estradiol	Estraderm	Standard
Good 1996	1	91	Plac		Patch			
	2	88	Est	0.05 mg	Patch	estradiol	Alora	Standard
	3	94	Est	0.10 mg	Patch	estradiol	Alora	High
Speroff (Study 1) 1996	1	54	Plac		Patch			
	2	54	Est	0.02 mg	Patch	estradiol	FemPatch	UltraLow

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Chung 1996	1	40	Plac		Oral			
	2	43	Est	2mg	Oral	estradiol	Estrofem	Standard
Speroff (Study 2) 1996	1	37	Plac		Patch			
	2	37	Est	0.02 mg	Patch	estradiol	FemPatch	UltraLow
	3	37	Est	0.04 mg	Patch	estradiol	FemPatch	Low
Speroff (Study 3) 1996	1	53	Plac		Patch			
	2	53	Est	0.04 mg	Patch	estradiol	FemPatch	Low
Bacchi-Modena 1997	1	56	Plac		Patch			
	2	53	Est	0.05 mg	Patch	estradiol	Estraderm MX	Standard
Baerug 1998	1	41	Plac		Oral			
	2	38	EP comb	1mg E + 0.25mg P	Oral	estradiol + norethisterone acetate	Activelle	Low
	3	40	EP comb	1mg E + 0.5mg P	Oral	estradiol + norethisterone acetate	Activelle	Low
Bech 1998	1	51	Plac		Oral			
	2	50	EP comb	2 mg E + 1 mg P	Oral	estradiol + norethisterone acetate	Kliogest	Standard
	3	50	EP seq	2 mg E + 1 mg P	Oral	estradiol + norethisterone acetate	Trisekvens (also Trisequens)	Standard
de Vrijer 1999	1	86	Plac		Patch			
	2	82	Est	0.05 mg	Patch	estradiol	Estraderm MX 50	Standard

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	3	86	Est	0.10 mg	Patch	estradiol	Estraderm MX 100	High
Leonetti 1999	1	47	Plac		SknCrm			
	2	43	Prog	20 mg	SknCrm	progesterone		
Studd 1999	1	60	Plac		NasSpr			
	2	58	EP comb	0.1mg E + 5mg P	NasSpr	estradiol + medroxyprogesterone acetate	Aerodiol + medroxyprogesterone acetate	Low
	3	62	EP comb	0.20mg E + 5mg P	NasSpr	estradiol + medroxyprogesterone acetate	Aerodiol + medroxyprogesterone acetate	Low
	4	54	EP comb	0.30mg E + 5mg P	NasSpr	estradiol + medroxyprogesterone acetate	Aerodiol + medroxyprogesterone acetate	Standard
	5	62	EP comb	0.40mg E + 5mg P	NasSpr	estradiol + medroxyprogesterone acetate	Aerodiol + medroxyprogesterone acetate	High
Polo-Kantola 1999	1	32	Plac		SknGel			
	2	30	Est		SknGel	estradiol	Estrogel or Evorel	Standard
Casper 1999	1	34	Plac		VayRin			
	2	33	Est	0.0075 mg	VayRin	estradiol	Estring	Low
Cohen 1999	1	129	Plac		Patch			
	2	130	Est	0.0375mg	Patch	estradiol	Vivelle	Low
Rebar 2000	1	10	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
		3						
	2	101	Est	0.3 mg	Oral	esterified estrogen	Estratab	Low
Speroff (Study 1) 2000	1	43	Plac		Oral			
	2	45	EP comb	0.001 mg EE + 0.2 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	UltraLow
	3	41	EP comb	0.0025 mg EE + 0.5 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	Low
	4	45	EP comb	0.005 mg EE + 1 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	Low
	5	45	EP comb	0.010 mg EE + 1 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	Standard
Rovati 2000	1	80	Plac		Patch			
	2	80	Est	0.025 mg	Patch	estradiol	Dermestril	UltraLow
	3	77	Est	0.05 mg	Patch	estradiol	Dermestril	Standard
	4	74	Est	0.05 mg	Patch	estradiol	Dermestril	Standard
Notelovitz 2000	1	49	Plac		Oral			
	2	48	Est	1 mg	Oral	estradiol		Low
	3	48	Est	0.5 mg	Oral	estradiol		UltraLow
Strickler 2000	1	105	Plac		Oral			
	2	96	Est	0.625 mg	Oral	conjugated equine estrogens		Standard

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Notelovitz 2000	1	66	Plac		Oral			
	2	68	Est	0.25 mg	Oral	estradiol		UltraLow
	3	64	Est	0.5 mg	Oral	estradiol		UltraLow
	4	67	Est	1.0 mg	Oral	estradiol		Low
	5	68	Est	2.0 mg	Oral	estradiol		Standard
DeAloysio 2000	1	52	Plac		Patch			
	2	52	Est	0.025 mg	Patch	estradiol	Dermestril	UltraLow
	3	52	Est	0.0375 mg	Patch	estradiol	Dermestril	Low
von Holst 2000	1	93	Plac		Patch			
	2	93	Est	0.05 mg	Patch	estradiol	Fem7	Standard
Notelovitz 2000	1	53	Plac		Patch			
	2	54	EP seq	0.050mg + 0.140mg	Patch	estradiol+ estradiol/norethindrone acetate	Vivelle + CombiPatch	Standard
	3	59	EP seq	0.050mg E + 0.250mg P	Patch	estradiol+ estradiol/norethindrone acetate	Vivelle + CombiPatch	Standard
	4	53	EP seq	0.050mg E + 0.400mg P	Patch	estradiol+ estradiol/norethindrone acetate	Vivelle + CombiPatch	Standard
Alexandersen 2000	1	50	Plac		Oral			
	2	50	EP seq	0.75mg E + 0.35mg P	Oral	piperazine estrone sulphate + norethisterone		Low

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	3	50	EP seq	1.5mg E + 0.7mg P	Oral	piperazine estrone sulphate + norethisterone		Standard
	4	50	EP comb	2mg E + 1mg P	Oral	estradiol + norethisterone acetate		Standard
Speroff (Study 2) 2000	1	67	Plac		Oral			
	2	67	EP comb	0.0025 mg EE + 0.5 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	Low
	3	67	EP comb	0.005 mg EE + 1 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	Low
	4	65	EP comb	0.010 mg EE + 1 mg NA	Oral	ethinyl estradiol (EE) + norethindrone acetate (NA)	FemHRT	Standard
Rigano 2001	1	191	Plac					
	2	171	Est	0.05 mg	Patch	estradiol	Dermestril	Standard
Utian (CEE alone arms) 2001	1	28	Plac		Oral			
	2	30	Est	0.3mg	Oral	conjugated equine estrogen		UltraLow
	3	32	Est	0.45mg	Oral	conjugated equine estrogen		Low
	4	27	Est	0.625mg	Oral	conjugated equine estrogen		Standard
Simon 2001	1	48	Plac		Oral			
	2	72	Est	0.625 mg	Oral	synthetic conjugated estrogen-A	Cenestin	Standard
Soares 2001	1	25	Plac		Patch			
	2	25	Est	0.1 mg	Patch	estradiol	Systen/Evorel	High

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Utian (CEE/MPA arms) 2001	1	28	Plac		Oral			
	2	33	EP comb	0.3mg E + 1.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate		UltraLow
	3	29	EP comb	0.45mg E + 1.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate		Low
	4	28	EP comb	0.45mg E + 2.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate		Low
	5	34	EP comb	0.625mg E + 2.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate		Standard
Rozenbaum 2002	1	57	Plac		NasSpr			
	2	54	Est	0.15 mg	NasSpr	estradiol	Aerodiol	Low
	3	54	Est	0.30 mg	NasSpr	estradiol	Aerodiol	Standard
Shulman (Study 1) 2002	1	93	Plac		Patch			
	2	96	EP comb	0.045 mg E + 0.030 mg P	Patch	estradiol + levonorgestrel		Low
	3	104	EP comb	0.045 mg E + 0.040 mg P	Patch	estradiol + levonorgestrel		Low
von Holst 2002	1	88	Plac		Patch			
	2	84	EP seq	0.05 mg E + 0.01 mg P	Patch	estradiol + levonorogestrel	Fem7 Combi	Standard
Archer 2003	1	73	Plac		SknGel			
	2	75	Est	0.75 mg	SknGel	estradiol	EstroGel	Low
	3	73	Est	1.5 mg	SknGel	estradiol	EstroGel	Low

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Vestergaard 2003	1	504	Plac		Oral			
	2	502	EP seq	2 mg E + 1 mg P	Oral	estradiol + norethisterone acetate	Trisequens	Standard
Speroff 2003	1	108	Plac		VayRin			
	2	113	EP comb	0.05 mg	VayRin	estradiol + progestin	Femring	High
	3	112	EP comb	0.10 mg	VayRin	estradiol + progestin	Femring	High
Jirapinyo 2003	1	60	Plac		Oral			
	2	60	EP comb	2 mg E + 1 mg P	Oral	estradiol + norethisterone acetate	Kliogest	Standard
Haines 2003	1	50	Plac		Oral			
	2	52	Est	1 mg	Oral	estradiol		Low
	3	50	Est	2 mg	Oral	estradiol		Standard
Hays 2003	1	8102	Plac		Oral			
	2	8506	EP comb	0.625mg E + 2.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate	Prempro	Standard
Gambacciani 2003	1	25	Plac		Oral			
	2	25	EP comb	1 mg E + 0.5 mg P	Oral	estradiol + norethisterone	Activelle	Low
Gelfand 2003	1	60	Plac		Oral			
	2	59	EP comb	1 mg E + 0.09 mg P	Oral	estradiol + norgestimate	Ortho-Prefest	Low
Wren 2003	1	42	Plac		SknCr			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
					m			
	2	38	Prog	32 mg	SknCrm	progesterone	Pro-Feme	
Simunic 2003	1	784	Plac		VagTab			
	2	828	Est	0.025mg	VagTab	estradiol	Vagifem	Low
Parsons 2003	1	46	Plac		VagCrm		Replens (nonhormonal moisturizer)	
	2	48	Est	0.625 mg	VagCrm	conjugated estrogen	Premarin	Standard
Berlex (SIP) 2003	1	88	Plac		Patch			
	2	92	EP comb	.045 mg E + .03 mg P	Patch	Estradiol + Levonorgestrel	Climara Pro	Standard
Rudolph 2004	1	64	Plac		Oral			
	2	65	EP comb	2mg E + 2mg P	Oral	estradiol valerate + dienogest	Climodien/Lafamme	High
Yang 2004	1	25	Plac		Oral			
	2	26	EP comb	0.625mg E + 2.5mg P	Oral	conjugated estrogen + medroxyprogesterone acetate	Premelle	Standard
Schurmann 2004	1	61	Plac		Oral			
	2	55	EP comb	1mg E + 1mg P	Oral	estradiol + drospirenone		Low
	3	52	EP comb	1mg E + 2mg P	Oral	estradiol + drospirenone		Low
	4	57	EP comb	1mg E + 3mg P	Oral	estradiol + drospirenone		Low
Utian 2004	1	72	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	68	Est	0.3mg	Oral	synthetic conjugated estrogen	Enjuvia	UltraLow
	3	72	Est	0.625mg	Oral	synthetic conjugated estrogen	Enjuvia	Standard
	4	69	Est	1.25mg	Oral	synthetic conjugated estrogen	Enjuvia	High
Dessole 2004	1	44	Plac		VagOvu			
	2	44	Est	1mg	VagOvu	estriol	Colpogyn	Low
Duramed (SIP) 2004	1	51	Plac		Oral			
	2	53	Est	.45mg	Oral	synthetic conjugated estrogens	Cenestin	Low
Brunner 2005	1	5429	Plac		Oral			
	2	5310	Est	0.625 mg	Oral	conjugated equine estrogens	Premarin	Standard
Onalan 2005	1	54	Plac	1000 mg	Oral	calcium	Calcium Sandoz Forte	
	2	79	EP comb	0.625 mg E + 2.5 mg P	Oral	conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA)	Premelle 2.5	Standard
	3	77	EP comb	0.625 mg E + 5.0 mg P	Oral	conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA)	Premelle 5	Standard
Bayer Healthcare (SIP) 2005	1	176	Plac		Oral			
	2	175	EP comb	0.50 mg E + 0.25 mg P	Oral	estradiol + drospirenone	Angeliq	Low
Novartis (SIP)	1	51	Plac		Patch			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
2005								
	2	57	EP comb	0.05 mg E + 0.14 mg P	Patch	estradiol + norethindrone acetate	CombiPatch	Low
	3	52	EP comb	0.05 mg E + 0.25 mg P	Patch	estradiol + norethindrone acetate	CombiPatch	Low
Speroff (Study 1) 2006	1	94	Plac		Oral			
	2	100	Est	0.9 mg	Oral	estradiol acetate	Femtrace	Standard
	3	95	Est	1.8 mg	Oral	estradiol acetate	Femtrace	High
Simon 2006	1	100	Plac		SknCrm			
	2	100	Est	2.5 mg/1g of cream	SknCrm	estradiol	Estrasorb	Low
Nielsen 2006	1	118	Plac		NasSpr			
	2	114	EP seq	0.15 mg E + 200mg P	NasSpr	estradiol (S21400) + progesterone	Aerodiol + progesterone	Low
	3	103	EP seq	0.30 mg E + 200 mg P	NasSpr	estradiol (S21400) + progesterone	Aerodiol + progesterone	Standard
Osmanagaoglu 2006	1	51	Plac		Oral			
	2	53	EP comb	2 mg E + 2 mg P	Oral	estradiol valerate (EV) + dienogest (P)	Climodien	High
Speroff (Study 2) 2006	1	108	Plac		Oral			
	2	113	Est	0.45 mg	Oral	estradiol acetate	Femtrace	Low

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Bachmann (d) 2007	1	133	Plac		Patch			
	2	147	Est	0.014 mg	Patch	estradiol		UltraLow
	3	145	EP comb	0.023 mg E + 0.0075 mg P	Patch	estradiol + levonorgestrel		UltraLow
Maki 2007	1	91	Plac		Oral			
	2	89	EP comb	0.625mg E + 2.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate	Prempro	Standard
Endrikat 2007	1	162	Plac		Oral			
	2	162	EP comb	1mg E + 2mg P	Oral	estradiol valerate + dienogest		Standard
Lee 2007	1	37	Plac		Oral			
	2	35	EP comb	1 mg E + 2 mg P	Oral	estradiol + drospirenone		Low
Panay 2007	1	200	Plac		Oral			
	2	194	EP comb	0.5 mg E + 0.1 mg P	Oral	estradiol + norethisterone acetate		UltraLow
	3	181	EP comb	0.5 mg E + 0.25 mg P	Oral	estradiol + norethisterone acetate		UltraLow
Simon 2007	1	137	Plac		SknGel			
	2	136	Est	0.52 mg	SknGel	estradiol	Elestrin	Low
	3	142	Est	1.02 mg	SknGel	estradiol	Elestrin	Low
	4	69	Est	1.56 mg	SknGel	estradiol	Elestrin	Low
Pefanco 2007	1	25	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	32	EP seq	0.25mg + 100mg P	Oral	estradiol + progesterone		UltraLow
Bayer Healthcare (SIP) 2007	1	83	Plac		Patch			
	2	82	Est	.025 mg	Patch	estradiol	Climara	UltraLow
Buster (Study 1) 2008	1	75	Plac		SknSpr			
	2	76	Est	4.59 mg	SknSpr	estradiol	Evamist	Low
Veerus 2008	1	381	Plac		Oral			
	2	415	EP comb	0.625 mg + 2.5 mg	Oral	combined estrogens + medroxyprogestrone acetate		Standard
Davis 2008	1	277	Plac		Patch			
	2	267	Test	0.15 mg	Patch			
	3	267	Test	0.30 mg	Patch			
Bachmann 2008	1	47	Plac		VagTab			
	2	92	Est	0.01 mg	VagTab	estradiol	Vagifem	Low
	3	91	Est	0.025 mg	VagTab	estradiol	Vagifem	Low
Welton 2008	1	1087	Plac		Oral			
	2	1043	EP comb	0.625 E + 2.5/5.0 P	Oral	conjugated equine estrogen + medroxyprogesterone acetate	Prempro	Standard
Buster (Study 2) 2008	1	76	Plac		SknSpr			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	74	Est	3.06 mg	SknSpr	estradiol	Evamist	Low
Buster (Study 3) 2008	1	77	Plac		SknSpr			
	2	76	Est	1.53 mg	SknSpr	estradiol	Evamist	Low
Simon (SIP) 2008	1	123	Plac		Oral			
	2	125	Est	0.3 mg	Oral	synthetic conjugated estrogens	Enjuvia	Low
Benster 2009	1	43	Plac		SknCrm			
	2	46	Prog	5 mg	SknCrm	progestin	Progestelle	
	3	44	Prog	20 mg	SknCrm	progestin	Progestelle	
	4	43	Prog	40 mg	SknCrm	progestin	Progestelle	
	5	45	Prog	60 mg	SknCrm	progestin	Progestelle	
Utian 2009	1	63	Plac		Oral			
	2	127	Est	0.45 E + 20 BZA	Oral	conjugated equine estrogens + bazedoxifene		Low
	3	128	Est	0.625 E + 20 BZA	Oral	conjugated equine estrogen + bazedoxifene		Standard
Lobo 2009	1	427	Plac		Oral			
	2	1286	Est	0.45 E + (10-40 BZA	Oral	conjugated equine estrogen + bazedoxifene		Low
	3	1261	Est	0.625 E + (10-40) BZA	Oral	conjugated equine estrogen + bazedoxifene		Standard
Haines 2009	1	80	Plac		Patch			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	80	Est	0.014 mg	Patch	estradiol		UltraLow
Bachmann (d) 2009	1	36	Plac		Patch			
	2	42	Est	0.014 mg	Patch	estradiol		UltraLow
	3	43	EP comb	0.023mg E + 0.0075mg P	Patch	estradiol + levonorgestrel		UltraLow
Hedrick 2009	1	125	Plac		SknGel			
	2	122	Est	0.25 mg	SknGel	estradiol	Divigel	Low
	3	123	Est	0.5 mg	SknGel	estradiol	Divigel	Low
	4	125	Est	1.0 mg	SknGel	estradiol	Divigel	Low
Baksu 2009	1	32	Plac		Oral			
	2	35	Est	0.625 mg	Oral	conjugated estrogen	Premarin	Standard
	3	33	Est	0.3 mg	NasSpr	estradiol hemihidrate	Aerodiol	Standard
	4	32	Est	1.5 mg	SknGel	estradiol hemihidrate	Estreva	Standard
Bachmann (Study 1) 2009	1	72	Plac		VagCrm			
	2	143	Est	0.3 mg	VagCrm	conjugated estrogen		UltraLow
Freedman 2009	1	140	Plac		VagCrm			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	135	Est	0.179mg	VagCrm	synthetic conjugated estrogens-A		Standard
Gast 2009	1	141	Plac		Oral			
	2	144	EP comb	0.45 mg E + 1.5 mg MPA oral + 0.625 mg cream	Oral	conjugated estrogen + medroxyprogesterone acetate	Premarin	Low
Bachmann (Study 2) 2009	1	68	Plac		VagCrm			
	2	140	Est	0.3 mg	VagCrm	conjugated estrogen		Low
Hassa 2010	1	83	Plac		Injec			
	2	83	Est	0.625 mg	Oral	conjugated equine estrogen	Premarin	Standard
	3	81	Est	0.56 mg	Patch	estradiol	Climara	Standard
Stevenson 2010	1	127	Plac		Oral			
	2	124	EP comb	0.5 mg E + 2.5 mg D	Oral	estradiol and dydrogesterone		UltraLow
	3	62	EP comb	1 mg E + 5 mg D	Oral	estradiol and dydrogesterone		Low
Bachmann 2010	1	105	Plac		Oral			
	2	219	Est	0.45 E + 20 BZA	Oral	conjugated equine estrogen + bazedoxifene		Low
	3	218	Est	0.625 E + 20 BZA	Oral	conjugated equine estrogen + bazedoxifene		Standard
Raghunandan	1	25	Plac		VagCr			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
2010					m			
	2	25	Est	0.625 mg	VagCrm	conjugated equine estrogen	Premarin	Standard
	3	25	ET comb	0.625 mg E + 2% T	VagCrm	conjugated equine estrogen + testosterone	Premarin + testosterone	Standard
Hedrick 2010	1	124	Plac		SknGel			
	2	121	Est	0.25 mg	SknGel	estradiol	Divigel	Low
	3	119	Est	0.50 mg	SknGel	estradiol	Divigel	Low
	4	124	Est	1 mg	SknGel	estradiol	Divigel	Low
Liu 2011	1	168	Plac		Oral			
	2	172	Est	0.30 mg	Oral	esterified estrogen		Low
	3	172	ET comb	0.30 mg E + 0.30 mg MT	Oral	esterified estrogen + methyltestosterone		Low
	4	174	ET comb	0.30 mg E + 0.60 mg MT	Oral	esterified estrogen + methyltestosterone		Low
	5	168	Est	0.45 mg EE	Oral	esterified estrogen		Low
	6	175	Test	0.60 mg	Oral	methyltestosterone		
Lin 2011	1	61	Plac		Oral			
	2	183	EP comb	1 mg E + 2 mg P	Oral	estradiol + drospirenone		Low
Demetrio 2011	1	36	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	30	Est	0.625 mg	Oral	conjugated equine estrogen	Premarin	Standard
Liu 2012	1	52	Plac		Oral			
	2	53	Est	0.3mg	Oral	synthetic conjugated estrogen-B	Enjuvia	UltraLow
	3	52	Est	0.625mg	Oral	synthetic conjugated estrogen-B	Enjuvia	Standard
Archer 2012	1	114	Plac		SknGel			
	2	118	Est	0.27 mg	SknGel	Estradiol	EstroGel	Low
	3	119	Est	0.375 mg	SknGel	Estradiol	EstroGel	Low
Archer 2012	1	113	Plac		SknGel			
	2	116	Est	0.27	SknGel	estradiol	EstroGel 0.06%	Low
	3	115	Est	0.375	SknGel	estradiol	EstroGel 0.06%	Low
Cano 2012	1	53	Plac		VagGel			
	2	114	Est	0.05	VagGel	estriol		UltraLow
Polisseni 2013	1	44	Plac		Oral			
	2	44	EP comb	1 E + 0.5 P	Oral	estradiol + NETA		Low
Raz 2013	1	26	Plac		Oral			
	2	33		EP comb	Oral	CEE or estradiol with progesterone		Low
Archer 2013	1	176	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	177	EP comb	0.5 E + 0.25 P	Oral	estradiol + drospirenone		UltraLow
	3	178	EP comb	0.5 E + 0.5 P	Oral	estradiol + drospirenone		UltraLow
	4	179	Est	0.3	Oral	estradiol		UltraLow
Pinkerton 2013	1	116	Plac		Oral			
	2	115	Est	0.45 E + 20 BZA	Oral	conjugated equine estrogen + bazedoxifene		Low
	3	123	Est	0.625 E + 20 BZA	Oral	conjugated equine estrogen + bazedoxifene		Standard
	4	56	EP comb	0.45 E + 1.5 P	Oral	conjugated equine estrogen + medrozyprogesterone acetate		Low

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; (d): duplicate patient population with other included article; E: estrogen; EP comb: estrogen plus progestin; Est: estrogen alone; ET comb: estrogen plus testosterone; (m): trial contains data from multiple publications; NasSpr: nasal spray; P: progestin; Prog: progestin alone; Plac: placebo; RxCat: treatment category; SD: standard deviation; (SIP); data came from a package insert; SknGel: skin gel; Test: testosterone alone; VagCrm: vaginal cream; VagOvu: vaginal ovule; VagPes: vaginal pessary; VagRin: vaginal ring; VagTab: vaginal tablet

Table E-47. Therapies used in trials comparing antidepressant with placebo

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Suvanto-Luukkonen 2005	1	50	Plac		Oral			
	2	50	Antide	10mg-30mg	Oral	fluoxetine	Seronil	
	3	49	Antide	10mg-30mg	Oral	citalopram	Cipramil	
Evans 2005	1	40	Plac		Oral			
	2	40	Antide	75mg	Oral	venlafaxine	Effexor XR	
Kerwin 2007	1	41	Plac		Oral			
	2	46	Antide	50mg	Oral	sertraline		
Kalay 2007	1	25	Plac		Oral			
	2	25	Antide	10-40mg	Oral	citalopram		

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Speroff 2008	1	77	Plac		Oral			
	2	141	Antide	50 mg	Oral	desvenlafaxine succinate	Pristiq	
	3	145	Antide	100 mg	Oral	desvenlafaxine succinate	Pristiq	
	4	137	Antide	150 mg	Oral	desvenlafaxine succinate	Pristiq	
	5	120	Antide	200 mg	Oral	desvenlafaxine succinate	Pristiq	
Soares 2008	1	28	Plac		Oral			
	2	28	Antide	12.5-25mg	Oral	paroxetine controlled release		
Archer 2009	1	180	Plac		Oral			
	2	182	Antide	100 mg	Oral	desvenlafaxine		
	3	179	Antide	150 mg	Oral	desvenlafaxine		
Archer 2009	1	151	Plac		Oral			
	2	150	Antide	100 mg	Oral	desvenlafaxine		
	3	151	Antide	150 mg	Oral	desvenlafaxine		
Kornstein 2010	1	125	Plac		Oral			
	2	247	Antide	100-200mg	Oral	devenlafaxine	Pristiq	
Soares 2010	1	224	Antide	100 mg - 200 mg	Oral	desvenlafaxine	Pristiq	
	2	237	Antide	10-20 mg	Oral	escitalopram	Lexapro	
Freeman 2011	1	101	Plac		Oral			
	2	104	Antide	10-20mg	Oral	escitalopram		
Bouchard 2012	1	150	Plac		Oral			
	2	137	Antide	100 mg	Oral	desvenlafaxine		
Pinkerton 2012	1	181	Plac		Oral			
	2	184	Antide	100	Oral	desvenlafaxine		
Simon (Study 2) 2013	1	284	Plac		Oral			
	2	284	Antide	7.5	Oral	paroxetine	Brisdelle	
Pinkerton 2013	1	1052	Plac		Oral			
	2	1066	Antide	100	Oral	desvenlafaxine		
Simon (Study 1) 2013	1	305	Plac		Oral			
	2	301	Antide	7.5		paroxetine	Brisdelle	

Antide: antidepressant; Plac: placebo; RxCat: treatment category

Table E-48. Therapies used in trials comparing other prescriptions with placebo

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Clayden 1974	1	43	Plac		Oral			
	2	42	Clon	0.05-0.15mg	Oral	clonidine		
Guttuso 2003	1	29	Plac		Oral			
	2	30	Gab/Pre	900 mg	Oral	gabapentin		
Butt 2008	1	98	Plac		Oral			
	2	99	Gab/Pre	300mg	Oral	gabapentin		
Joffe 2010	1	29	Plac		Patch			
	2	30	Eszop	3mg	Patch			
Depomed (c) 2012	1	177	Plac		Oral			
	2	174	Gab/Pre	1200mg	Oral			
	3	181	Gab/Pre	1800mg	Oral			
Depomed (c) 2012	1	183	Plac		Oral			
	2	186	Gab/Pre	1200mg	Oral			
	3	190	Gab/Pre	1800mg	Oral			
Pinkerton 2013	1	294	Plac		Oral			
	2	299	Gab/Pre	1800	Oral	gastroretentive gabapentin		

(c): data came from posted results on the clinical trial registry; Clon: clonidine; Eszop: eszopiclone; Gab/Pre: gabapentin/pregabalin; Plac: placebo;

Table E-49. Therapies used in trials comparing nonprescription nonhormone with placebo

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Chenoy 1994	1	28	Plac		Oral			
	2	28	See Note	4000 mg primrose oil + 80 vitamin E	Oral			
Murkies 1995	1	30	Plac	45g	Suppl	unbleached wheat flour		
	2	28	Isofl	45g	Suppl	soy flour		
Hirata 1997	1	36	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	35	Dong Q	4.5g	Oral	Angelica sinensis		
Albertazzi 1998	1	53	Plac		Suppl			
	2	51	Isofl	76 mg	Suppl	soy protein	Supro Brand	
Baber 1999	1	26	Plac		Oral			
	2	25	Isofl	40 mg	Oral	isoflavone	Promensil	
Wiklund 1999	1	191	Plac		Oral			
	2	193	Gins	200 mg	Oral		Ginsana G115	
Barnhart 1999	1	30	Plac		Oral			
	2	30	DHEA	50mg	Oral			
Upmalis 2000	1	86	Plac		Oral			
	2	89	Isofl	50mg	Oral	soy isoflavones		
Kotsopoulos 2000	1	50	Plac		Suppl	casein		
	2	44	Isofl	118 mg	Suppl			
Davis 2001	1	27	Plac		Suppl			
	2	28		See Note	Suppl			
Faure 2002	1	36	Plac		Oral			
	2	39	Isofl	70mg	Oral	soy isoflavones	Phytosoya	
Han 2002	1	40	Plac		Oral			
	2	40	Isofl	100mg	Oral			
Tice 2003	1	85	Plac		Oral			
	2	83	Isofl	57.2 mg	Oral	isoflavones	Rimostil	
	3	84	Isofl	82 mg	Oral	isoflavones	Promensil	
Penotti 2003	1	34	Plac		Oral			
	2	28	Isofl	72mg	Oral	isoflavones		
Burke 2003	1	70	Plac		Suppl			
	2	76	Isofl	42 mg	Suppl	soy protein		
	3	65	Isofl	58 mg	Suppl	soy protein		
Sammartino 2003	1	31	Plac		Oral	calcium		

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	32	Isofl	36 mg	Oral	genistein		
Nahas 2004	1	25	Plac		Oral			
	2	25	Isofl	60 mg	Oral	isoflavones	Isosoy	
Atkinson 2004	1	103	Plac		Oral			
	2	102	Isofl	26mg biochanin A + 16mg formononetin + 1mg genistein + 0.5mg daidzein	Oral	red clover derivatives	Promensil	
Hartley 2004	1	27	Plac		Oral			
	2	30	Gins	120 mg GK501 + 200 mg G115	Oral	GK501 + G115	Gincosan	
Winther 2005	1	32	Plac		Oral			
	2	32	See Note	80 mg GC + 240 mg PI 82	Oral	GC Fem + PI 82	Femal	
Frei-Kleiner 2005	1	41	Plac		Oral			
	2	81	B Coh	avg 42 mg (29-55 mg)	Oral			
Verhoeven 2005	1	64	Plac		Oral			
	2	60	See Note	50 mg Isoflavones + 8 mg deoxyacetein +1500 mg primrose oil + 0.00125 Vit D + 200 mg calcium	Oral	soy extract + black cohosh		
Kok 2005	1	102	Plac	36.5 g	Suppl			
	2	100	Isofl	52 mg genistein, 41 mg daidzein, 6 mg glycitein	Suppl		Solae soy protein	
Hidalgo 2005	1	53	Plac		Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	53	Isofl	80 mg	Oral	red clover isoflavone		
Dodin 2005	1	94	Plac		Suppl	wheat germ		
	2	85	Flax	40g	Suppl	flax seed		
Osmers 2005	1	141	Plac		Oral			
	2	145	B Coh	40 mg	Oral	black cohosh	Remifemin	
Mucci 2006	1	45	Plac		Oral			
	2	44	See Note	isoflavones: 60 mg; lactobacillus sporogenes: 500 million spores; magnolia extract: 60 mg; magnesium: 50 mg	Oral	isoflavones + lactobacillus sporogenes + magnolia extract + magnesium		
Heger (m) 2006	1	55	Plac		Oral			
	2	54	See Note	4 mg	Oral	rheum rhaponticum	Phytoestrol N	
Lewis 2006	1	33	Plac		Suppl			
	2	33	Isofl	42 mg	Suppl	isoflavone		
	3	33	Flax	50 mg	Suppl	flaxseed		
Uebelhack 2006	1	150	Plac		Oral			
	2	151	See Note	3.75 mg Black Cohosh Native Extract + 70 mg St John's Wort Native Extract	Oral		Remifemin plus St John's wort	
Sammartino 2006	1	39	Plac		Oral	calcium		
	2	36	See Note	60 mg I + 20 mg L + 1.25 c. racemosa	Oral		Euclim	
Casini 2006	1	77	Plac		Oral			
	2	77	Isofl	60 mg	Oral	aglycone		

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Nahas 2007	1	38	Plac		Oral			
	2	38	Isofl	100 mg	Oral	isoflavone	Glycine max AT	
Yang 2007	1	75	Plac		Oral			
	2	80	See Note	200 mg	Oral	Maritime Pine Extract	Pycnogenol	
Chung 2007	1	35	Plac		Oral			
	2	42	See Note	0.0364mL extract from Cimicifugae + 84 mg dried extract from Hypericum perforatum	Oral		Gyno-plus	
Cheng 2007	1	25	Plac		Suppl			
	2	26	Isofl	60 mg	Suppl	isoflavones		
Ho 2007	1	91	Plac		Oral	starch		
	2	85	Isofl	80 mg	Oral	soy isoflavones		
Cancellieri 2007	1	65	Plac		Oral			
	2	60	Isofl	72 mg	Oral	soy beans, red clover, black cohosh		
Haines 2008	1	39	Plac		Oral			
	2	45	See Note	3 g	Oral			
Jou 2008	1	30	Plac		Suppl			
	2	34	Isofl	135 mg	Suppl	isoflavones	SoyLife	
	3	32	Isofl	135 mg	Suppl	isoflavones	SoyLife	
Khaodhiar 2008	1	45	Plac		Oral			
	2	48	Isofl	40 mg	Oral	daidzein-rich isoflavone aglycones		
	3	49	Isofl	60 mg	Oral	daidzein-rich isoflavone aglycones		
Ferrari 2009	1	94	Plac		Oral			
	2	82	Isofl	80 mg	Oral	isoflavones	Fisiogen/Zavital	
van der Sluijs 2009	1	46	Plac		Oral			
	2	46	See	3820 mg	Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
			Note					
D'Anna (m) 2009	1	117	Plac		Oral			
	2	119	Isofl	54 mg	Oral	isoflavone		
van Die 2009	1	50	Plac		Oral			
	2	50	See Note	900 mg H + 1000 mg V	Oral			
de Sousa-Munoz 2009	1	42	Plac		Oral			
	2	42	Isofl	120 mg	Oral	isoflavones	Isoflavin Beta	
Labrie 2009	1	53	Plac		VagOvu			
	2	53	DHEA	3.25 mg	VagOvu	DHEA	Prasterone	
	3	56	DHEA	6.5 mg	VagOvu	DHEA	Prasterone	
	4	54	DHEA	13 mg	VagOvu	DHEA	Prasterone	
Panjari 2009	1	43	Plac		Oral			
	2	46	DHEA	50 mg	Oral			
Basaria 2009	1	46	Plac		Suppl	casein protein		
	2	38	Isofl	160 mg	Suppl	isoflavones (soy protein)		
Radhakrishnan 2009	1	41	Plac		Oral	casein		
	2	44	Isofl	75 mg	Suppl	soy protein		
Lee 2010	1	44	Plac		Oral			
	2	43	Isofl	350 mg	Oral	isoflavone	Rexflavone	
Garcia 2010	1	28	Plac		Oral			
	2	103	See Note	300 mg E. ulmoides +150 mg V radiata	Oral		Nutrafem	
Lipovac 2010	1	59	Plac		Oral			
	2	50	Isofl	80 mg	Oral	red clover extract (MF11RCE)		

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Shen 2010	1	44	Plac	500 mg	Oral	starch		
	2	47	See Note	500 mg	Oral	green tea polyphenols		
Jassi 2010	1	25	Plac	30 g	Suppl	casein protein		
	2	25	Isofl	60 mg	Suppl	soy protein		
	3	25	Isofl	60 mg	Oral	soy isoflavones		
Evans 2011	1	42	Plac		Oral			
	2	41	Isofl	30 mg	Oral	genistein	geniVida	
Hsu 2011	1	25	Plac		Suppl			
	2	25	See Note	24 mg	Suppl			
Andrikoula 2011	1	34	Plac		Oral			
	2	36		See Note	Oral			
Levis 2011	1	126	Plac		Oral			
	2	122	Isofl	200 mg	Oral	soy protein (genistein and daidzein)	Novasoy	
Plotnikoff 2011	1	59	Plac		Oral			
	2	62	See Note	7.5g	Oral	keishibukuryogab (TU-025)		
	3	57	See Note	12.5g	Oral	keishibukuryogab (TU-025)		
Chang 2011	1	33	Plac		Oral			
	2	31	See Note	257.1 mg	Oral	cynanchum wilfordii + phlomis umbrosa +angelica gigas	EstroG-100	
Auerbach 2012	1	38	Plac		Oral	sunflower oil		
	2	43	See Note	0.254 mg	Oral	pomegranate seed oil	PEKANA	
Cianci 2012	1	60	Plac		Oral			
	2	60	Isofl	60 mg	Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Kim 2012	1	36	Plac		Oral			
	2	36	Gins	3000	Oral	red ginseng		
Xia 2012	1	36	Plac		Oral			
	2	36	See Note	3500 mg	Oral	Du zhong + Bu gu zhi + Dan shen	Jiawei Quig'e Fang	
Ye 2012	1	30	Plac		Oral			
	2	30	Isofl	84 mg	Oral	soy germ isoflavone	SoyLife EXTRA	
	3	30	Isofl	126 mg	Oral	soy germ isoflavone	SoyLife EXTRA	
Aso 2012	1	60	Plac		Oral			
	2	66	Isofl	10mg	Oral	equol		
Amato 2012	1	134	Plac		Oral			
	2	135	Isofl	80	Oral	aglycone soy isoflavone		
	3	134	Isofl	120	Oral	aglycone soy isoflavone		
Colau 2012	1	51	Plac		Oral			
	2	50	B Coh				Actheane	
Lima 2012	1	25	Plac		VagGel			
	2	30	Isofl	50	VagGel	isoflavone	Glycine max L. Merr.	
Pandit 2012	1	25	Plac		Oral			
	2	29		See Note	Oral			
Schellenberg 2012	1	54	Plac		Oral			
	2	57	B Coh	6.5	Oral			
	3	55	B Coh	13	Oral			
von Hagens 2012	1	32	Plac		Oral			
	2	62		See Note	Oral	ovaria bovis, ovaria comp.		
Yang 2012	1	104	Plac		Oral			
	2	111		See Note	Oral		Gengnianningxin or Bushen	
Colacurci 2013	1	62	Plac		Oral			
	2	62	Isofl	60	Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Crawford 2013	1	38	Plac		Oral			
	2	28	Isofl	33-66 mg	Oral		Novosoy 400	
	3	64	Isofl	100-200 mg	Oral		Novosoy 400	
Kohama 2013	1	77	Plac		Oral			
	2	79	See Note	30	Oral	procyanidins	Pycnogenol	
Zhong 2013	1	54	Plac		Oral			
	2	54		DongQ	Oral	xian mao, xian ling pi, ba ji tian, dang gui, zhi mu, huang bai	Er-Xian decoction	
Chi 2013	1	33	Plac		Oral			
	2	37	Isofl		Oral			
Mainini 2013	1	75	Plac		Oral			
	2	75	Isofl	80	Oral			
Constantine 2014	1	456	Plac		Oral			
	2	463	See Note	60	Oral	ospemifene		
Constantine 2014	1	63	Plac		Oral			
	2	363	See Note	60	Oral	ospemifene		
Constantine 2014	1	268	Plac		Oral			
	2	276	See Note	60		ospemifene		

B coh: black cohosh; DHEA: Dehydroepiandrosterone; DongQ: dong quai; Gins: ginseng; Isofl: isoflavone; (m): trial contains data from multiple publications; Plac: placebo; Suppl: dietary supplement

Table E-50. Therapies used in trials comparing hormone and nonprescription nonhormone with placebo

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Crisafulli 2004	1	30	Plac		Oral			
	2	30	Isofl	54mg	Oral	genistein		
	3	30	EP comb	1mg E + 0.5mg P	Oral	estradiol + norethisterone acetate	Activelle	Low
Newton 2006	1	84	Plac		Oral			
	2	32	EP comb	0.625 mg E + 2.5 mg P	Oral	conjugated equine estrogen + medroxyprogesterone		Standard
	3	80	B Coh	160 mg	Oral	black cohosh		
	4	76	See Note	black cohosh: 200 mg; alfalfa: 400 mg; boron: 4 mg; chaste tree: 200 mg; dong quai: 400 mg; false unicorn: 200 mg; licorice: 200 mg; oats: 400 mg; pomegranate: 400 mg; ginseng: 400 mg	Oral	multibotanical	ProGyne	
	5	79	See Note	black cohosh: 200 mg; alfalfa: 400 mg; boron: 4 mg; chaste tree: 200 mg; dong quai: 400 mg; false unicorn: 200 mg; licorice: 200 mg; oats: 400 mg; pomegranate: 400 mg; ginseng: 400 mg	Oral	multibotanical	ProGyne	
Yalamanchili 2012	1	123	Plac		Oral			
	2	123		See Note	Oral	calcitriol	Rocaltrol	
	3	121	EP	0.625 E + 2.5 P	Oral	conjugated estrogens +	Premarin +	Standa

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
			comb			MPA	Provera	rd
	4	122	EP comb	0.625 E + 2.5 P	Oral	conjugated estrogens + MPA + calcitriol	Premarin + Provera + Rocaltrol	Standard
Gupta 2013	1	25	Plac		Oral			
	2	25	Est	0.625	Oral	conjugated equine estrogen	Premarin	Standard
	3	25	DHEA	25	Oral	DHEA	Evandra	

B coh: black cohosh; EP comb: estrogen plus progestin combined; Isofl: isoflavone; Plac: placebo

Table E-51. Therapies used in trials comparing hormone with hormone

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Polvani 1991	1	170	EP seq	0.625 mg E + 10 mg P	Oral	conjugated equine estrogens + medroxyprogesterone acetate		Standard
	2	203	EP seq	0.05 mg E + 10 mg P	Patch	estradiol + medroxyprogesterone acetate		Standard
Henriksson 1994	1	106	Est	0.0095mg	VayRin	estradiol	Silastic	Low
	2	51	Est	0.5mg	VagPes	estriol	Ovesterin	Low
Studd 1995	1	104	EP seq	0.625 mg E + 20 mg P	Oral	conjugated estrogen + dydrogesterone	Premarin + Duphaston	Standard
	2	100	EP seq	0.05 mg E + 20 mg P	Patch	estradiol + dydrogesterone	Menorest + Duphaston	Standard
Ayton 1996	1	131	Est	0.0075mg	VayRin	estradiol	Estring	Low
	2	63	Est	0.625mg	VagCrm	conjugated estrogen	Premarin	Standard

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Hilditch 1996	1	35	EP seq	0.625mg E + 10mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate	Premarin + Provera	Standard
	2	39	EP seq	0.014mg E + 10mg P	Patch	estradiol + medroxyprogesterone acetate	Estraderm + Provera	UltraLow
Egarter 1996	1	51	EP seq	2mg E + 10mg P	Oral	estradiol valerate + medroxyprogesterone acetate	Dilena or Divina	High
	2	50	EP seq	0.625mg E + 10mg P	Oral	conjugated estrogen + medrogestone	Premarin + Colpron	Standard
Hirvonen 1997	1	60	EP seq	1.0 mg E + 10 mg P	SknGel	estradiol + peroral dydrogesterone	Divigel + Terolut	Low
	2	60	EP seq	0.05 mg E + 10 mg P	Patch	estradiol + peroral dydrogesterone	Estraderm + Terolut	Standard
Hirvonen 1997	1	84	EP seq	1 mg E + 20 mg P	SknGel	estradiol + medroxyprogesterone acetate	Divigel + Provera	Low
	2	32	EP seq	2 mg E + 10 mg P	SknGel	estradiol + medroxyprogesterone acetate	Divigel + Provera	Standard
	3	57	EP seq	2 mg E + 10 mg P	Oral	estradiol valerate + medroxyprogesterone	Divina	High
Rozenberg 1997	1	153	EP comb	0.05 mg E + P (see comment)	Patch	estradiol + dydrogerterone or estradiol + norethisterone		Standard
	2	154	EP comb	0.05 mg E + 0.17 mg P	Patch	estradiol + norethisterone acetate		Standard
	3	158	EP comb	0.05 mg E + 0.35 P	Patch	estradiol + norethisterone acetate		Standard
	4	153	EP seq	0.05 mg E + 0.17 mg P	Patch	estradiol + norethisterone acetate		Standard
	5	156	EP seq	0.05 mg E + 0.35 mg P	Patch	estradiol + norethisterone acetate		Standard
Al-Azzawi 1997	1	129	Est	0.05 mg	Patch	estradiol	Estraderm	Standard

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	134	Est	0.05 mg	Patch	estradiol	Lyrelle 50	Standard
	3	131	Est	0.08 mg	Patch	estradiol	Lyrelle 80	High
Lubbert 1997	1	1232	EP comb	0.05 mg E + ? mg P	Patch	estradiol + progestogen	Menorest + progestogen	Standard
	2	1227	EP seq	0.05 mg + ? mg P	Patch	estradiol + progestogen	Menorest + progestogen	Standard
Barentsen 1997	1	83	Est	0.0075mg	VayRin	estradiol	Estring	Low
	2	82	Est	0.5mg	VagCrm	estriol	Synapause	Low
Bachmann 1997	1	129	EP comb	0.0075mg	VayRin	estradiol + medroxyprogesterone	Estring	Low
	2	67	Est	0.625 mg	VagCrm	conjugated equine estrogen	Premarin	Standard
Good 1999	1	79	Est	0.625 mg	Oral	conjugated equine estrogen	Premarin	Standard
	2	82	Est	1.25 mg	Oral	conjugated equine estrogen	Premarin	High
	3	80	Est	0.05 mg	Patch	estradiol	Alora	Standard
	4	80	Est	0.1 mg	Patch	estradiol	Alora	High
Mattsson 2000	1	342	EP seq	2 mg E + 10 mg P	Oral	estradiol + dydrogesterone		Standard
	2	317	EP seq	0.3 mg E + 10 mg P	NasSpr	estradiol + dydrogesterone	Aerodiol	Standard
Saure 2000	1	186	EP seq	1.5 mg E + 0.15 P	Oral	estradiol (E2) + desogestrel	Liseta	Standard
	2	190	EP seq	2 mg E + 10 mg P	Oral	estradiol valerate + medroxyprogesterone acetate	Klimalet	High
Graser 2000	1	199	EP	2 mg E + 2 mg P	Oral	estradiol valerate + dienogest	Climodien	High

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
			comb					
	2	186	EP comb	2 mg E + 3 mg P	Oral	estradiol valerate + dienogest		High
	3	196	EP comb	2 mg E + 1 mg Estriol + 1.0 mg P	Oral	estradiol + estriol + norethisterone acetate	Kliogest	Standard
Rioux 2000	1	80	Est	0.025 mg	VagTab	estradiol	Vagifem	Low
	2	79	Est	1.25 mg	VagCrm	conjugated equine estrogen	Premarin	Standard
Dugal 2000	1	48	Est	0.025 mg	VagTab	estradiol	Vagifem	Low
	2	48	Est	0.5 mg	VagPes	estriol	Ovesterin	Low
Parsey 2000	1	95	Est	0.025mg	Patch	estradiol	Climara	UltraLow
	2	98	Est	0.3mg	Oral	conjugated equine estrogen	Premarin	UltraLow
Meuwissen 2001	1	314	EP seq	2mg E + 0.5mg P	Oral	estradiol valerate + norgestrel	Cyclocur	High
	2	320	EP seq	2mg E + 0.5mg P	Oral	estradiol + trimegestone		Standard
Lopes 2001	1	185	EP seq	0.05 mg E + 10 or 20 mg P	Patch	estradiol + dydrogesterone	Estraderm + dydrogesterone	Standard
	2	176	EP seq	0.3 mg E + 10 or 20 mg P	NasSpr	estradiol + dydrogesterone	Aerodiol + dydrogesterone	Standard
Ozsoy 2002	1	100	EP seq	2 mg E + 5 mg P	Oral	estradiol + medroxyprogesterone acetate		Standard
	2	101	EP seq	0.300 mg E + 5 mg P	NasSpr	estradiol + medroxyprogesterone acetate	Aerodiol + medroxyprogesterone acetate	Standard

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Loh 2002	1	48	EP comb	1mg E + 0.5mg P	Oral	estradiol + norethisterone acetate		Low
	2	48	EP comb	2mg E + 1mg P	Oral	estradiol + norethisterone acetate		Standard
Buckler (d) 2003	1	75	EP seq	1 mg E + 1 mg P	Oral	estradiol + norethisterone	Elleste Solo + Micronor-HRT	Low
	2	84	EP seq	0.05 mg E + 1 mg P	VayRin	estradiol acetate + norethisterone	Menoring + Micronor-HRT	High
Lobo 2003	1	111	EP comb	0.625 mg	Oral	esterified estrogens	Estratab	Standard
	2	107	ET comb	0.625 mg E + 1.25 mg T	Oral	esterified estrogens + methyltestosterone	Estratest-HS	Standard
Pornel 2005	1	387	EP seq	1 mg E + 0.25 P	Oral	estradiol + trimegestone	Totelle	Low
	2	377	EP seq	1 mg E + 1 mg P	Oral	estradiol valerate + norethisterone	Climagest	Standard
Gambacciani 2005	1	432	EP comb	1 mg E + 0.125 mg P	Oral	estradiol + trimegestone		Low
	2	242	EP comb	1 mg E + 0.5 mg P	Oral	estradiol + norethisterone		Low
	3	176	EP comb	2 mg E + 1 mg P	Oral	estradiol + norethisterone		Standard
Utian 2005	1	79	EP comb	0.9 mg	Oral	estradiol acetate + progestin	Femtrace	Standard
	2	85	EP comb	0.625 mg	Oral	conjugated equine estrogens + progestin	Premarin	Standard
	3	84	EP comb	1 mg	Oral	estradiol + progestin	Estrace	Low
Davis 2005	1	60	Est	0.05 mg	Patch	estradiol	Estraderm	Standard
	2	60	Est	0.30 mg	NasS	estradiol	Aerodiol	Standar

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
					pr			d
Raynaud 2005	1	136	EP seq	0.05 mg + 1.2mg P	Patch	estradiol + norethisterone acetate	Oesclim + Milligynon	Standard
	2	134	EP seq	0.04 mg + 1.2mg P	Patch	estradiol + norethisterone acetate	Estrapatch + Milligynon	Low
	3	135	EP seq	0.06 mg E + 1.2m P	Patch	estradiol + norethisterone acetate	Estrapatch + Milligynon	High
Braunstein 2005	1	119	Est		Patch			
	2	106	ET comb	? mg E + 0.15 mg T	Patch	estrogen + testosterone		
	3	110	ET comb	? mg E + 0.3 mg T	Patch	estrogen + testosterone		
	4	111	ET comb	? mg E + 0.45 mg T	Patch	estrogen + testosterone		
Simon 2005	1	279	Est		Patch			
	2	283	Test	0.3 mg	Patch	testosterone		
Weisberg 2005	1	126	Est	0.008mg	VayRin	estradiol	ESTring	Low
	2	59	Est	0.025mg	VagTab	estradiol	Vagifem	Low
Buster 2005	1	266	Est		Patch			
	2	266	Test	0.3 mg	Patch	testosterone		
Akhila 2006	1	35	EP comb	0.625 mg E + 2.5 mg P	Oral	conjugated equine estrogen + depomedroxyprogesterone acetate	Premarin + MPA	Standard
	2	25	EP comb	1.5 mg E + 2.5 mg P	SknGel	estradiol + depomedroxyprogesterone acetate	Estrogel + MPA	Standard
	3	28	EP	0.05 mg E + 2.5	Patch	estradiol +	Estraderm + MPA	Standar

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
			comb	mg P		depomedroxyprogesterone acetate		d
Serrano 2006	1	55	EP seq	0.625 mg E + 10 mg P	Oral	conjugated estrogens + medroxyprogesterone acetate	Premarin + medroxyprogesterone acetate	Standard
	2	59	EP seq	0.05 mg + 10 mg P	Patch	estradiol + medroxyprogesterone acetate	Climara + medroxyprogesterone acetate	Standard
Cieraad 2006	1	98	EP seq	1 mg E + 10 mg P	Oral	estradiol + dydrogesterone		Low
	2	91	EP seq	0.625 mg E + 0.15 mg P	Oral	conjugated equine estrogens + norgestrel		Standard
Davis 2006	1	39	Est		Patch			
	2	37	ET comb	?mg E + 0.3 mg T	Patch			
Long 2006	1	37	Est	0.625mg	Oral	conjugated equine estrogen		Standard
	2	36	Est	0.625mg/1g cream	VagCrm	conjugated equine estrogen	Premarin	Standard
Shifren 2006	1	273	EP comb	?mg E	Patch			
	2	276	ET comb	?mg E + 0.3 mg T	Patch	testosterone		
Limpaphayom (m) 2006	1	342	EP comb	0.3 mg E + 1.5 mg P	Oral	conjugated estrogens + medroxyprogesterone acetate		UltraLow
	2	342	EP comb	0.45 mg E + 1.5 mg P	Oral	conjugated estrogens + medroxyprogesterone acetate		Low
	3	344	EP comb	0.625 mg E + 2.5 mg P	Oral	conjugated estrogens + medroxyprogesterone acetate		Standard
Odabasi 2007	1	32	EP comb	0.3mg E + 90mg P	NasSpr	estradiol + progesterone	Aerodiol + Crinone	Standard

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
	2	29	EP comb	0.050mg E + 90mg P	Patch	estradiol + progesterone	Climara + Crinone	Standard
Pitkin (d) 2007	1	152	EP comb	1 mg E + 2.5 mg P	Oral	estradiol valerate (E2V) + medroxyprogesterone acetate (MPA)		Standard
	2	153	EP comb	1 mg E + 5 mg P	Oral	estradiol valerate (E2V) + medroxyprogesterone acetate (MPA)		Standard
	3	154	EP comb	2 mg E + 5 mg P	Oral	estradiol valerate (E2V) + medroxyprogesterone acetate (MPA)		High
Penteado 2008	1	27	EP comb	0.625 mg E + 2.5 mg P	Oral	conjugated equine estrogens + medroxyprogesterone acetate		Standard
	2	29	ET comb	0.625 mg E + 2.5 mg P + 2.0 mg T	Oral	conjugated equine estrogens + medroxyprogesterone acetate + methyltestosterone		Standard
Panay 2010	1	142	Est		Patch			
	2	130	ET comb	0.30 mg	Patch			

(d): duplicate patient population with other included article; EP comb: estrogen plus progestin combined; EP seq: estrogen plus progestin sequential; Est: estrogen alone; ET comb: estrogen plus testosterone combine; (m): trial contains data from multiple publications; NasSpr: nasal spray; RxCat: treatment category; SknGel: skin gel; VagCrm: vaginal cream; VagOvu: vaginal ovule; VagPes: vaginal pessary; VagRin: vaginal ring; VagTab: vaginal tablet

Table E-52. Therapies used in trials comparing hormone with nonprescription nonhormone

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Nappi 2005	1	32	B Coh	40 mg	Oral		Remifemin	
	2	32	EP seq	0.00357mg E + 10 mg P	Patch	estradiol + dihydrogesterone	Estraderm + Dufaston	UltraLow
Nathorst-Boos 2006	1	53	EP comb		SknGel			
	2	53	See Note	10 mg	SknGel	testosterone	Testogel	Unknown

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Kaari 2006	1	35	Est	0.625 mg	Oral	conjugated equine estrogens		Standard
	2	33	Isofl	120	Oral	glycoside + aglycone		
Chandeying 2007	1	30	EP comb	0.625mg E + 2.5mg P	Oral	conjugated equine estrogen + medroxyprogesterone acetate		Standard
	2	30	See Note	50mg	Oral			
Menati 2013	1	26	See Note	1140	Oral			
	2	26	EP comb	0.312 E + 2.5 P	Oral	conjugated estrogen + MPA		Low
Zhang 2013	1	31	B Coh		Oral	cimicifuga foetida		
	2	30	EP seq		Oral	E2V + progestin		Standard
	3	28	EP seq		Oral	E2V + MPA		Standard

B coh: black cohosh; EP comb: estrogen plus progestin combined; EP seq: estrogen plus progestin sequential; Est: estrogen alone;Isofl: isoflavone

Table E-53. Therapies used in trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Liske 2002	1	74	B Coh	39 mg	Oral		Remifemin	
	2	75	B Coh	127.3 mg	Oral		Remifemin	
Hidalgo 2006	1	478	See Note	60 mg I + 440 mg PO + 10 mg Vit E	Oral			
	2	447	See Note	120 mg I + 880 mg PO + 20 mg Vit E	Oral			

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Zervoudis (a) 2008	1	31	See Note		Oral			
	2	31	Vit E	500 IU	Oral			
Agosta 2011	1	301	See Note	60 mg	Oral			
	2	335	See Note	60 mg	Oral			
Le Donne 2011	1	31	See Note	5 mg	VagPes			
	2	31	Isofl	0.097 mg	VagPes	genistein		
Virojchaiwong 2011	1	26	See Note	25 mg	Oral			
	2	26	See Note	50 mg	Oral	Pueraria mirifica		
Yang 2012	1	65	Isofl	35	Oral	isoflavone	Phyto Soya	
	2	65	Isofl	70	Oral	isoflavone	Phyto Soya	

(a): data came from a conference abstract; B coh: black cohosh; Isofl: isoflavone; IU: international unit; VagPes: vaginal pessary; VitE: vitamin E

Table E-54. Therapies used in trials comparing nonprescription nonhormone with antidepressant

Study	Arm	N	RxCat	Dose	Route	Generic	Trade	Est Dose
Oktem 2007	1	40	B Coh	40 mg	Oral		Remixin	
	2	40	Antide	20 mg	Oral	fluoxetine	Prozac HCl	

Antide: antidepressant; B coh: black cohosh

Table E-55. Study quality for trials comparing hormone with placebo

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Martin 1971	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Campbell 1977	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Baumgardner 1978	Unc	Yes	Unc	Unc	Yes	Unc	Yes	Yes	Yes	Poor
Coope 1981	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Jensen 1983	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Foidart 1991	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Eriksen 1992	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Wiklund 1993	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Derman 1995	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Saletu 1995	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	No	Poor
Good 1996	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Speroff (Study 1) 1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Poor
Chung 1996	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor
Speroff (Study 2) 1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
Speroff (Study 3) 1996	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Poor
Bacchi-Modena 1997	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Baerug 1998	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Bech 1998	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
de Vrijer 1999	Unc	Unc	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Leonetti 1999	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Poor
Studd 1999	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Polo-Kantola 1999	Yes	Yes	Yes	Yes	No	Unc	Yes	Yes	No	Poor
Casper 1999	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	No	Poor
Cohen 1999	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Rebar 2000	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Speroff (Study 1) 2000	Unc	Yes	Unc	Unc	No	Unc	Yes	Yes	No	Poor
Rovati 2000	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Notelovitz 2000	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Strickler 2000	Yes	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Notelovitz 2000	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
DeAloysio 2000	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
von Holst 2000	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Notelovitz 2000	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Alexandersen 2000	Unc	No	Yes	No	Yes	Unc	Yes	Yes	Yes	Poor
Speroff (Study 2) 2000	Unc	Yes	Unc	Unc	No	Unc	Yes	Yes	Yes	Poor
Rigano 2001	No	Unc	Unc	Unc	Unc	Unc	Unc	Yes	Unc	Poor
Utian (CEE alone arms) 2001	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Simon 2001	Unc	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Soares 2001	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Utian (CEE/MPA arms) 2001	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Rozenbaum 2002	Yes	Unc	Unc	Yes	No	Unc	Yes	Yes	Yes	Poor
Shulman (Study 1) 2002	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Fair
von Holst 2002	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Archer 2003	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Vestergaard 2003	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Poor
Speroff 2003	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Fair
Jirapinyo 2003	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Haines 2003	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Hays 2003	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Gambacciani 2003	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Gelfand 2003	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Wren 2003	Unc	Unc	Unc	Yes	No	Unc	Yes	Yes	No	Poor
Simunic 2003	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Parsons 2003	Yes	No	Yes	Yes	No	No	Yes	Yes	Unc	Poor
Berlex (SIP) 2003	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Rudolph 2004	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Yang 2004	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Schurmann 2004	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Utian 2004	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Dessole 2004	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Duramed (SIP) 2004	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Brunner 2005	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Onalan 2005	Yes	Yes	Unc	Yes	Yes	Unc	Yes	Yes	Unc	Poor
Bayer Healthcare (SIP) 2005	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Novartis (SIP) 2005	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Speroff (Study 1) 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Simon 2006	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Nielsen 2006	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Osmanagaoglu 2006	Unc	No	Unc	Unc	No	No	Yes	Yes	Unc	Poor
Speroff (Study 2) 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Bachmann (d) 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Maki 2007	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Endrikat 2007	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Lee 2007	No	Yes	Unc	Yes	Yes	Yes	Yes	Yes	No	Poor
Panay 2007	No	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Simon 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Pefanco 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Unc	Yes	Poor
Bayer Healthcare (SIP) 2007	Unc	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Buster (Study 1) 2008	Yes	No	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Veerus 2008	Unc	No	No	Unc	Unc	No	Yes	Yes	Yes	Poor
Davis 2008	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Bachmann 2008	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Good
Welton 2008	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Buster (Study 2) 2008	Yes	No	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Buster (Study 3) 2008	Yes	No	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Simon (SIP) 2008	No	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Benster 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Utian 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Lobo 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Haines 2009	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Bachmann (d) 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Hedrick 2009	Unc	Yes	Unc	Yes	No	No	Yes	Yes	Yes	Poor
Baksu 2009	Yes	No	No	Unc	No	No	Yes	Yes	Unc	Poor
Bachmann (Study 1) 2009	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Freedman 2009	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Gast 2009	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Bachmann (Study 2) 2009	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Hassa 2010	Unc	No	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Stevenson 2010	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Bachmann 2010	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Raghunandan 2010	Unc	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Unc	Poor
Hedrick 2010	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Liu 2011	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Lin 2011	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	Yes	Poor
Demetrio 2011	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Liu 2012	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Archer 2012	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Archer 2012	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Cano 2012	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Polisseni 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Raz 2013	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	
Archer 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Pinkerton 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-56. Study quality for trials comparing antidepressant with placebo

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Suvanto-Luukkonen 2005	Unc	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Evans 2005	Yes	Unc	Unc	Unc	Yes	Unc	Yes	Yes	Unc	Poor
Kerwin 2007	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Kalay 2007	Yes	No	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Speroff 2008	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Soares 2008	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Archer 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Archer 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Kornstein 2010	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	No	Poor
Soares 2010	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Freeman 2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Bouchard 2012	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Pinkerton 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Simon (Study 2) 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Pinkerton 2013	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Good
Simon (Study 1) 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-57. Study quality for trials comparing other prescriptions with placebo

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Clayden 1974	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Guttuso 2003	Unc	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Poor
Butt 2008	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Joffe 2010	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Depomed (c) 2012										
Depomed (c) 2012										
Pinkerton 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-58. Study quality for trials comparing nonprescription nonhormone with placebo

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Chenoy 1994	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Murkies 1995	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Hirata 1997	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Albertazzi 1998	Yes	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Fair
Baber 1999	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Wiklund 1999	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Barnhart 1999	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Upmalis 2000	Unc	Yes	Unc	No	Yes	Unc	Yes	Yes	No	Poor
Kotsopoulos 2000	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Davis 2001	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Faure 2002	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Han 2002	Yes	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Good
Tice 2003	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Penotti 2003	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Burke 2003	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Sammartino 2003	Yes	No	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Nahas 2004	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Atkinson 2004	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	No	Poor
Hartley 2004	Unc	Unc	Unc	Unc	No	Unc	Yes	Yes	No	Poor
Winther 2005	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Frei-Kleiner 2005	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Verhoeven 2005	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Kok 2005	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Hidalgo 2005	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
Dodin 2005	Yes	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Fair
Osmers 2005	Unc	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Poor
Mucci 2006	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Heger (m) 2006	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Lewis 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Uebelhack 2006	Yes	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Good

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Sammartino 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Casini 2006	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Nahas 2007	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Poor
Yang 2007	No	Yes	Unc	Yes	Yes	Yes	Yes	Yes	No	Poor
Chung 2007	No	Yes	Unc	Unc	No	Yes	Yes	Yes	No	Poor
Cheng 2007	Yes	Yes	Unc	Yes	Unc	Yes	Yes	Yes	No	Poor
Ho 2007	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Cancellieri 2007	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Haines 2008	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Jou 2008	Yes	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Unc	Poor
Khaodhiar 2008	Yes	Yes	Unc	No	No	Yes	Yes	Yes	No	Poor
Ferrari 2009	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Poor
van der Sluijs 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
D'Anna (m) 2009	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	No	Poor
van Die 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
de Sousa-Munoz 2009	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Labrie 2009	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Panjari 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Basaria 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Radhakrishnan 2009	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
Lee 2010	Unc	Yes	Yes	Unc	No	Yes	Yes	Yes	No	Poor
Garcia 2010	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Lipovac 2010	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Shen 2010	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Jassi 2010	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Evans 2011	No	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Hsu 2011	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Andrikoula 2011	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Levis 2011	Unc	Yes	Unc	No	Yes	Yes	Yes	Yes	No	Poor
Plotnikoff 2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Chang 2011	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Auerbach 2012	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	No	Poor
Cianci 2012	Yes	No	Unc	Unc	Unc	No	Yes	Yes	Unc	Poor
Kim 2012	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Xia 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Ye 2012	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Poor
Aso 2012	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	No	Poor
Amato 2012	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Colau 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Lima 2012	Unc	Yes	Unc	Yes		No	Yes	Yes	Yes	Poor
Pandit 2012	Unc	Yes	Unc	Yes	No	Unc	Yes	No	Unc	Poor
Schellenberg 2012	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
von Hagens 2012	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Yang 2012	Yes	Unc	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Colacurci 2013	Yes	Unc	Unc	Yes		No	Yes	Yes	Unc	Poor
Crawford 2013	Yes	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Kohama 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Zhong 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Chi 2013	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Mainini 2013	Yes	Yes	Unc	No	Yes	Yes	Yes	Yes	Unc	Poor
Constantine 2014	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Constantine 2014	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Constantine 2014	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-59. Study quality for trials comparing hormone and nonprescription nonhormone with placebo

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Crisafulli 2004	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Newton 2006	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Yalamanchili 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
Gupta 2013	Unc	Unc	Unc	Yes	No	Unc	Yes	No	Unc	Poor

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-60. Study quality for trials comparing hormone with hormone

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Polvani 1991	Unc	No	No	No	Yes	Yes	Yes	Yes	No	Poor
Henriksson 1994	Unc	No	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Studd 1995	Unc	Unc	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Ayton 1996	Yes	No	No	Unc	No	Yes	Yes	Yes	Yes	Poor
Hilditch 1996	No	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Egarter 1996	No	No	No	Unc	No	No	Yes	Yes	Unc	Poor
Hirvonen 1997	Yes	No	No	Yes	No	No	Yes	Yes	Unc	Poor
Hirvonen 1997	Yes	No	No	No	Yes	Yes	Yes	No	Unc	Poor
Rozenberg 1997	Yes	No	No	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Al-Azzawi 1997	Unc	No	No	Yes	No	No	Yes	Yes	Unc	Poor
Lubbert 1997	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Poor
Barentsen 1997	Unc	No	No	Unc	No	Yes	Yes	Yes	Yes	Poor
Bachmann 1997	Yes	No	No	No	No	Unc	Yes	Yes	No	Poor
Good 1999	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Mattsson 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Saure 2000	Yes	Yes	Yes	Yes	No	Yes	Yes	Unc	Yes	Fair
Graser 2000	Unc	Yes	Unc	Unc	Unc	Yes	Yes	Yes	Yes	Poor
Rioux 2000	Yes	No	No	No	Yes	No	Yes	Yes	Unc	Poor
Dugal 2000	Unc	No	No	Unc	No	Unc	Yes	Yes	Yes	Poor
Parsey 2000	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Meuwissen 2001	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Lopes 2001	Unc	No	No	Yes	No	Yes	Yes	Yes	Unc	Poor
Ozsoy 2002	No	No	No	Yes	No	Yes	Yes	Yes	Unc	Poor
Loh 2002	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Buckler (d) 2003	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Lobo 2003	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Yes	Poor
Pornel 2005	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	No	Poor
Gambacciani 2005	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Utian 2005	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Good
Davis 2005	Unc	No	No	Yes	No	Yes	Yes	Yes	Unc	Poor
Raynaud 2005	Unc	No	No	Unc	Yes	Unc	Yes	Yes	Yes	Poor
Braunstein 2005	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Simon 2005	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Weisberg 2005	No	No	No	Yes	Yes	Yes	Yes	Yes	Unc	Poor
Buster 2005	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Akhila 2006	Unc	Unc	Unc	Unc	Unc	Unc	Yes	Yes	Unc	Poor
Serrano 2006	Yes	No	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Cieraad 2006	Unc	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Poor
Davis 2006	Yes	Yes	Unc	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Long 2006	Unc	No	Unc	Unc	Yes	Yes	Yes	Yes	No	Poor
Shifren 2006	Unc	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor
Limpaphayom (m) 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Odabasi 2007	Unc	No	No	Unc	Yes	Yes	Yes	Yes	Unc	Poor
Pitkin (d) 2007	Unc	Yes	Unc	Yes	No	Unc	Yes	Yes	Yes	Poor
Penteado 2008	Unc	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Panay 2010	Yes	Yes	Unc	Unc	Yes	Yes	Yes	Yes	Yes	Poor

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-61. Study quality for trials comparing hormone with nonprescription nonhormone

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Nappi 2005	Yes	Unc	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Nathorst-Boos 2006	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unc	Poor
Kaari 2006	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor
Chandeying 2007	Unc	No	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Menati 2013	Yes	Yes	Unc	Yes	No	Yes	No	Yes	Unc	Poor
Zhang 2013	Yes	Unc	Unc	Yes	No	Yes	No	Yes	Unc	Poor

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-62. Study quality for trials comparing nonprescription nonhormone with nonprescription nonhormone

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Liske 2002	Yes	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Fair
Hidalgo 2006	Unc	No	No	Yes	No	Unc	Yes	Yes	Unc	Poor
Zervoudis (a) 2008										
Agosta 2011	Unc	Unc	Unc	Yes	No	No	Yes	Yes	Unc	Poor
Le Donne 2011	Unc	Yes	Unc	Unc	No	Yes	Yes	Yes	Unc	Poor
Virojchaiwong 2011	No	Yes	Unc	Yes	No	Yes	Yes	Yes	Yes	Poor
Yang 2012	Yes	Unc	Unc	Yes	No	Yes	Yes	Yes	Unc	Poor

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Table E-63. Study quality for trials comparing nonprescription nonhormone with antidepressant

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall
Oktem 2007	No	Unc	Unc	Yes	Yes	No	Yes	Yes	No	Poor

(a): data came from a conference abstract; (c): data came from posted results on the clinical trial registry; CEE: conjugated equine estrogen; (d): duplicate patient population with other included article; (m): trial contains data from multiple publications; MPA: medroxyprogesterone acetate; (SIP); data came from a package insert; Unc: uncertain

Q1: Was initial assembly of comparable groups: adequate randomization including equal distribution of potential confounders?

Q2: Were the researchers and subjects blinded to the study group assignment?

Q3: Was there adequate concealment of the study group assignments?

Q4: Was there maintenance of comparable groups (includes attrition, crossovers, adherence and contamination)?

Q5: Was there important differential loss to follow-up or overall high loss to follow-up?

Q6: Were measurements equal, reliable and valid (includes masking of outcome assessment)?

Q7: Were definitions of interventions clear?

Q8: Were all important outcomes considered and defined?

Q9: At analysis, was there adjustment for potential confounders (cohort studies) and intention-to-treat analysis (RCTs)?

Q10: Overall Quality Asessment

Appendix F. Vasomotor Symptom Supplemental Tables and Plots

Figure F-1. Vasomotor symptoms forest plot of pairwise comparisons—estrogen (high dose) compared with placebo

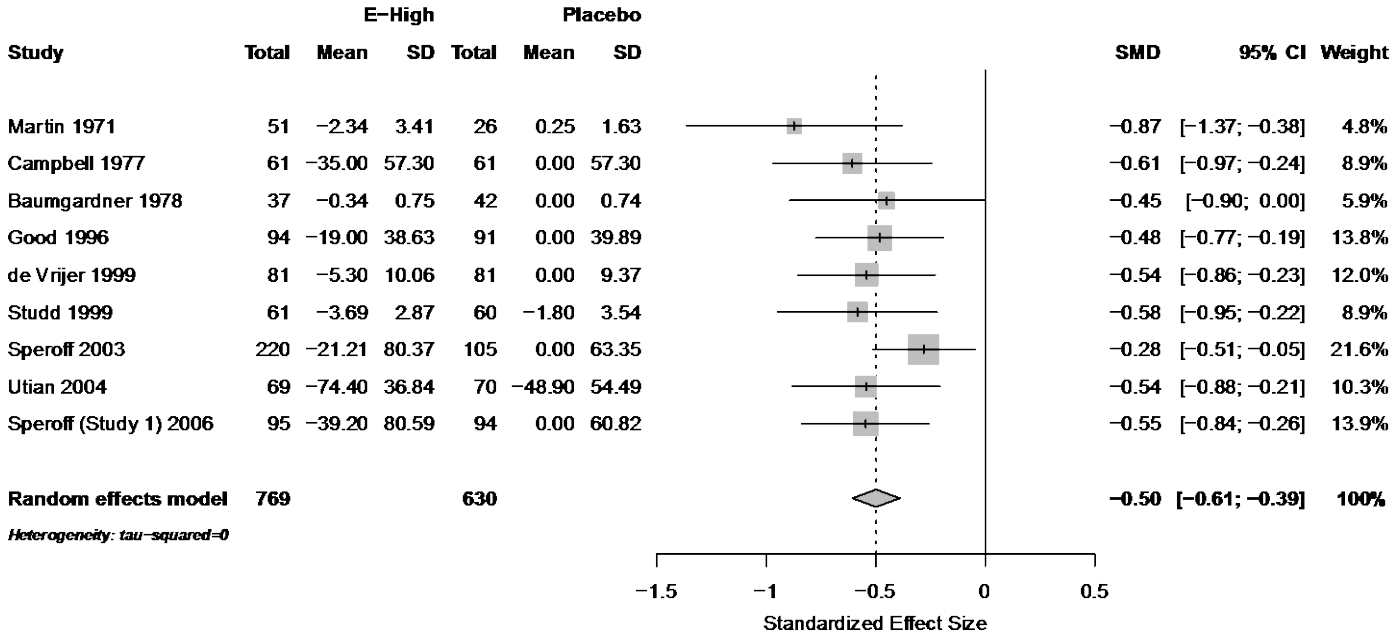


Figure F-2. Vasomotor symptoms forest plot of pairwise comparisons—estrogen (standard dose) compared with placebo

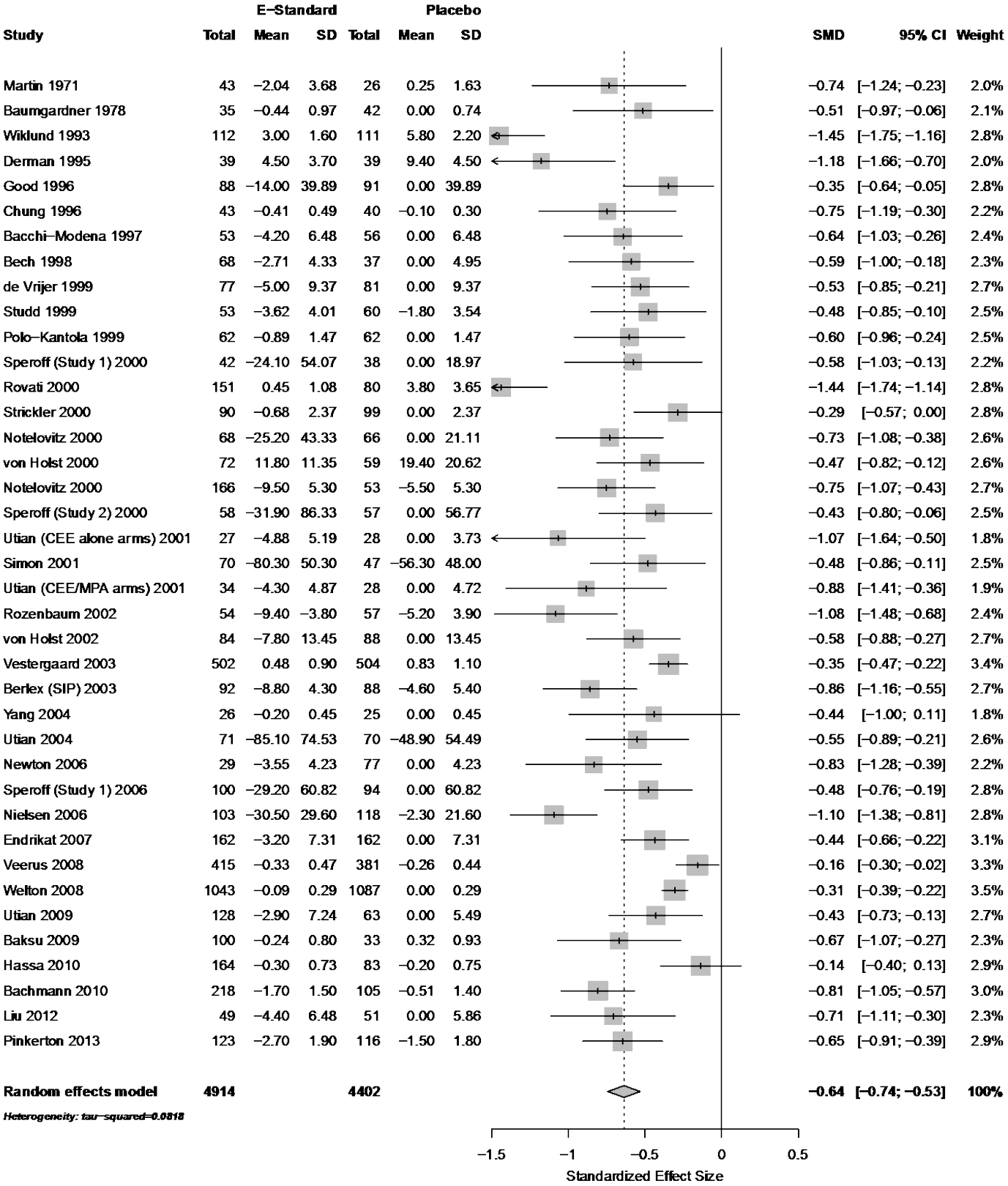


Figure F-3. Vasomotor symptoms forest plot of pairwise comparisons—estrogen (low/ultralow dose) compared with placebo

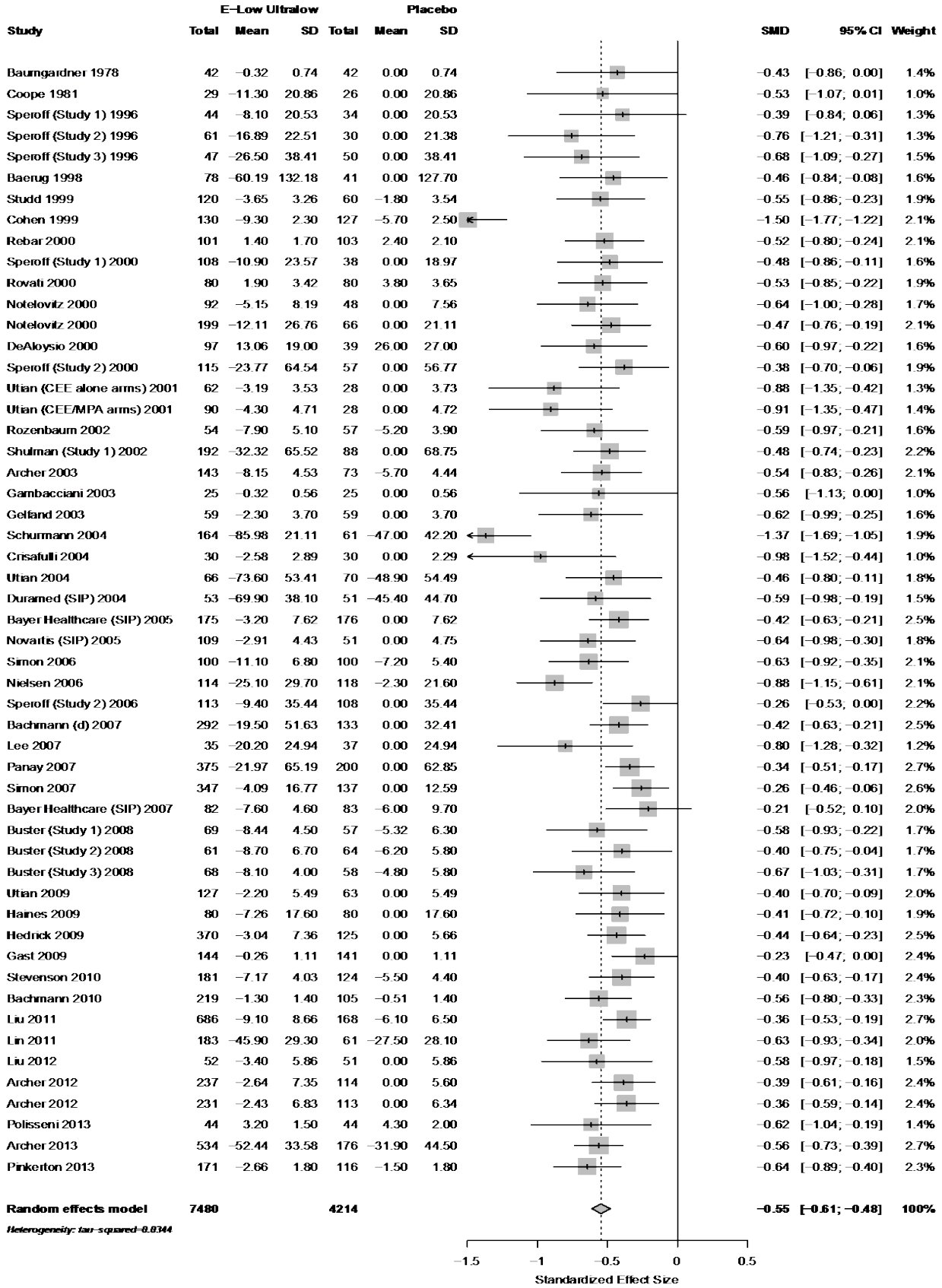


Figure F-4. Vasomotor symptoms forest plot of pairwise comparisons—SSRIs or SNRIs compared with placebo

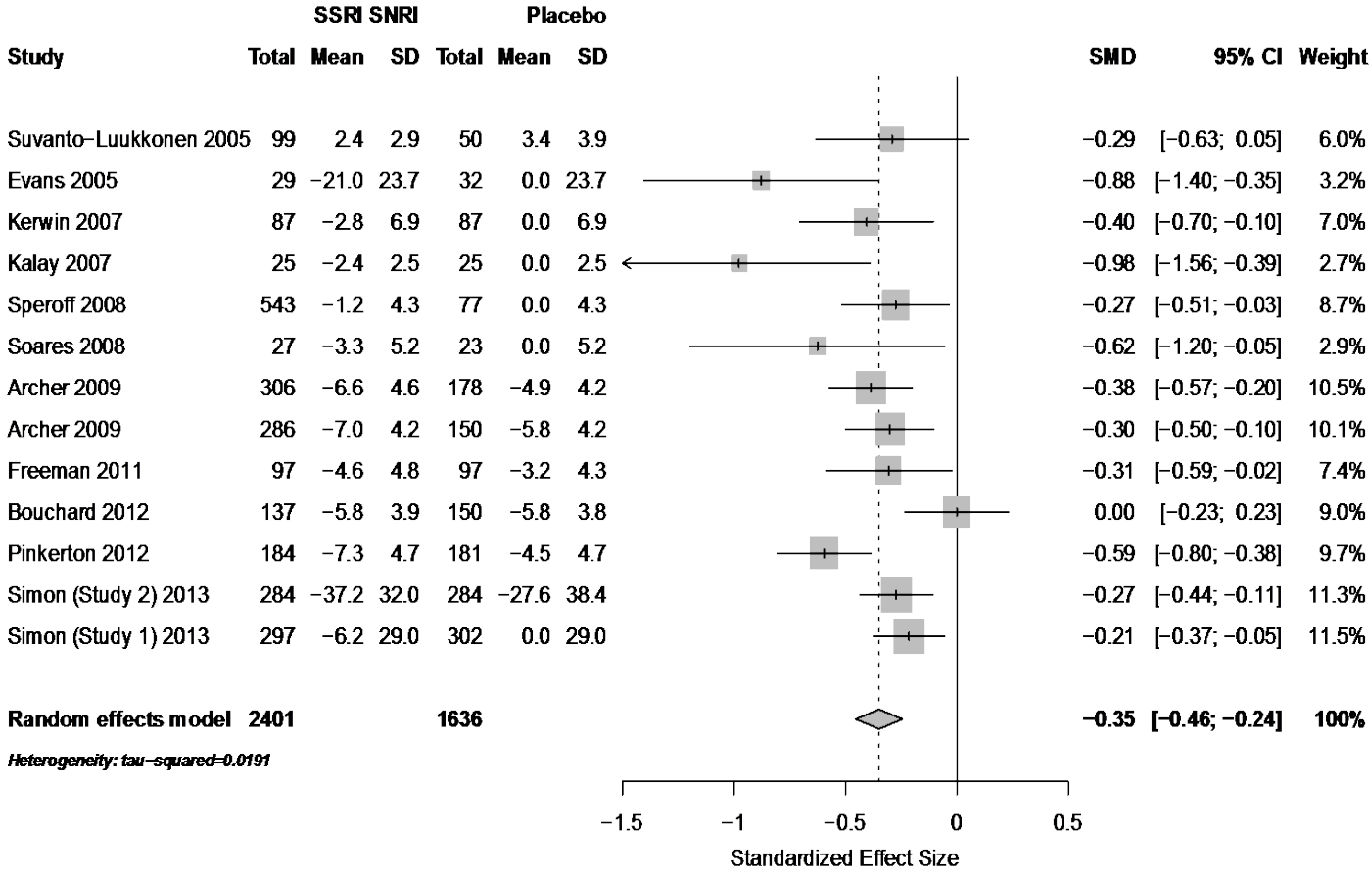


Figure F-5. Vasomotor symptoms forest plot of pairwise comparisons—isoflavones compared with placebo

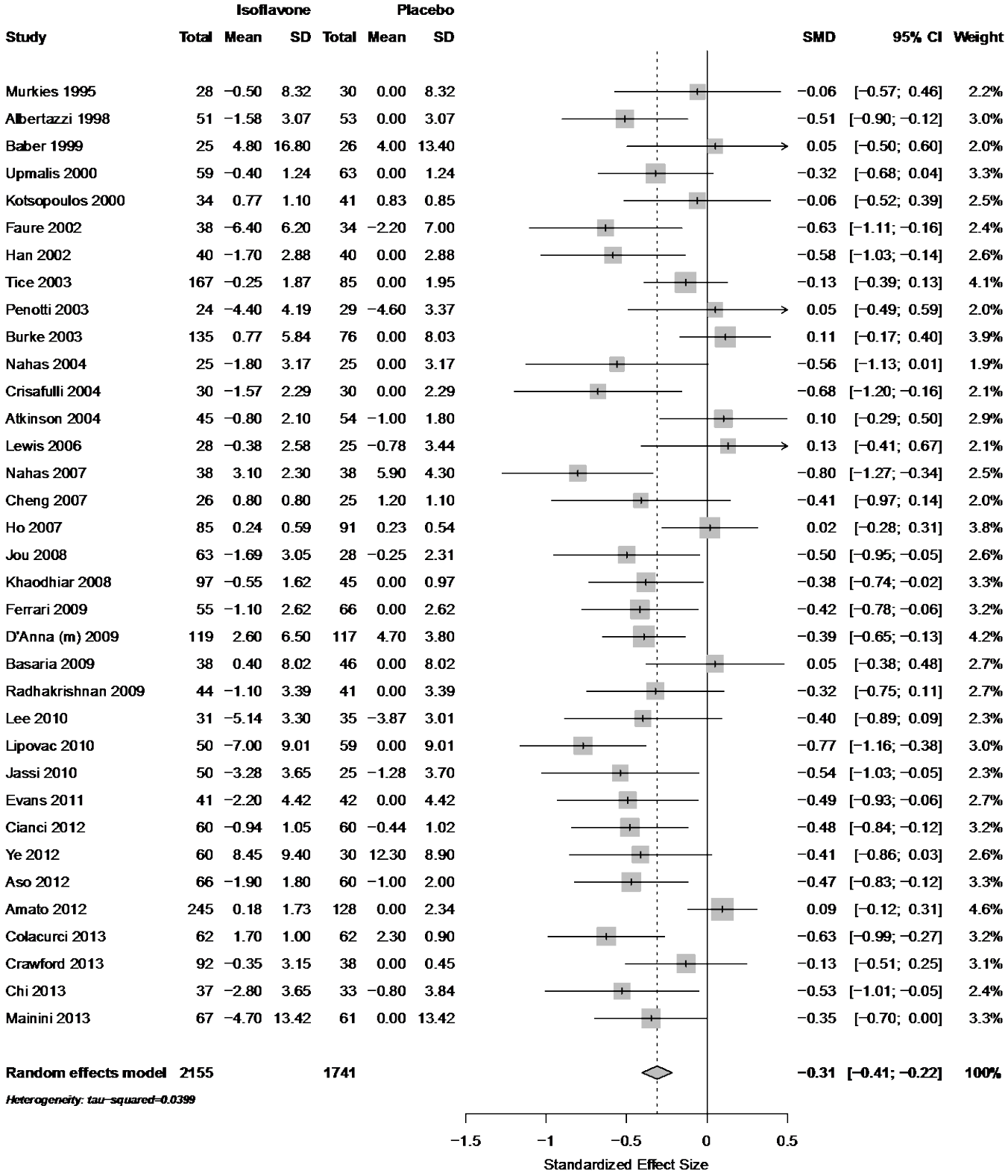


Figure F-6. Vasomotor symptoms forest plot of pairwise comparisons—gabapentin compared with placebo

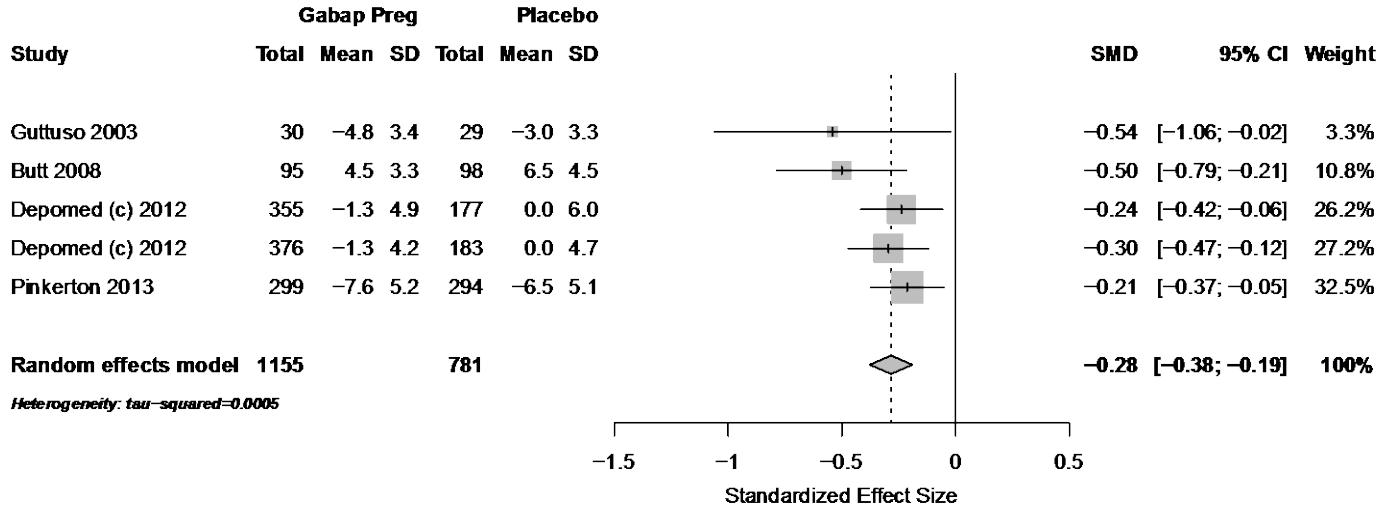


Figure F-7. Vasomotor symptoms forest plot of pairwise comparisons—black cohosh compared with placebo

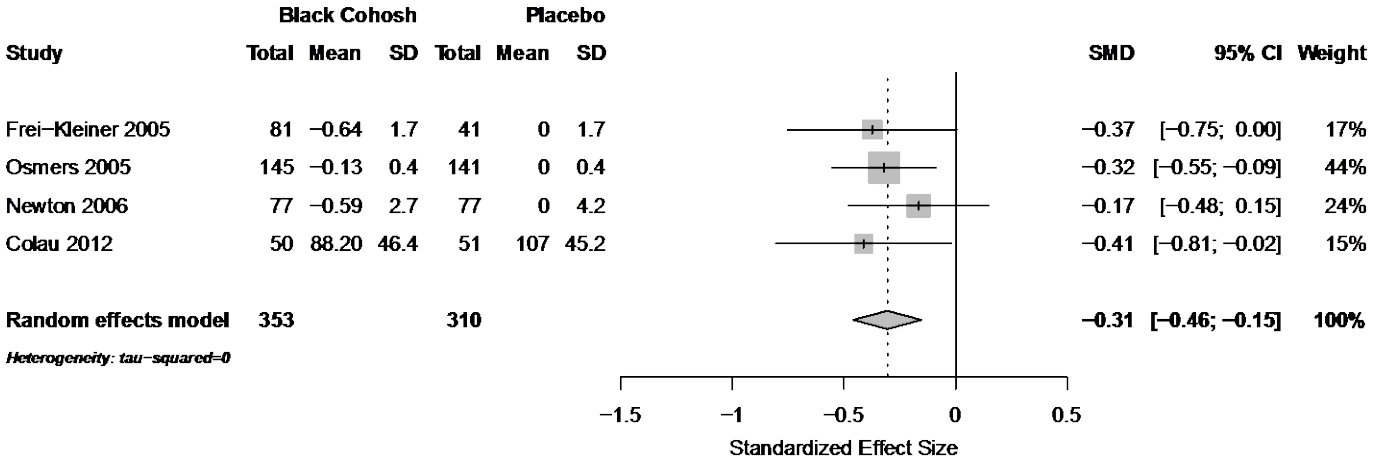


Figure F-8. Vasomotor symptoms forest plot of pairwise comparisons—estrogen (high dose) compared with estrogen (standard dose)

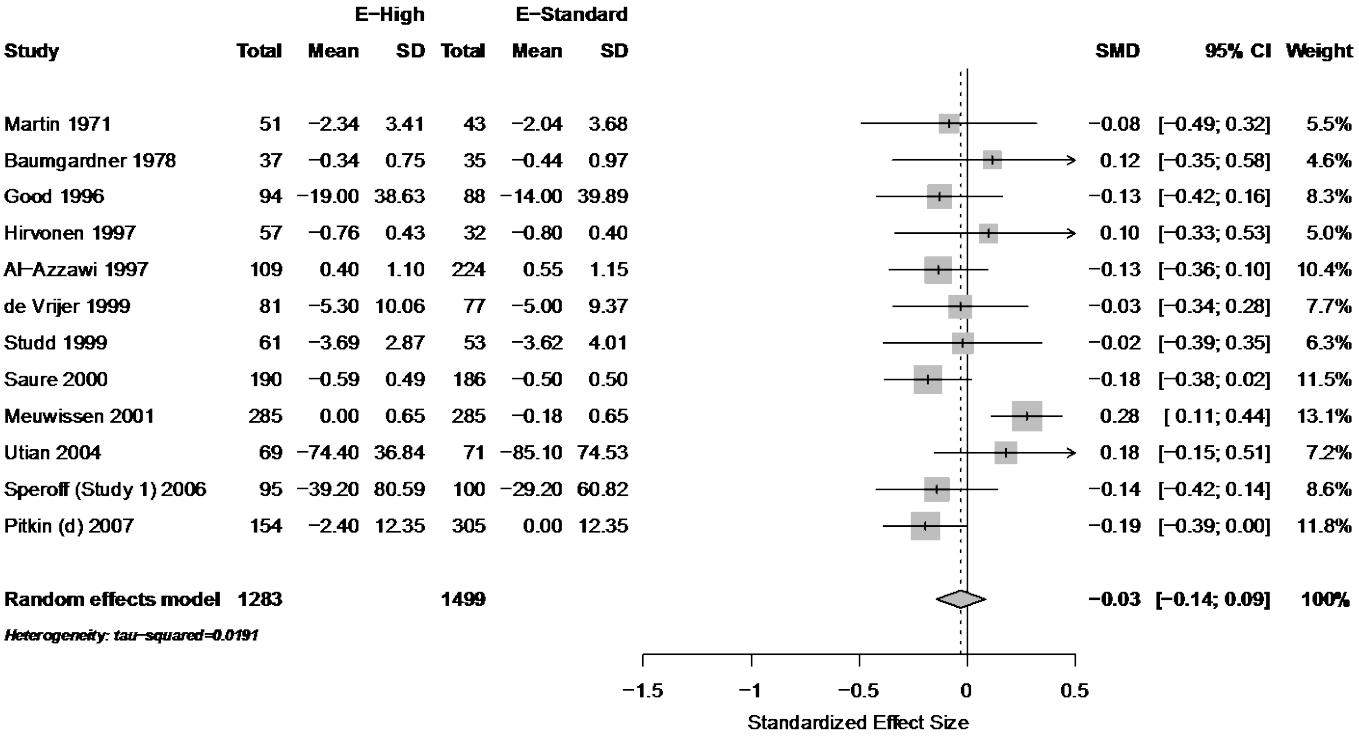


Figure F-9. Vasomotor symptoms forest plot of pairwise comparisons—estrogen (high dose) compared with estrogen (low/ultralow dose)

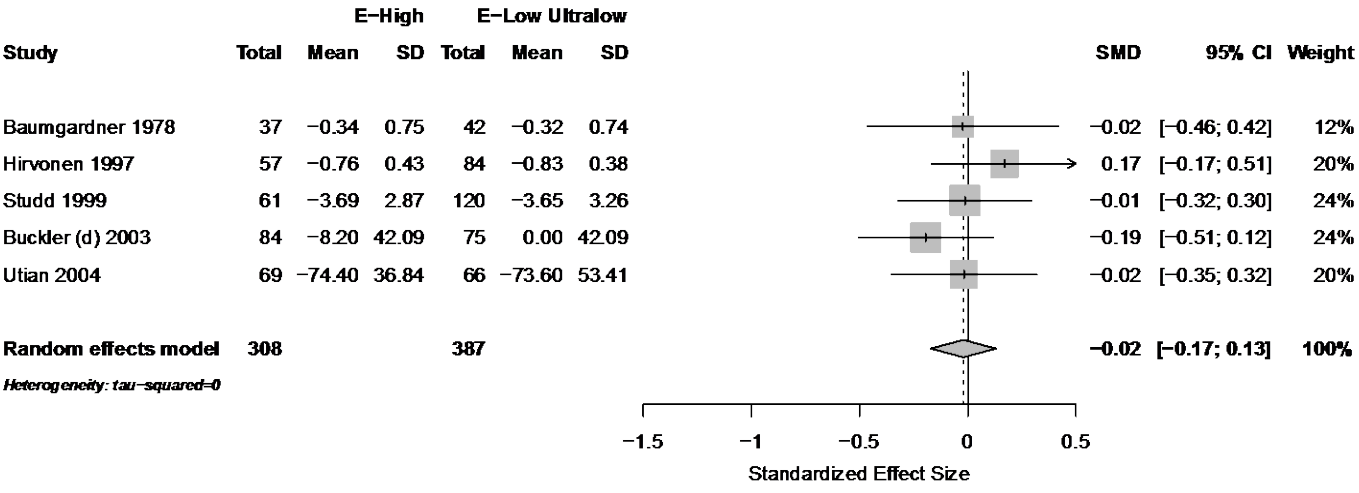


Figure F-10. Vasomotor symptoms forest plot of pairwise comparisons—estrogen (standard dose) compared with estrogen (low/ultralow dose)

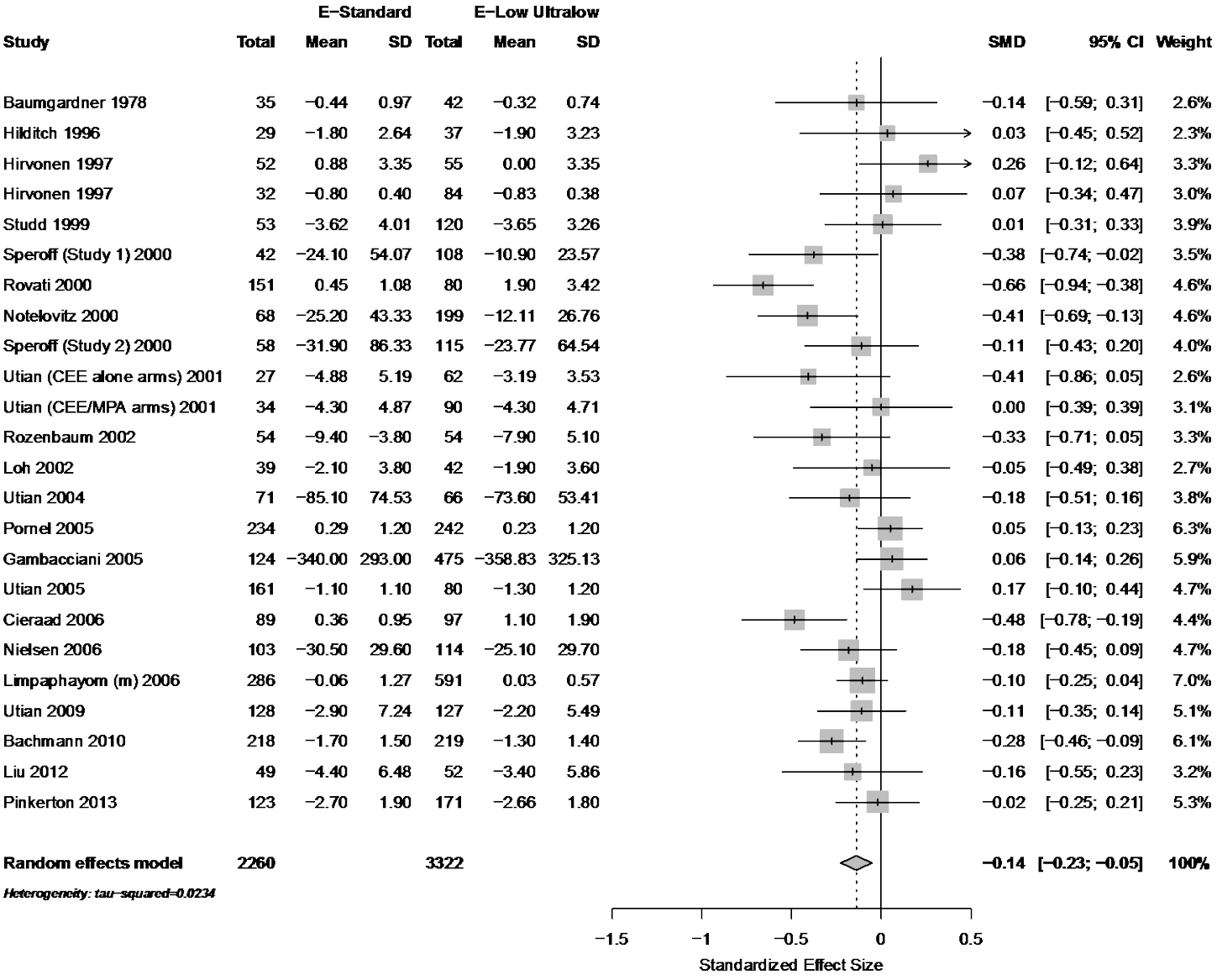


Figure F-11. Vasomotor symptoms forest plot of pairwise comparisons—ginseng compared with placebo

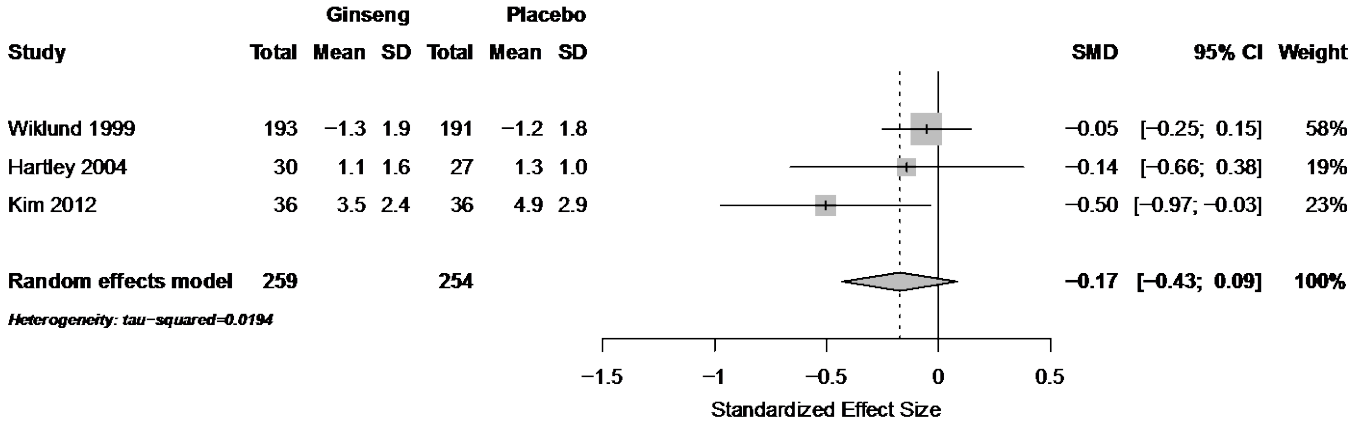
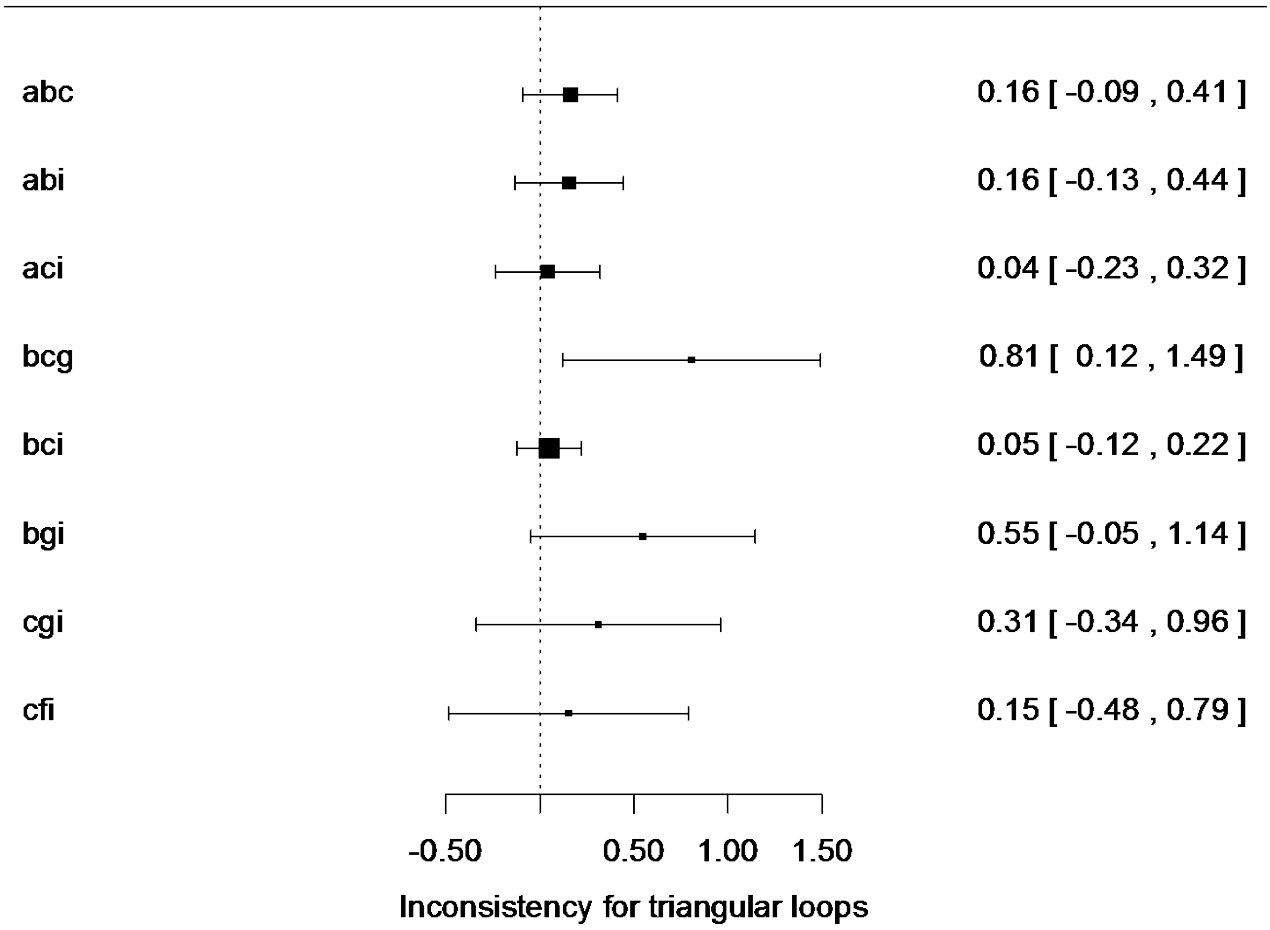


Figure F-12. Plot showing consistency of closed loops with letters representing treatments[a]



a: high dose estrogen; b: standard dose estrogen; c: low/ultralow dose estrogen; d: SSRI/SNRI; f: isoflavones; g: black cohosh; I: placebo.

[a] Inconsistency (95% CI excluding 0) is evident only in the treatment loop including standard dose estrogen-low/ultralow dose estrogen-black cohosh.

Table F-1. Difference between network result and calculable pairwise effect estimates[a]

E-High								
0.062	E-Standard							
-0.043	0.042	E-Low/Ultralow						
			SSRI/SNRI					
				Gabap/Preg				
		0.172			Isoflavone			
	0.485	-0.363				Black Cohosh		
							Ginseng	
-0.093	0.013	0.018	-0.021	-0.043	-0.005	0.065	-0.020	Placebo

[a] Pooled random effect estimates were used when multiple trials were available, otherwise single trial effects were used when only one trial was available. Small differences reflect network consistency.

Table F-2. Network analysis including trials (n=134) specifying vasomotor symptoms as a primary outcome and requiring symptoms; SMD and 95% credible interval

E-High								
0.04 (-0.08 to 0.17)	E-Standard							
-0.08 (-0.22 to 0.05)	-0.13 (-0.21 to -0.04)	E-Low/Ultralow						
-0.26 (-0.44 to -0.08)	-0.30 (-0.46 to -0.14)	-0.17 (-0.32 to -0.02)	SSRI/SNRI					
-0.30 (-0.54 to -0.06)	-0.34 (-0.56 to -0.12)	-0.22 (-0.43 to 0.00)	-0.04 (-0.29 to 0.21)	Gabapentin				
-0.29 (-0.45 to -0.13)	-0.33 (-0.46 to -0.21)	-0.21 (-0.33 to -0.09)	-0.03 (-0.20 to 0.13)	0.01 (-0.22 to 0.24)	Isoflavones			
-0.37 (-0.62 to -0.13)	-0.41 (-0.63 to -0.20)	-0.29 (-0.51 to -0.07)	-0.12 (-0.37 to 0.13)	-0.07 (-0.37 to 0.22)	-0.08 (-0.31 to 0.15)	Black Cohosh		
-0.43 (-0.77 to -0.10)	-0.48 (-0.80 to -0.16)	-0.35 (-0.66 to -0.03)	-0.18 (-0.51 to 0.16)	-0.13 (-0.51 to 0.24)	-0.14 (-0.47 to 0.18)	-0.06 (-0.44 to 0.31)	Ginseng	
-0.63 (-0.75 to -0.50)	-0.67 (-0.75 to -0.59)	-0.54 (-0.61 to -0.48)	-0.37 (-0.50 to -0.24)	-0.33 (-0.54 to -0.12)	-0.33 (-0.43 to -0.23)	-0.25 (-0.46 to -0.04)	-0.19 (-0.50 to 0.12)	Placebo

Table F-3. Rankings of comparative efficacy, standard deviations, and 95% credible intervals; trials (n=134) specifying vasomotor symptoms as a primary outcome and requiring symptoms

Treatment	Mean Rank	SD	95% CrI
E-High	1.9	0.6	(1-3)
E-Standard	1.3	0.5	(1-2)
E-Low/Ultralow	3.0	0.4	(2-4)
SSRI/SNRI	5.0	1.1	(4-7)
Gabapentin	5.7	1.4	(3-8)
Isoflavones	5.6	1.1	(4-8)
Black Cohosh	6.6	1.3	(4-8)
Ginseng	7.1	1.5	(4-9)
Placebo	8.9	0.3	(8-9)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Table F-4. Network analysis excluding trials judged to have included women without vasomotor symptoms (n=136); SMD and 95% credible interval

E-High								
0.03 (-0.10 to 0.16)	E-Standard							
-0.08 (-0.22 to 0.06)	-0.11 (-0.20 to -0.02)	E-Low/Ultralow						
-0.23 (-0.43 to -0.04)	-0.26 (-0.42 to -0.09)	-0.15 (-0.31 to 0.01)	SSRI/SNRI					
-0.28 (-0.53 to -0.02)	-0.31 (-0.54 to -0.08)	-0.20 (-0.42 to 0.03)	-0.05 (-0.31 to 0.21)	Gabapentin				
-0.27 (-0.44 to -0.10)	-0.29 (-0.43 to -0.16)	-0.18 (-0.31 to -0.06)	-0.04 (-0.21 to 0.14)	0.01 (-0.23 to 0.25)	Isoflavones			
-0.36 (-0.62 to -0.11)	-0.39 (-0.62 to -0.17)	-0.28 (-0.50 to -0.06)	-0.13 (-0.39 to 0.13)	-0.08 (-0.39 to 0.22)	-0.10 (-0.34 to 0.15)	Black Cohosh		
-0.41 (-0.75 to -0.07)	-0.44 (-0.77 to -0.11)	-0.33 (-0.65 to -0.00)	-0.18 (-0.53 to 0.17)	-0.13 (-0.52 to 0.25)	-0.14 (-0.48 to 0.19)	-0.05 (-0.43 to 0.34)	Ginseng	
-0.61 (-0.74 to -0.47)	-0.63 (-0.71 to -0.55)	-0.52 (-0.59 to -0.46)	-0.38 (-0.52 to -0.23)	-0.33 (-0.55 to -0.11)	-0.34 (-0.44 to -0.24)	-0.24 (-0.46 to -0.03)	-0.20 (-0.51 to 0.12)	Placebo

Table F-5. Vasomotor symptoms rankings of comparative efficacy, standard deviations, and 95% credible intervals; excluding trials judged to have included women without vasomotor symptoms

Treatment	Mean Rank	SD	95% CrI
E-High	1.8	0.7	(1-3)
E-Standard	1.4	0.5	(1-2)
E-Low/Ultralow	3.0	0.5	(2-4)
SSRI/SNRI	5.0	1.1	(3-7)
Gabapentin	5.7	1.5	(3-8)
Isoflavones	5.5	1.0	(4-8)
Black Cohosh	6.7	1.3	(4-8)
Ginseng	7.1	1.6	(4-9)
Placebo	8.9	0.3	(8-9)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Table F-6. Network analysis excluding black cohosh trials (n=147); SMD and 95% credible interval

E-High							
0.03 (-0.10 to 0.15)	E-Standard						
-0.06 (-0.19 to 0.07)	-0.08 (-0.17 to -0.00)	E-Low/Ultralow					
-0.22 (-0.40 to -0.03)	-0.24 (-0.40 to -0.09)	-0.16 (-0.31 to -0.01)	SSRI/SNRI				
-0.26 (-0.51 to -0.01)	-0.29 (-0.51 to -0.06)	-0.20 (-0.42 to 0.02)	-0.04 (-0.30 to 0.21)	Gabapentin			
-0.28 (-0.43 to -0.12)	-0.30 (-0.42 to -0.18)	-0.22 (-0.33 to -0.10)	-0.06 (-0.23 to 0.11)	-0.02 (-0.25 to 0.22)	Isoflavones		
-0.39 (-0.73 to -0.05)	-0.42 (-0.74 to -0.09)	-0.33 (-0.65 to -0.01)	-0.17 (-0.52 to 0.17)	-0.13 (-0.51 to 0.25)	-0.11 (-0.44 to 0.21)	Ginseng	
-0.59 (-0.71 to -0.46)	-0.61 (-0.69 to -0.54)	-0.53 (-0.59 to -0.46)	-0.37 (-0.51 to -0.23)	-0.33 (-0.54 to -0.11)	-0.31 (-0.41 to -0.22)	-0.20 (-0.51 to 0.12)	Placebo

Table F-7. Vasomotor symptoms rankings of comparative efficacy, standard deviations, and 95% credible intervals; excluding black cohosh trials

Treatment	Mean Rank	SD	95% CrI
E-High	1.9	0.8	(1-3)
E-Standard	1.4	0.5	(1-2)
E-Low/Ultralow	2.9	0.5	(2-4)
SSRI/SNRI	4.7	0.9	(4-7)
Gabapentin	5.3	1.2	(3-7)
Isoflavones	5.6	0.9	(4-7)
Ginseng	6.4	1.3	(4-8)
Placebo	7.9	0.3	(7-8)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Table F-8. Network analysis including trials rated good or fair quality (n=36); SMD and 95% credible interval

E-High								
0.01 (-0.24 to 0.26)	E-Standard							
-0.12 (-0.39 to 0.15)	-0.13 (-0.29 to 0.03)	E-Low/Ultralow						
-0.23 (-0.53 to 0.07)	-0.24 (-0.45 to -0.03)	-0.11 (-0.31 to 0.09)	SSRI/SNRI					
-0.35 (-0.83 to 0.12)	-0.36 (-0.79 to 0.06)	-0.23 (-0.66 to 0.19)	-0.12 (-0.56 to 0.31)	Gabapentin				
-0.44 (-0.76 to -0.13)	-0.45 (-0.69 to -0.21)	-0.32 (-0.55 to -0.09)	-0.21 (-0.46 to 0.04)	-0.09 (-0.54 to 0.35)	Isoflavones			
-0.39 (-0.81 to 0.02)	-0.40 (-0.75 to -0.05)	-0.27 (-0.62 to 0.08)	-0.16 (-0.53 to 0.21)	-0.04 (-0.56 to 0.48)	0.05 (-0.33 to 0.44)	Black Cohosh		
-0.06 (-0.70 to 0.58)	-0.07 (-0.67 to 0.53)	0.06 (-0.54 to 0.66)	0.17 (-0.44 to 0.78)	0.29 (-0.42 to 1.00)	0.38 (-0.23 to 1.00)	0.33 (-0.34 to 1.01)	Ginseng	
-0.56 (-0.82 to -0.31)	-0.57 (-0.71 to -0.43)	-0.44 (-0.57 to -0.32)	-0.33 (-0.49 to -0.17)	-0.21 (-0.61 to 0.19)	-0.12 (-0.31 to 0.07)	-0.17 (-0.51 to 0.16)	-0.50 (-1.09 to 0.08)	Placebo

Table F-9. Vasomotor symptoms rankings of comparative efficacy, standard deviations, and 95% credible intervals; including trials rated good or fair quality

Treatment	Mean Rank	SD	95% CrI
E-High	2.3	1.3	(1-5)
E-Standard	2.0	0.8	(1-4)
E-Low/Ultralow	3.7	1.0	(1-6)
SSRI/SNRI	5.0	1.1	(3-7)
Gabapetin	6.2	1.9	(2-9)
Isoflavones	7.2	1.0	(5-9)
Black Cohosh	6.6	1.6	(3-9)
Ginseng	3.4	2.4	(1-9)
Placebo	8.6	0.6	(7-9)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Table F-10. Network analysis restricted to trials examining moderate to severe hot flush reduction (n=55); SMD and 95% credible interval

E-High								
0.05 (-0.08 to 0.18)	E-Standard							
-0.07 (-0.20 to 0.07)	-0.11 (-0.20 to -0.03)	E-Low/Ultralow						
-0.23 (-0.41 to -0.04)	-0.27 (-0.43 to -0.12)	-0.16 (-0.31 to -0.01)	SSRI/SNRI					
-0.27 (-0.52 to -0.02)	-0.32 (-0.54 to -0.09)	-0.20 (-0.42 to 0.02)	-0.04 (-0.29 to 0.21)	Gabapentin				
-0.28 (-0.44 to -0.13)	-0.33 (-0.45 to -0.21)	-0.22 (-0.33 to -0.10)	-0.06 (-0.22 to 0.11)	-0.02 (-0.25 to 0.21)	Isoflavones			
-0.35 (-0.60 to -0.10)	-0.40 (-0.62 to -0.18)	-0.28 (-0.50 to -0.06)	-0.12 (-0.38 to 0.13)	-0.08 (-0.38 to 0.22)	-0.06 (-0.30 to 0.17)	Black Cohosh		
-0.40 (-0.74 to -0.07)	-0.45 (-0.77 to -0.13)	-0.33 (-0.65 to -0.02)	-0.18 (-0.51 to 0.16)	-0.13 (-0.51 to 0.24)	-0.12 (-0.44 to 0.21)	-0.05 (-0.43 to 0.33)	Ginseng	
-0.60 (-0.72 to -0.47)	-0.64 (-0.72 to -0.57)	-0.53 (-0.59 to -0.46)	-0.37 (-0.51 to -0.23)	-0.33 (-0.54 to -0.12)	-0.31 (-0.40 to -0.22)	-0.25 (-0.46 to -0.03)	-0.19 (-0.51 to 0.12)	Placebo

Table F-11. Vasomotor symptoms rankings of comparative efficacy, standard deviations, and 95% credible intervals; trials examining moderate to severe hot flush reduction

Treatment	Mean Rank	SD	95% CrI
E-High	2.0	0.7	(1-3)
E-Standard	1.3	0.4	(1-2)
E-Low/Ultralow	2.9	0.5	(2-4)
SSRI/SNRI	4.9	1.1	(4-7)
Gabapentin	5.6	1.4	(3-8)
Isoflavones	5.9	1.0	(4-8)
Black Cohosh	6.6	1.3	(4-8)
Ginseng	7.1	1.6	(4-9)
Placebo	8.9	0.3	(8-9)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Table F-12. Network analysis excluding large prevention-focused trials, SMD and 95% credible interval (n=150)

E-High								
0.05 (-0.07 to 0.17)	E-Standard							
-0.08 (-0.20 to 0.05)	-0.12 (-0.20 to -0.04)	E-Low/Ultralow						
-0.24 (-0.42 to -0.07)	-0.29 (-0.44 to -0.14)	-0.17 (-0.31 to -0.02)	SSRI/SNRI					
-0.29 (-0.52 to -0.05)	-0.33 (-0.55 to -0.11)	-0.21 (-0.43 to 0.00)	-0.04 (-0.29 to 0.20)	Gabapentin				
-0.30 (-0.45 to -0.15)	-0.35 (-0.47 to -0.23)	-0.23 (-0.34 to -0.12)	-0.06 (-0.22 to 0.10)	-0.02 (-0.24 to 0.21)	Isoflavones			
-0.36 (-0.60 to -0.12)	-0.41 (-0.63 to -0.19)	-0.29 (-0.50 to -0.07)	-0.12 (-0.37 to 0.13)	-0.07 (-0.37 to 0.22)	-0.06 (-0.29 to 0.17)	Black Cohosh		
-0.42 (-0.75 to -0.09)	-0.47 (-0.78 to -0.15)	-0.34 (-0.66 to -0.03)	-0.17 (-0.51 to 0.16)	-0.13 (-0.50 to 0.24)	-0.12 (-0.44 to 0.20)	-0.06 (-0.43 to 0.31)	Ginseng	
-0.61 (-0.73 to -0.49)	-0.66 (-0.74 to -0.59)	-0.54 (-0.60 to -0.47)	-0.37 (-0.50 to -0.24)	-0.33 (-0.53 to -0.12)	-0.31 (-0.40 to -0.22)	-0.25 (-0.46 to -0.04)	-0.19 (-0.50 to 0.11)	Pla-cebo

Table F-13. Vasomotor symptoms rankings of comparative efficacy, standard deviations, and 95% credible intervals; excluding large prevention-focused trials

Treatment	Mean Rank	SD	95% CrI
E-High	1.93	0.60	(1-3)
E-Standard	1.22	0.42	(1-2)
E-Low/Ultralow	2.94	0.41	(2-4)
SSRI/SNRI	4.92	1.05	(4-7)
Gabapentin	5.59	1.41	(3-8)
Isoflavones	5.86	1.03	(4-8)
Black Cohosh	6.59	1.31	(4-8)
Ginseng	7.08	1.52	(4-9)
Placebo	8.88	0.33	(8-9)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Appendix G. Quality of Life Supplemental Tables and Plots

Figure G-1. Forest plot of estrogen (standard) versus placebo

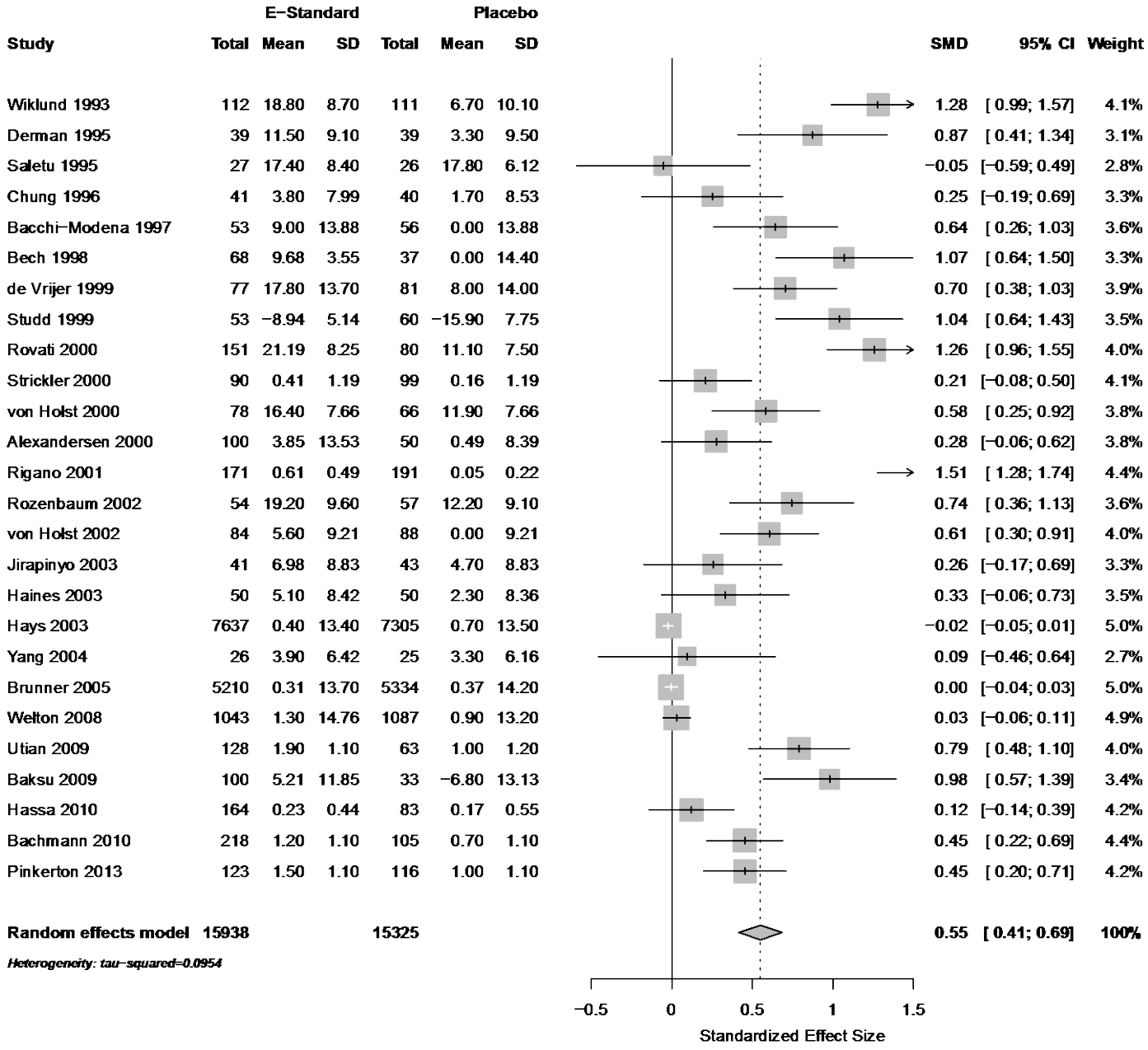


Figure G-2. Forest plot of estrogen (high) versus placebo

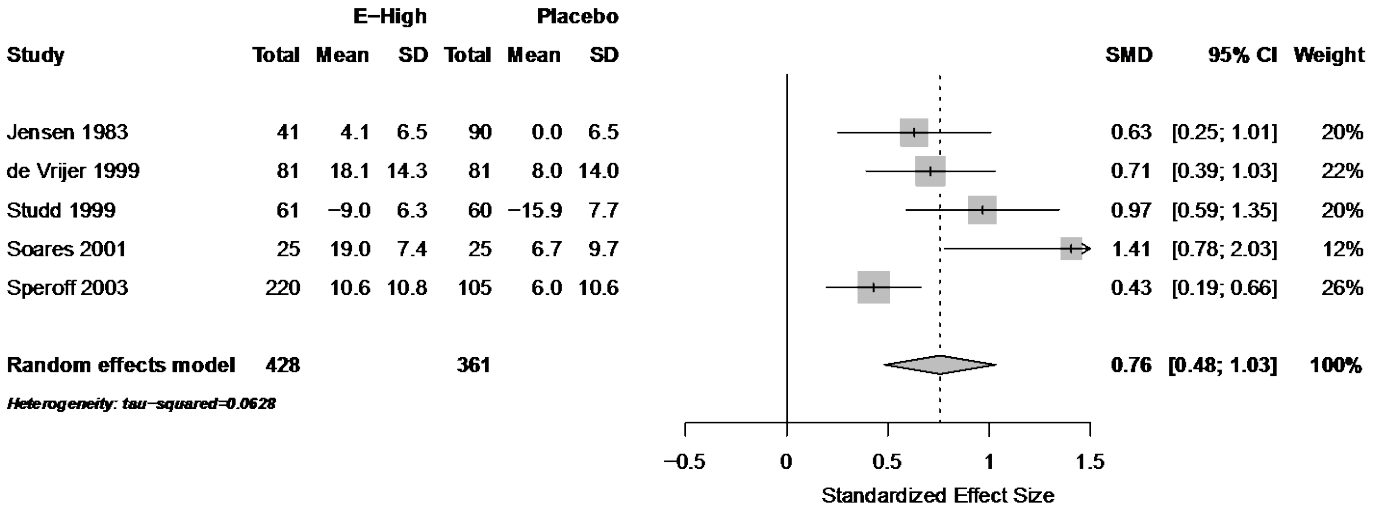


Figure G-3. Forest plot of estrogen (low/ultralow) versus placebo

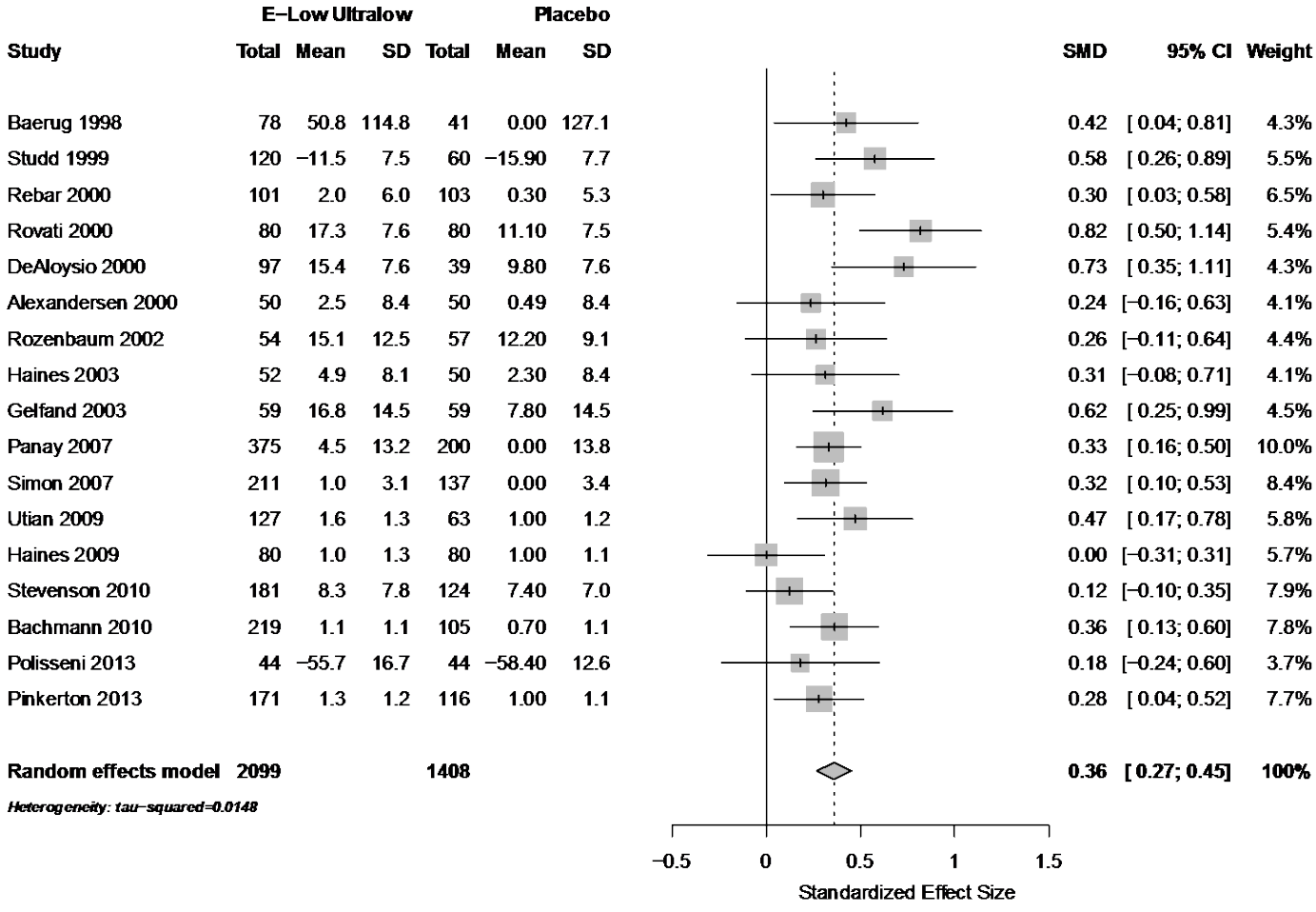


Figure G-4. Forest plot of SSRI/SNRI versus placebo

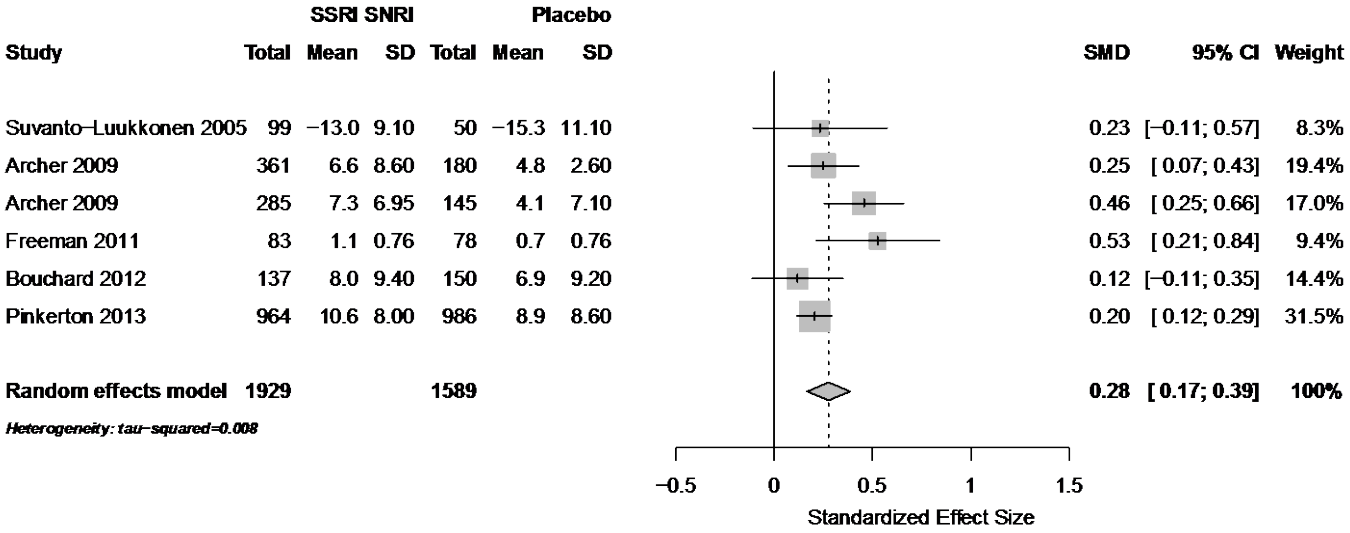


Figure G-5. Forest plot of isoflavones versus placebo

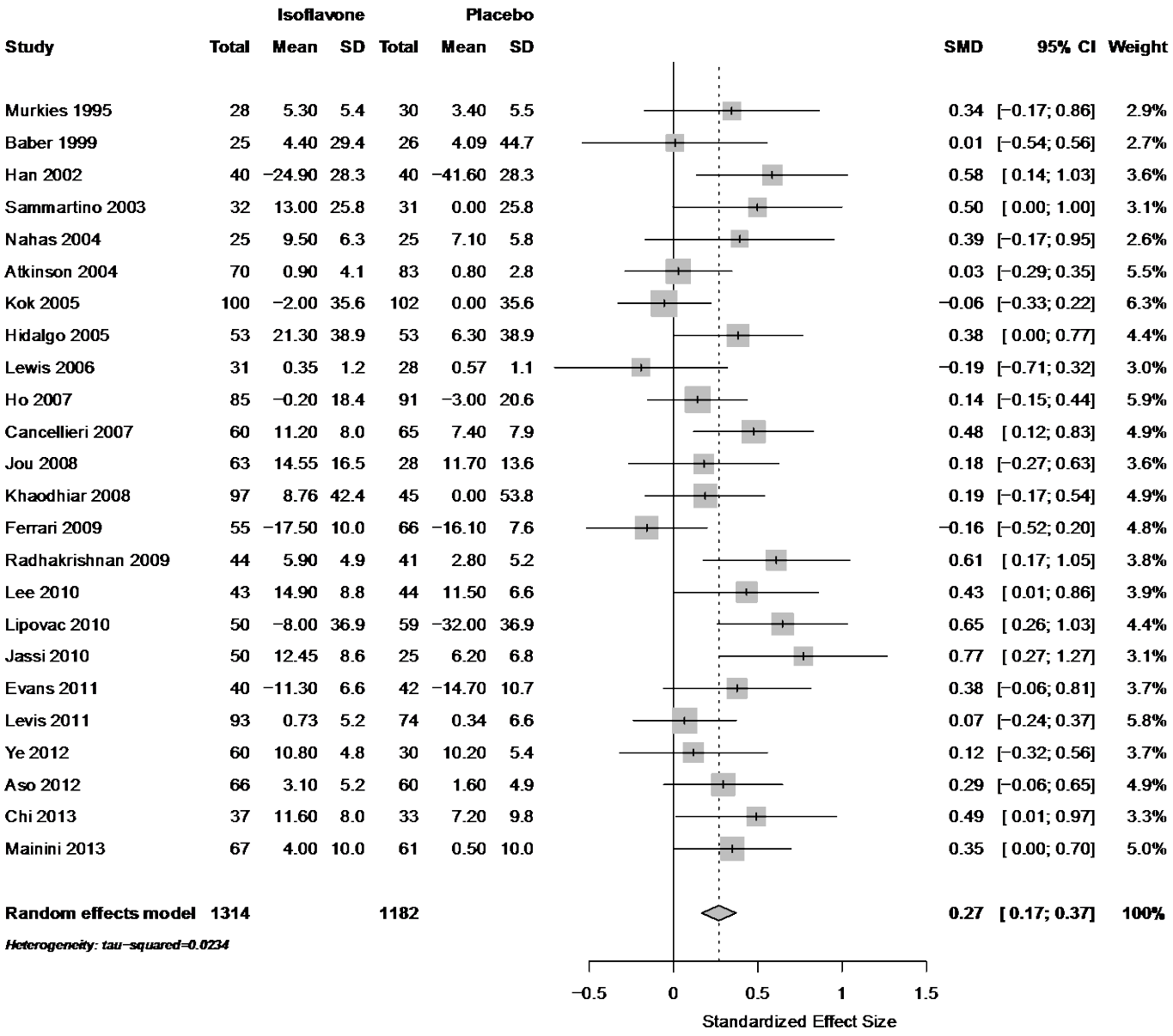


Figure G-6. Forest plot of black cohosh versus placebo

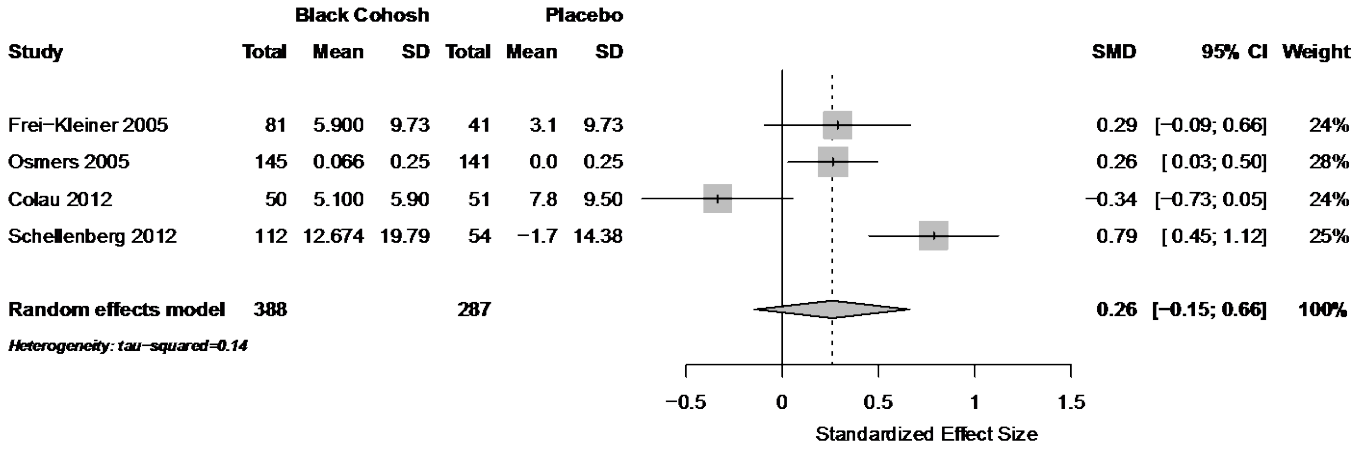


Figure G-7. Forest plot of ginseng versus placebo

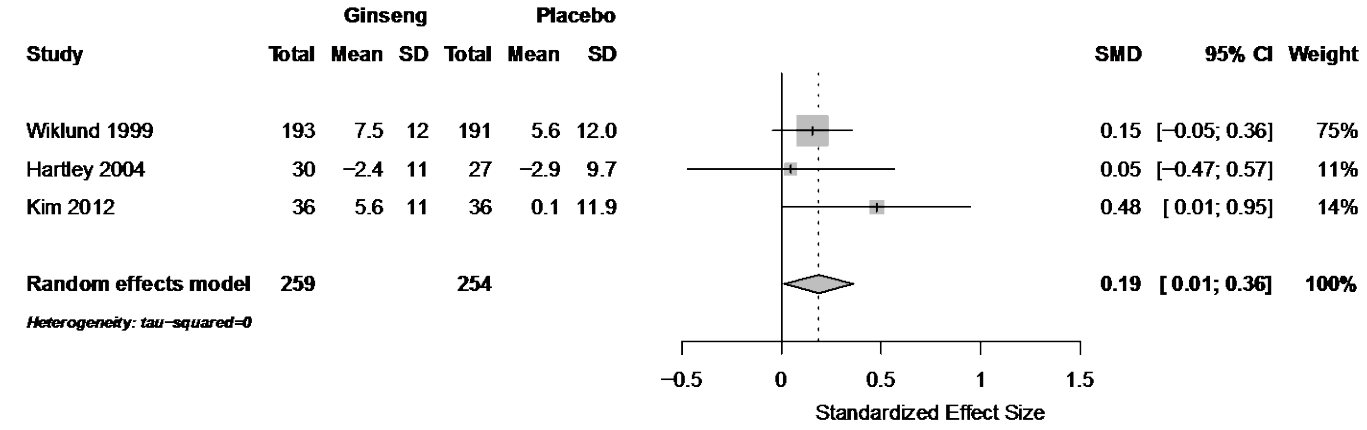


Figure G-8. Forest plot of estrogen (high) versus estrogen (standard)

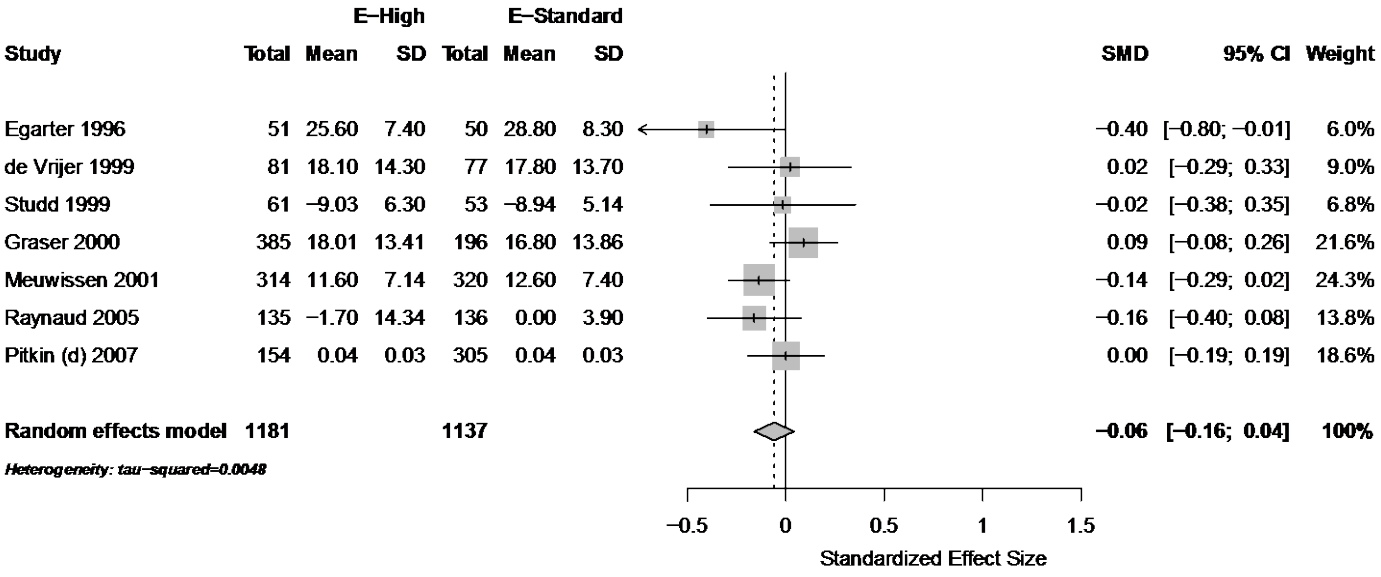


Figure G-9. Forest plot of estrogen (standard) versus estrogen (low/ultralow)

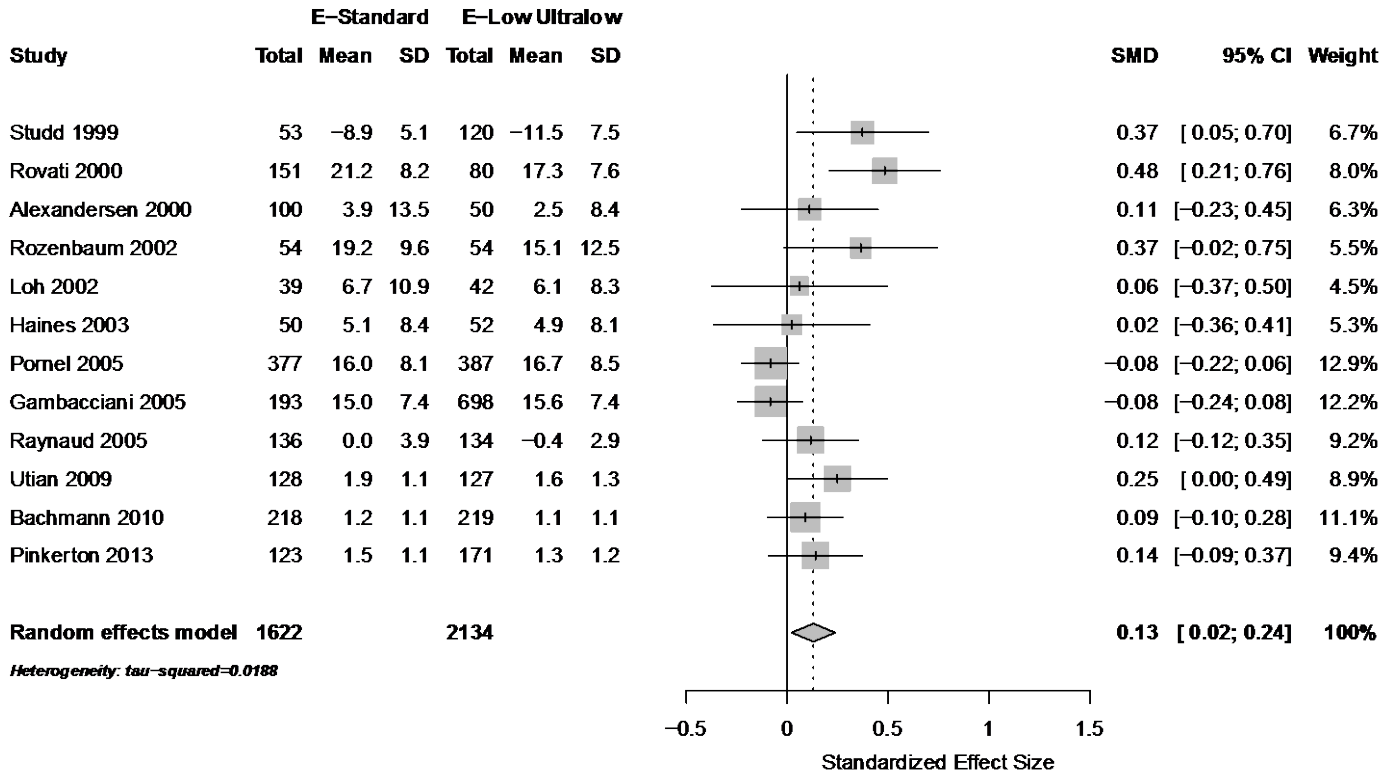


Table G-1. Network analysis excluding trials utilizing general quality of life instruments (SMDs and 95% credible intervals)

E-High					
-0.01 (-0.21 to 0.19)	E-Standard				
0.15 (-0.07 to 0.37)	0.16 (0.01 to 0.31)	E-Low/Ultralow			
0.27 (-0.06 to 0.59)	0.28 (0.00 to 0.55)	0.12 (-0.16 to 0.40)	SSRI/SNRI		
0.25 (-0.01 to 0.50)	0.26 (0.07 to 0.45)	0.10 (-0.11 to 0.31)	-0.02 (-0.31 to 0.27)	Isoflavone	
0.36 (0.01 to 0.72)	0.37 (0.06 to 0.69)	0.21 (-0.11 to 0.54)	0.09 (-0.29 to 0.48)	0.11 (-0.22 to 0.45)	Black Cohosh

0.27 (-0.23 to 0.78)	0.29 (-0.19 to 0.77)	0.13 (-0.36 to 0.61)	0.01 (-0.52 to 0.53)	0.03 (-0.46 to 0.51)	-0.08 (-0.64 to 0.46)	Ginseng	
0.56 (0.35 to 0.77)	0.57 (0.46 to 0.69)	0.41 (0.27 to 0.55)	0.29 (0.04 to 0.54)	0.31 (0.16 to 0.47)	0.20 (-0.10 to 0.50)	0.29 (-0.18 to 0.75)	Place bo

Table G-2. Quality-of-life rankings of comparative efficacy excluding trials utilizing general quality of life instruments, standard deviations, and 95% credible intervals (integer values because they arise from a distribution of integers)

Treatment	Mean Rank	SD	95% CrI
E-High	1.9	1.0	(1 to 4)
E-Standard	1.6	0.7	(1 to 3)
E-Low/Ultralow	3.7	1.0	(2 to 6)
SSRI/SNRI	5.1	1.4	(2 to 7)
Isoflavones	5.0	1.1	(3 to 7)
Black Cohosh	6.0	1.4	(3 to 8)
Ginseng	5.0	2.1	(1 to 8)
Placebo	7.8	0.4	(7 to 8)

SD: standard deviation; CrI: credible interval; E: estrogen; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor.

Appendix H. Psychological Symptoms Supplemental Tables and Plots

Figure H-1. Global psychological well-being—SSRI/SNRI compared with placebo

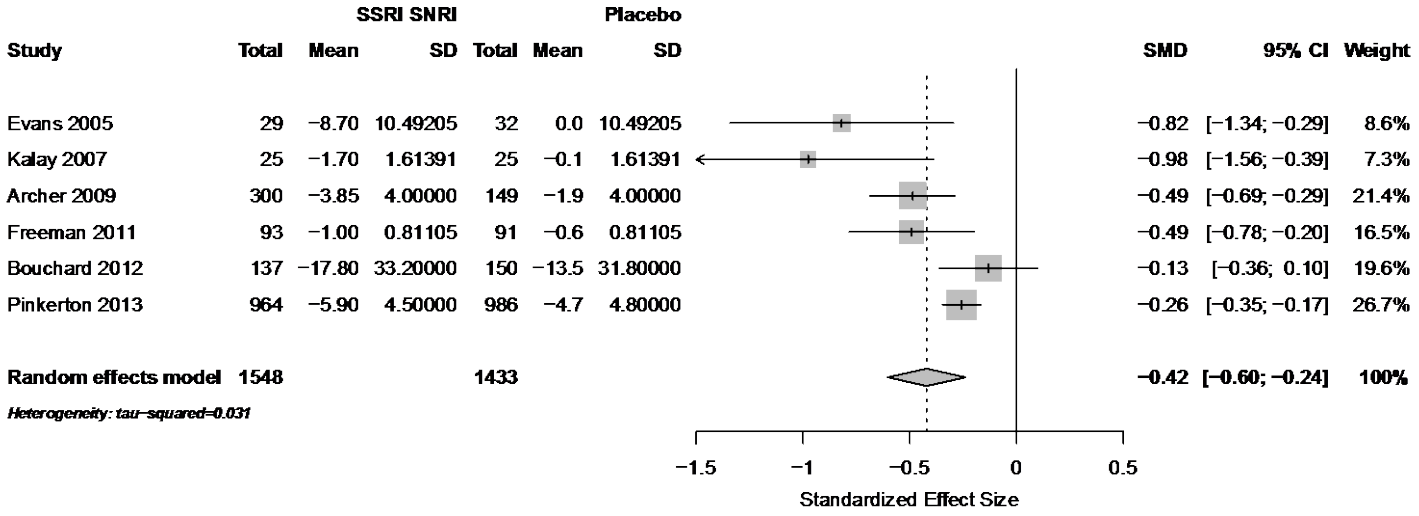


Figure H-2. Depressive symptoms—SSRI/SNRI compared with placebo

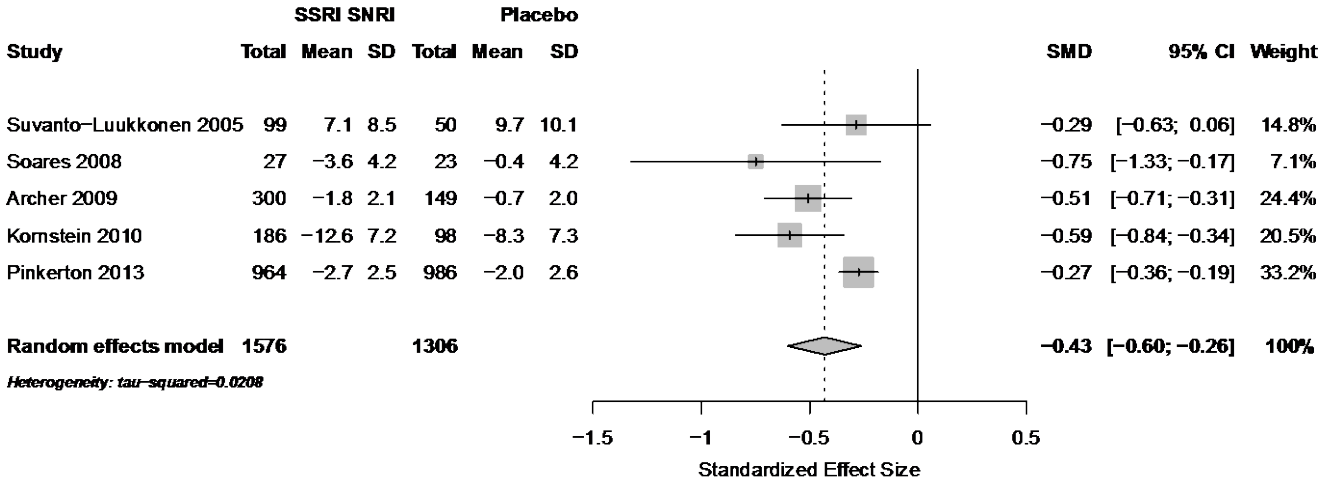


Figure H-3. Anxiety symptoms—SNRI compared with placebo

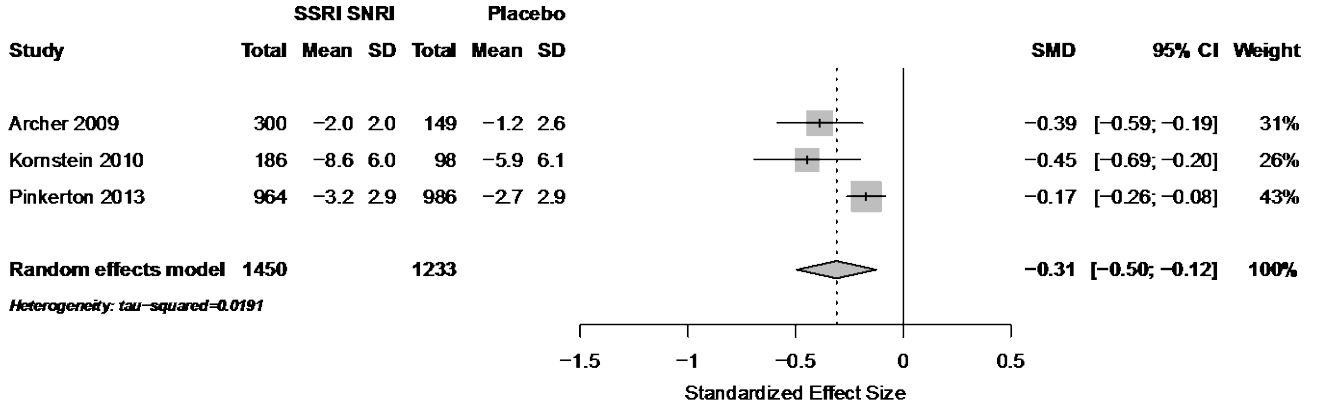


Figure H-4. Global psychological well-being—estrogen compared with placebo

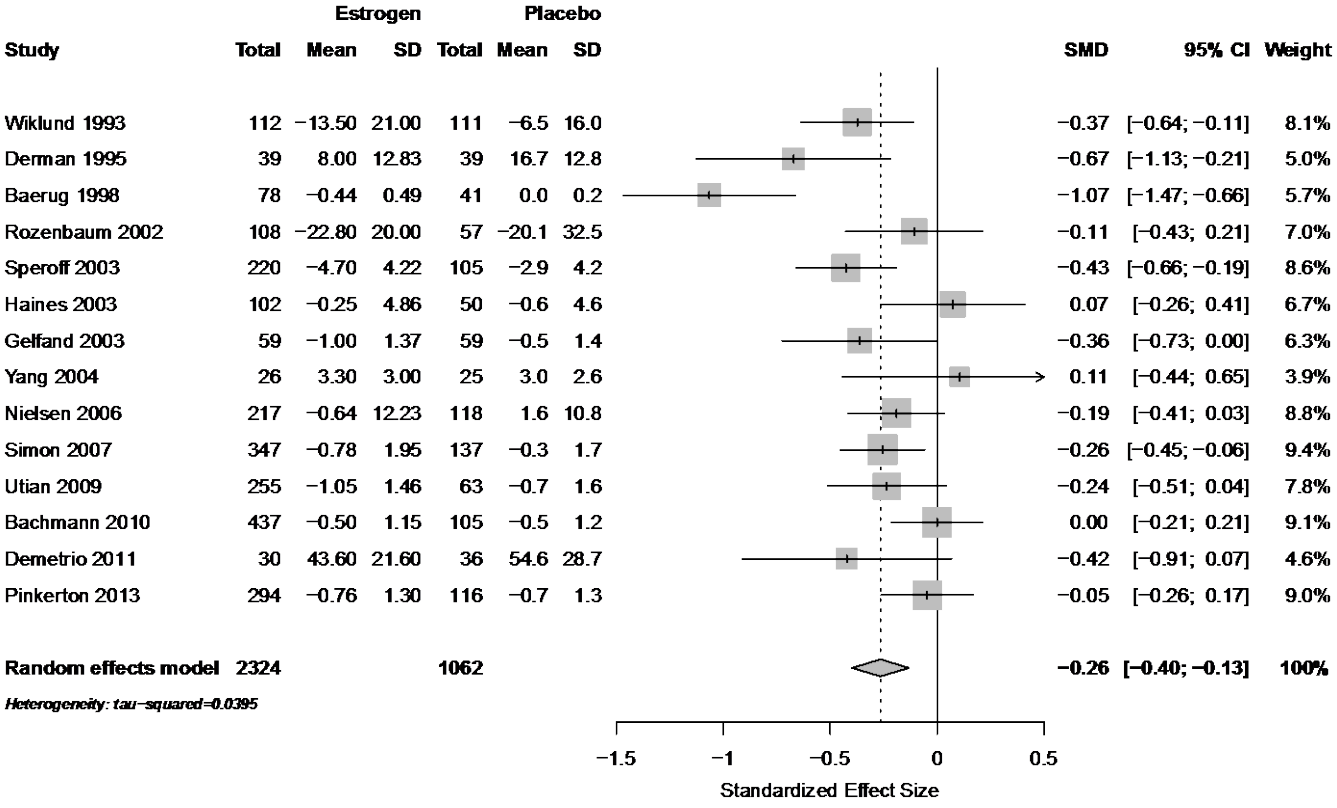


Figure H-5. Depressive symptoms—estrogen compared with placebo

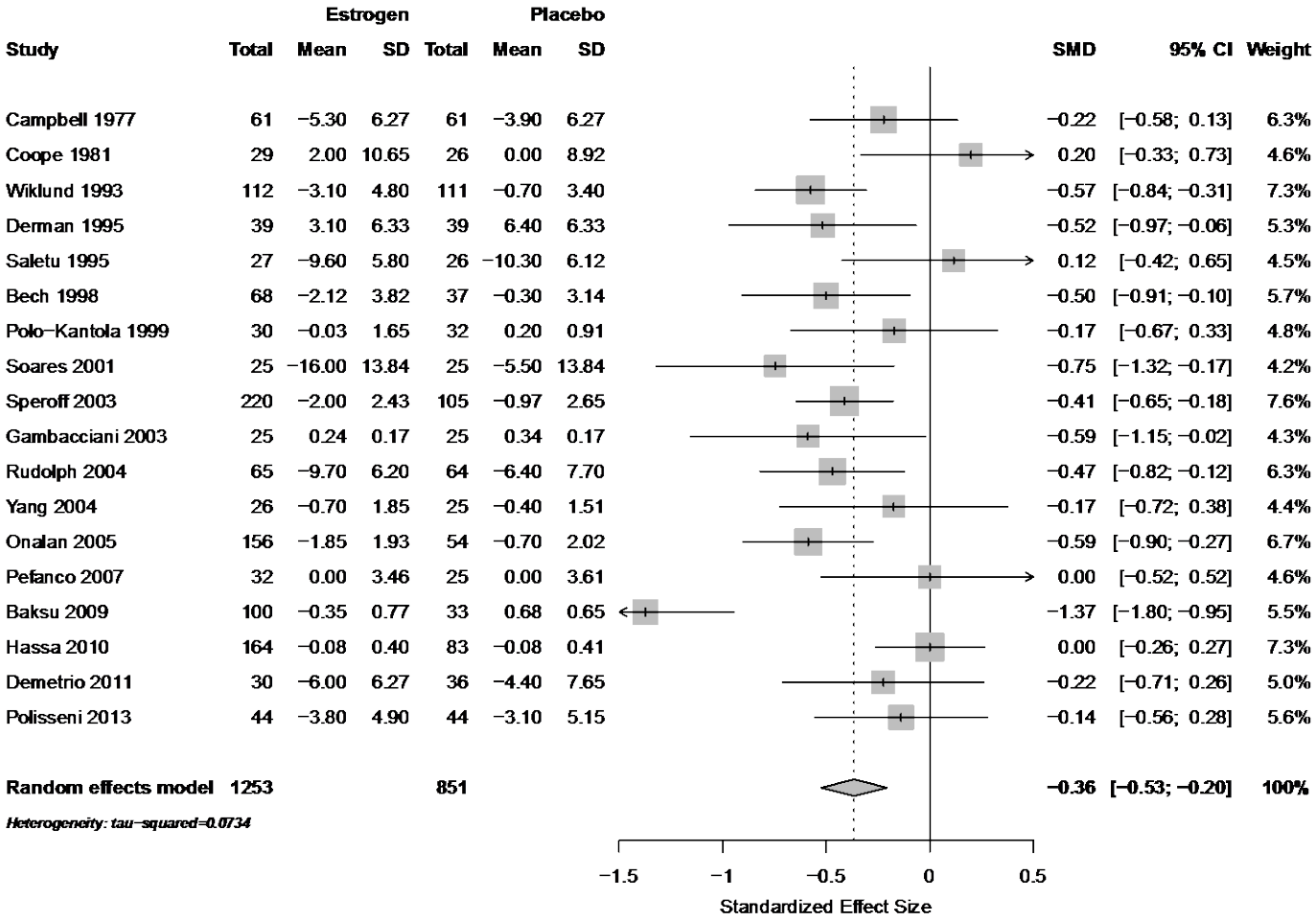


Figure H-6. Anxiety symptoms—estrogen compared with placebo

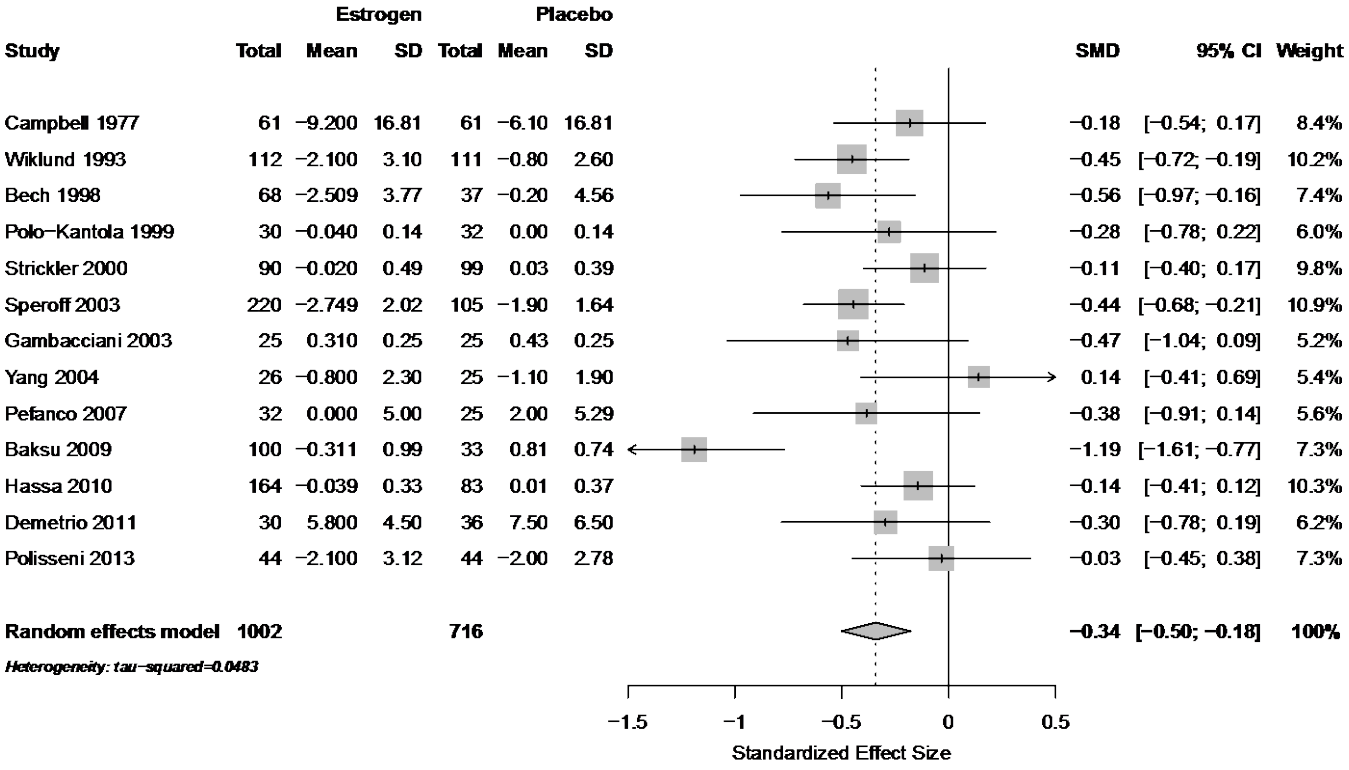


Figure H-7. Global psychological well-being—gabapentin compared with placebo

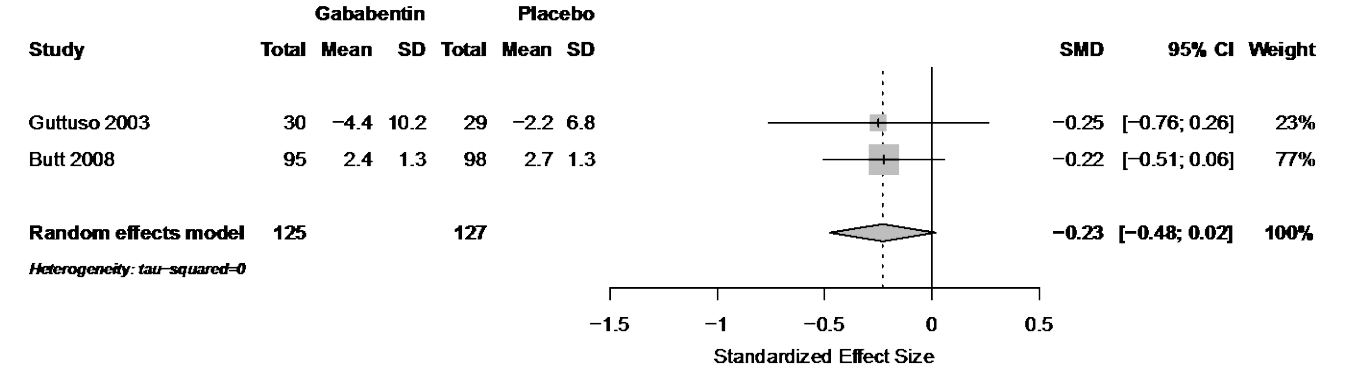


Figure H-8. Global psychological well-being—isoflavones compared with placebo

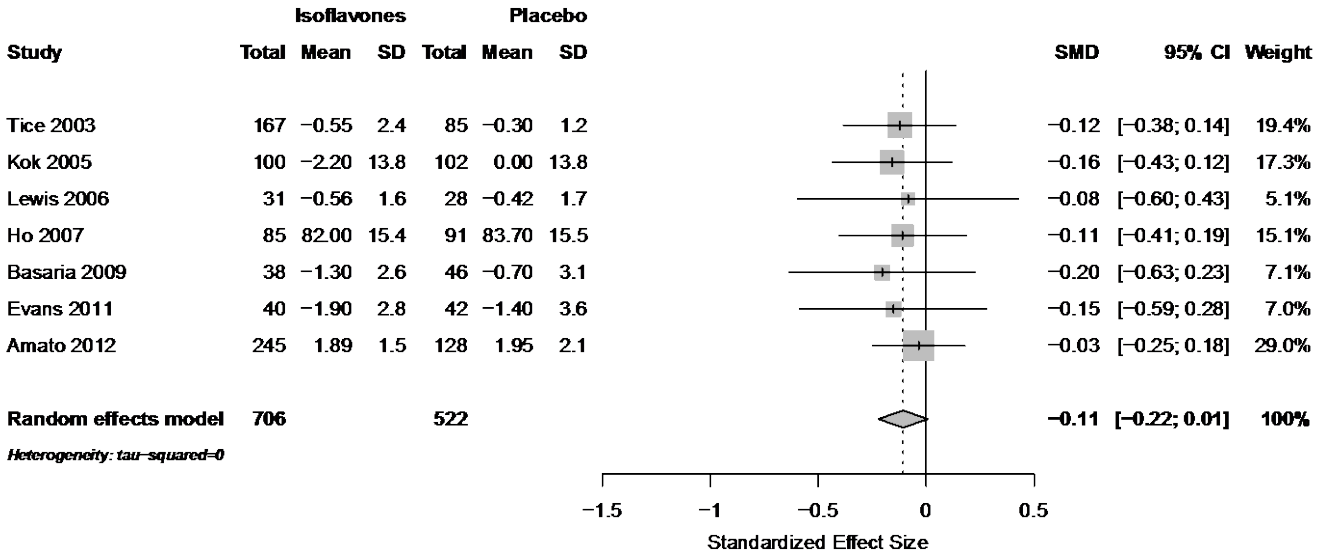


Figure H-9. Depressive symptoms—isoflavones compared with placebo

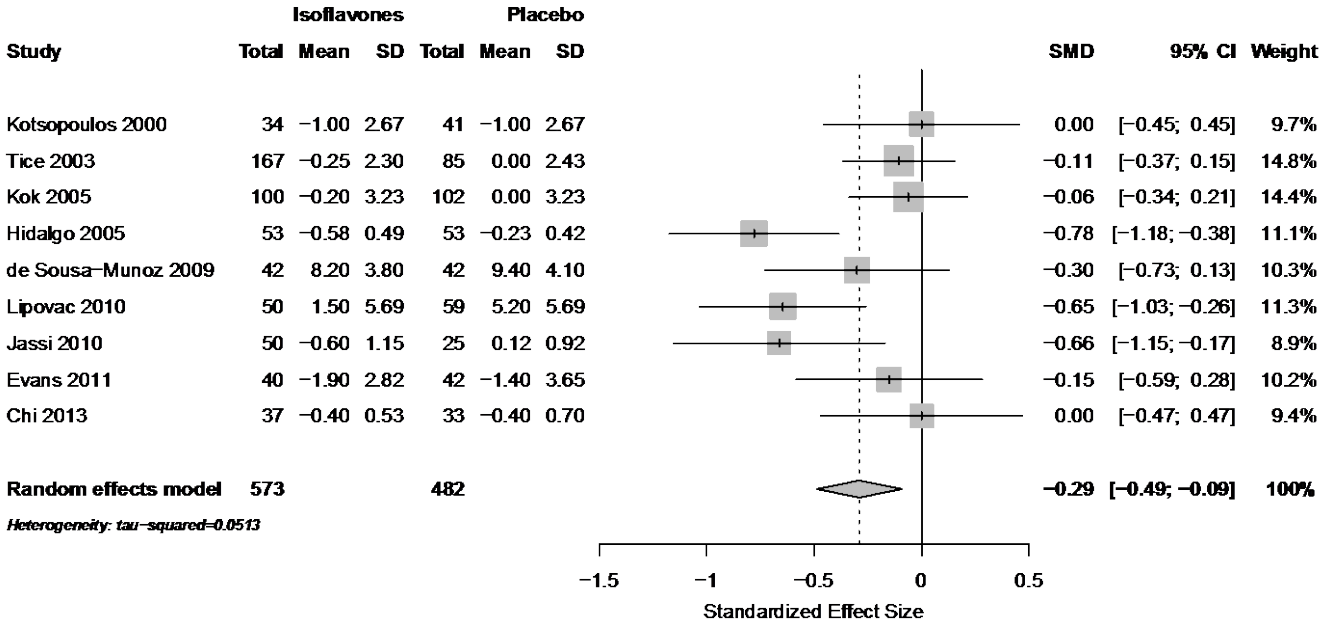


Figure H-10. Anxiety symptoms—isoflavones compared with placebo

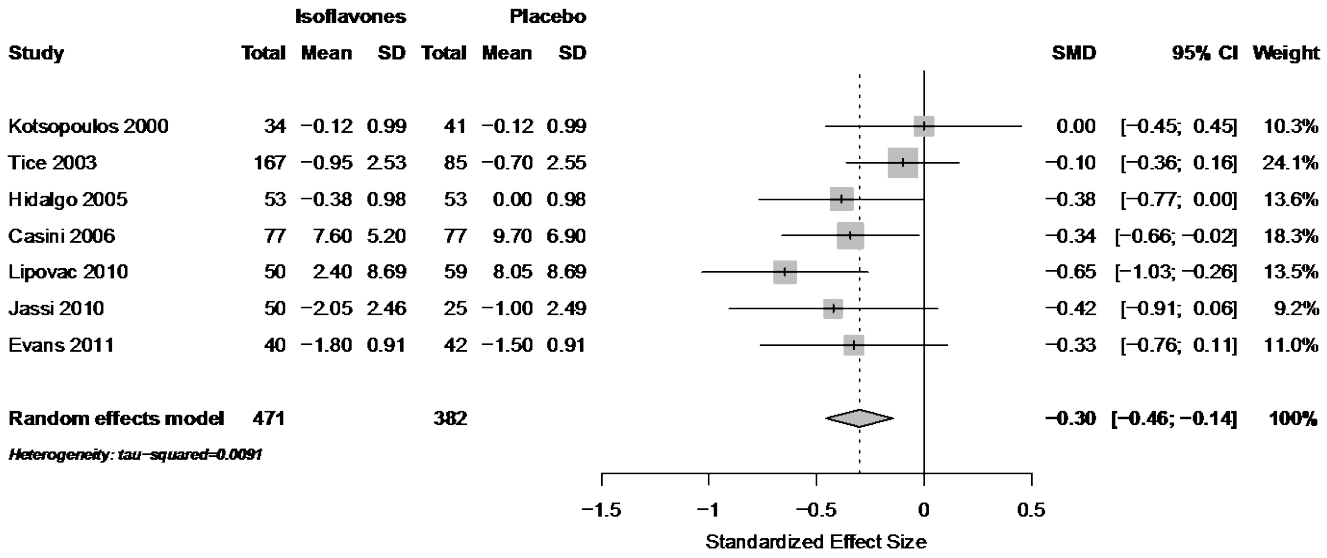


Table H-1. All pairwise psychological outcome SMDs for global psychological well-being

SSRI/SNRI						
	E-High					
	0.17 (-0.03 to 0.38) tau^2=0.00; n=1	E-Standard				
	0.14 (-0.17 to 0.45) tau^2=0.00; n=1	-0.06 (-0.14 to 0.02) tau^2=0.00; n=9	E-Low Ultralow			
				Gababentin		
					Isoflavones	
-0.42 (-0.60 to -0.24) tau^2=0.03; n=6	-0.43 (-0.66 to -0.19) tau^2=0.00; n=1	-0.10 (-0.18 to -0.03) tau^2=0.00;n=12[a]	-0.17 (-0.35 to 0.02) tau^2=0.06; n=9	-0.23 (-0.48 to 0.02) tau^2=0.00; n=2	-0.11 (-0.22 to 0.01) tau^2=0.00; n=7	Placebo

[a] Excluding two large prevention trials -0.22 (-0.35 to -0.08) tau2=0.02; n=10

Table H-2. All pairwise psychological outcome SMDs for depression symptoms

SSRI/SNRI					
	E-High				
	NS	E-Standard			
	0.00 (-0.31 to 0.31) tau^2=0.00; n=1	-0.21 (-0.44 to 0.02) tau^2=0.00; n=2	E-Low Ultralow		
				Isoflavones	
-0.43 (-0.60 to -0.26) tau^2=0.02; n=5	-0.41 (-0.57 to -0.25) tau^2=0.00; n=4	-0.31 (-0.48 to -0.15) tau^2=0.05;n=12[a]	-0.12 (-0.42 to 0.18) tau^2=0.03; n=4	-0.29 (-0.49 to -0.09) tau^2=0.05; n=9	Placebo

[a] Excluding two large prevention trials -0.41 (-0.67 to -0.16) tau2=0.12; n=10

Table H-3. All pairwise psychological outcome SMDs for anxiety symptoms

SSRI/SNRI					
	E-High				
	-0.03 (-0.22 to 0.17) tau^2=0.00; n=1	E-Standard			
	0.31 (0.00 to 0.63) tau^2=0.00; n=1	-0.16 (-0.60 to 0.28) tau^2=0.00; n=1	E-Low Ultralow		
				Isoflavones	
-0.31 (-0.50 to -0.12) tau^2=0.02; n=3	-0.35 (-0.60 to -0.10) tau^2=0.01; n=2	-0.31 (-0.55 to -0.06) tau^2=0.11;n=9[a]	-0.25 (-0.53 to 0.04) tau^2=0.00; n=3	-0.30 (-0.46 to -0.14) tau^2=0.01; n=7	Placebo

[a] Excluding one large prevention trials -0.37 (-0.61 to -0.12) tau2=0.09; n=8

Appendix I. Sexual Function Plots

Figure I-1. Pain during sex—vaginal estrogens compared with placebo

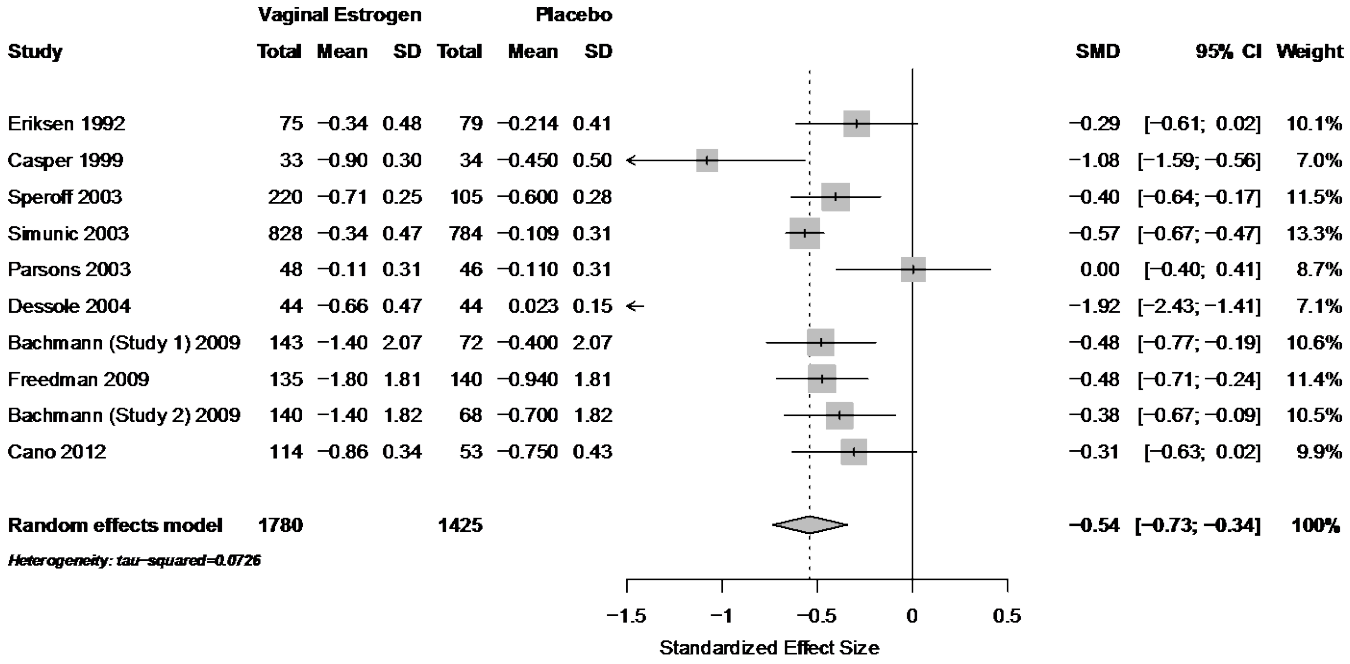


Figure I-2. Pain during sex—oral estrogen compared with placebo

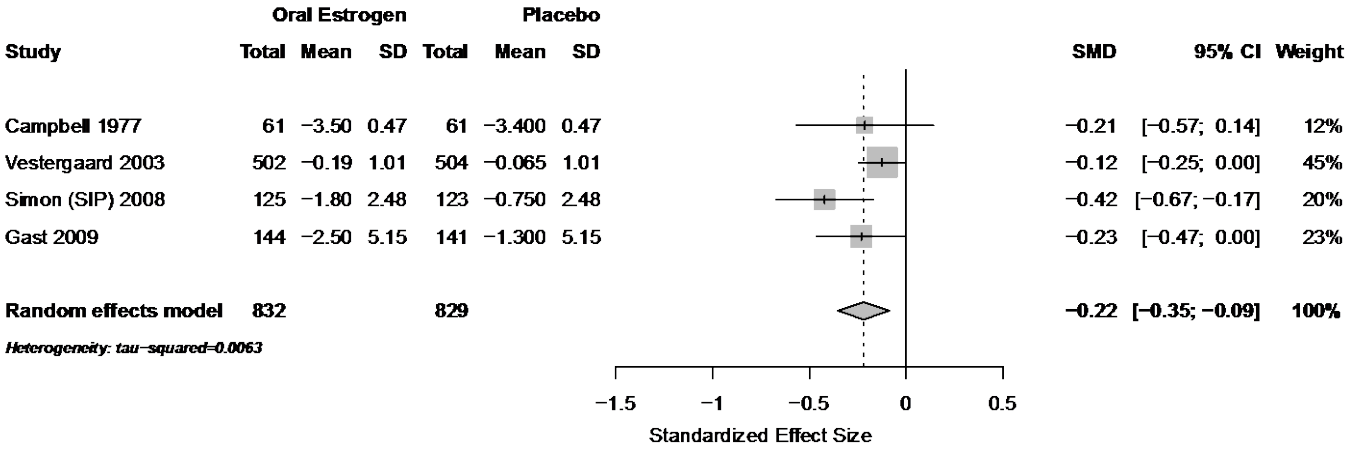


Figure I-3. Pain during sex—all estrogens compared with placebo

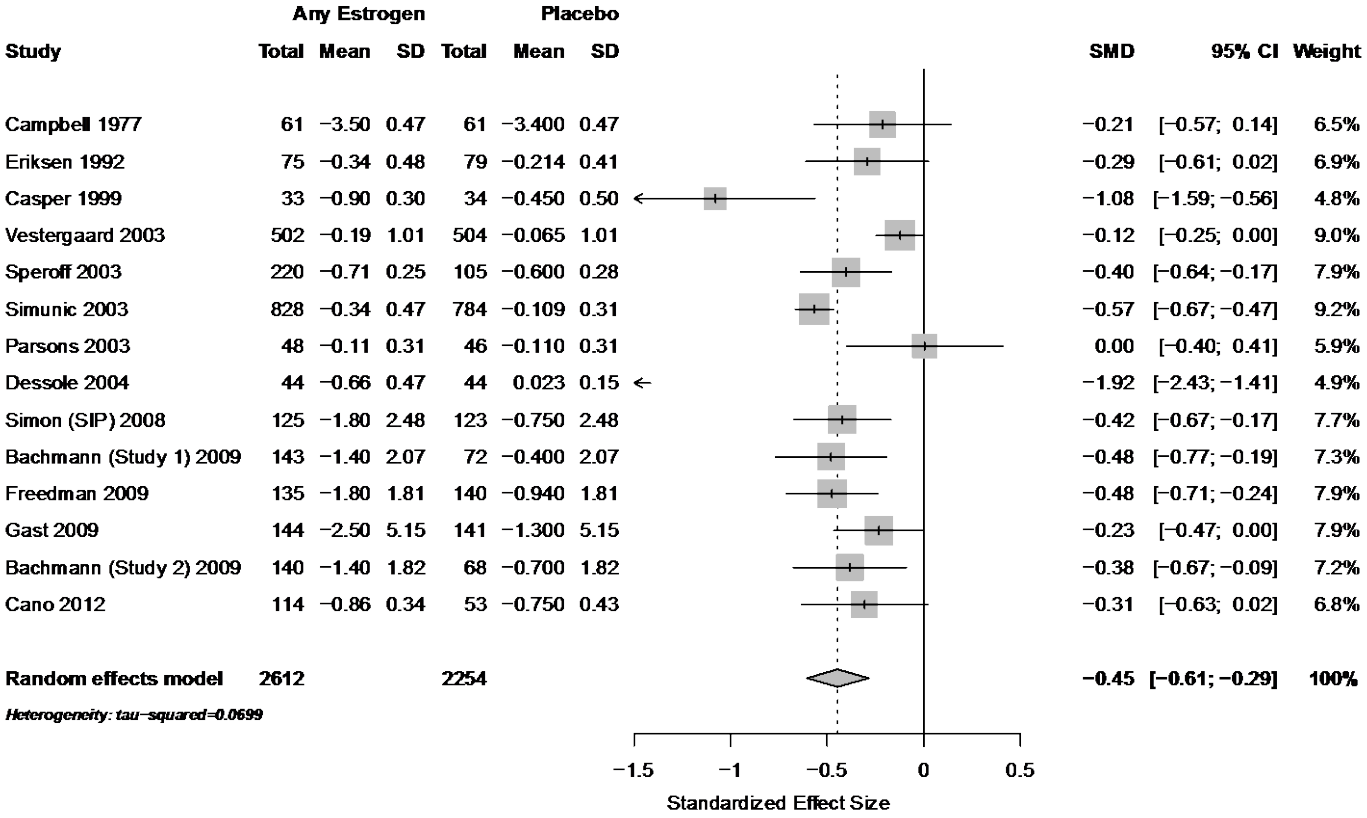


Figure I-4. Global assessment of sexual function—all estrogens compared with placebo

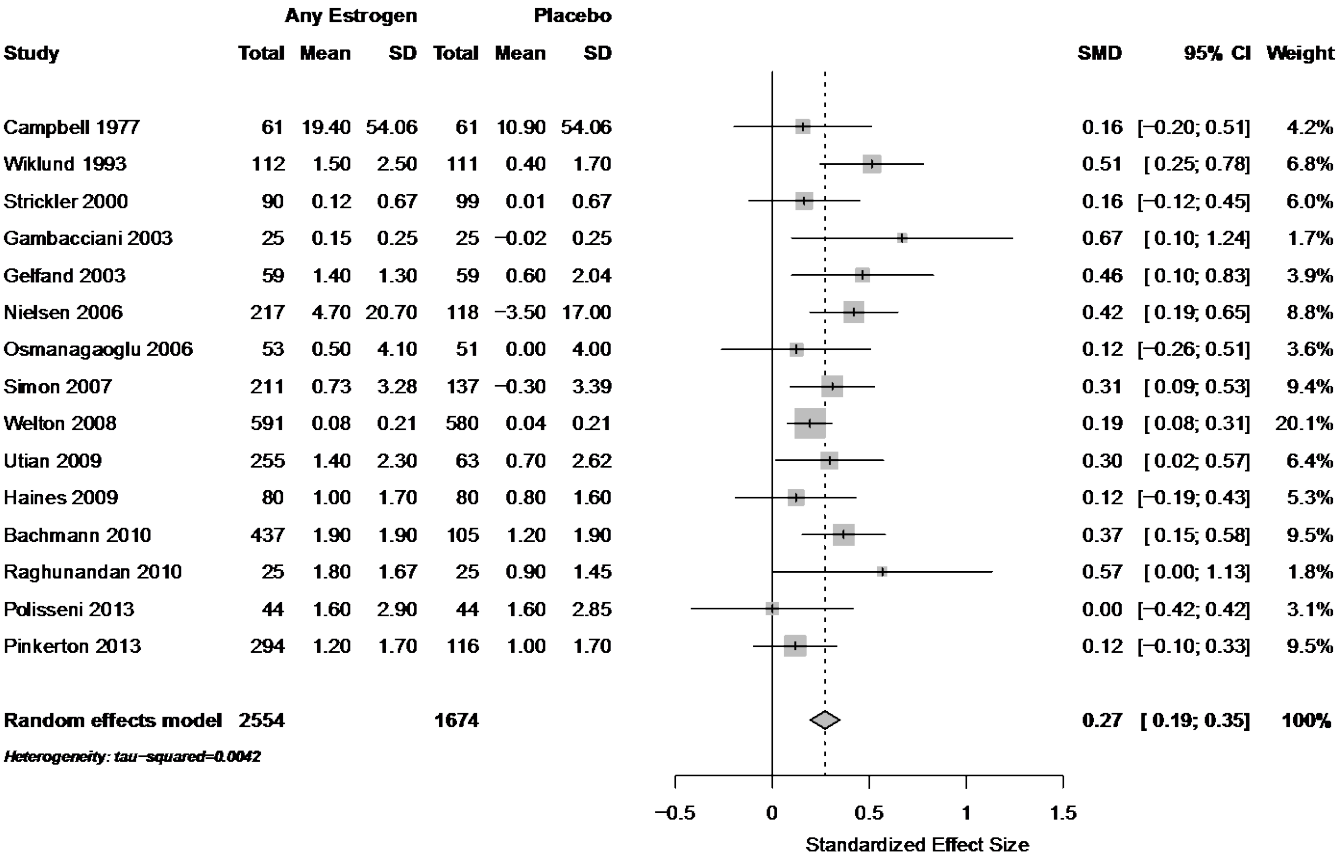


Figure I-5. Global assessment of sexual function—SSRI/SNRI compared with placebo

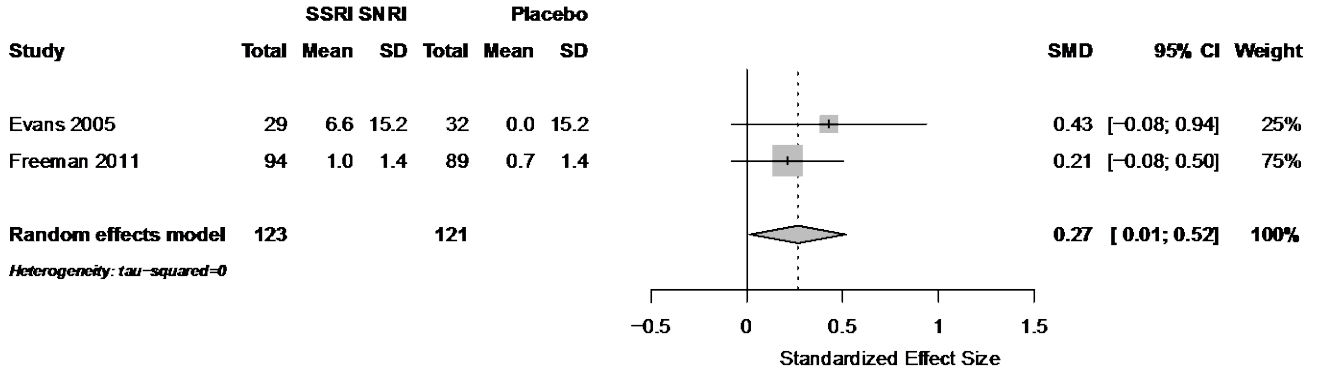


Figure I-6. Global assessment of sexual function—isoflavones compared with placebo

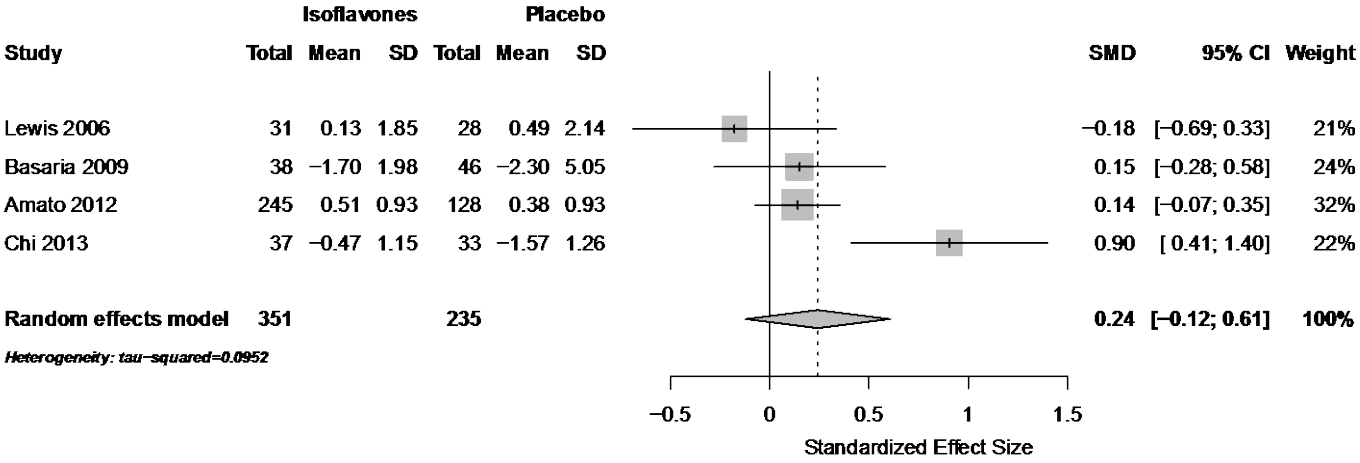


Figure I-7. Sexual interest—all estrogens compared with placebo

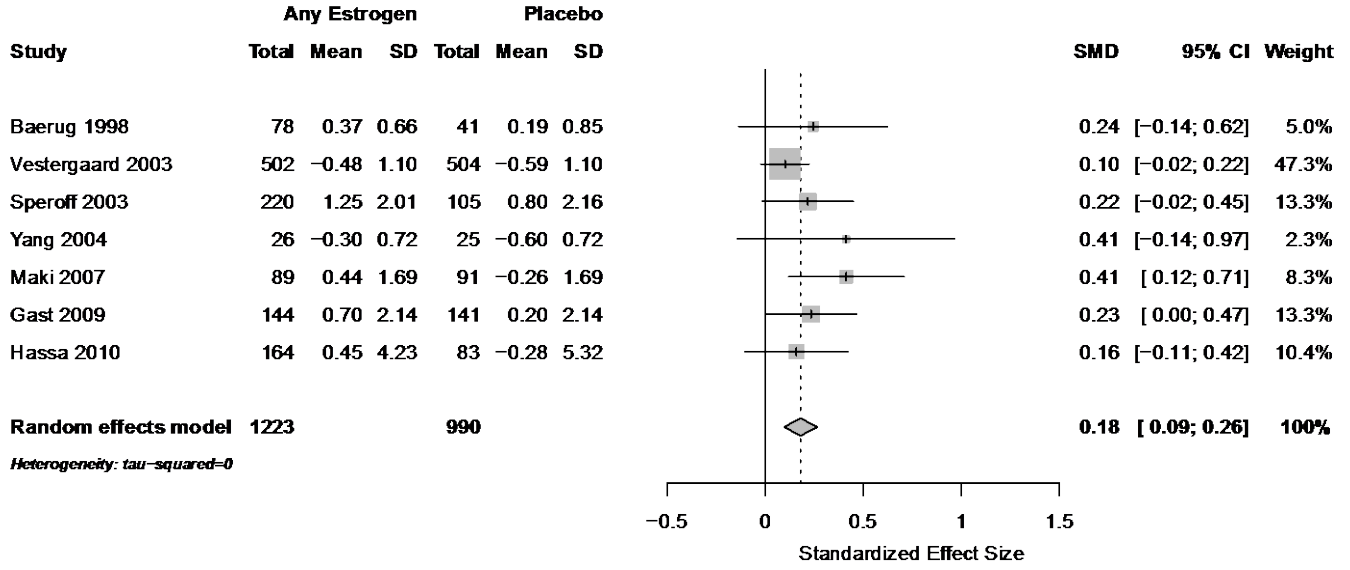


Figure I-8. Sexual interest—SNRI compared with placebo

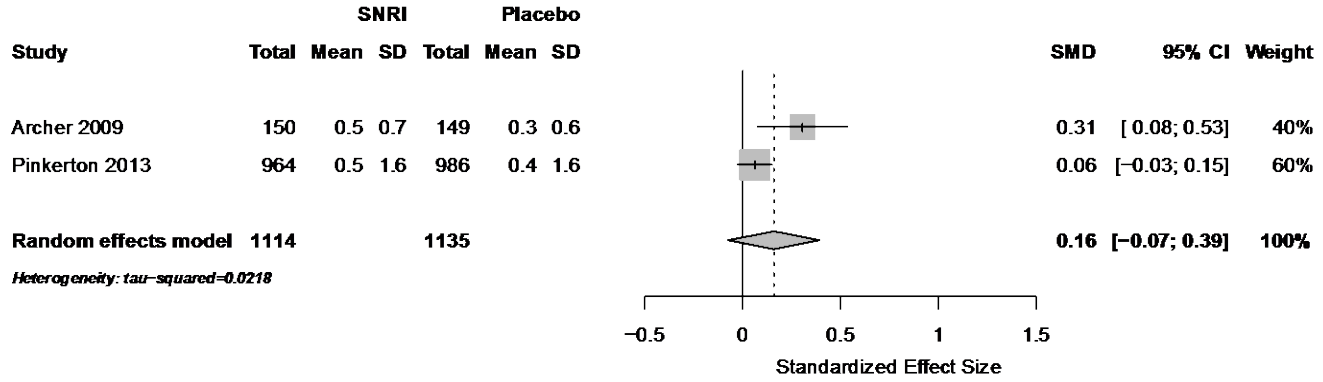


Figure I-9. Sexual interest—isoflavones compared with placebo

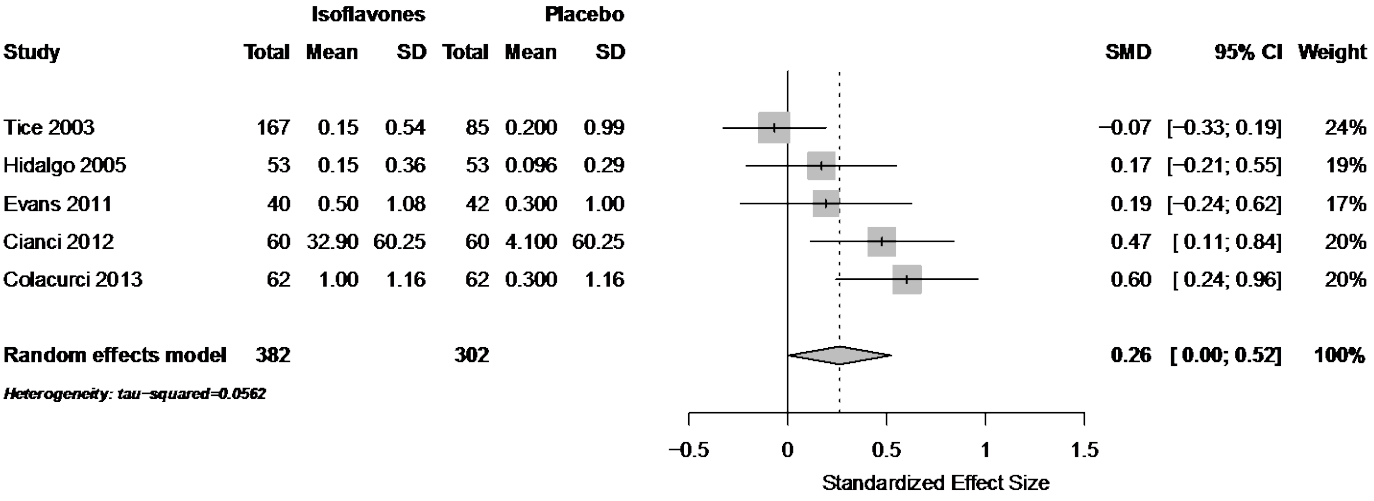


Figure I-10. Mean difference in satisfying sexual episodes over 4 weeks—testosterone compared with placebo in women with intact uteri

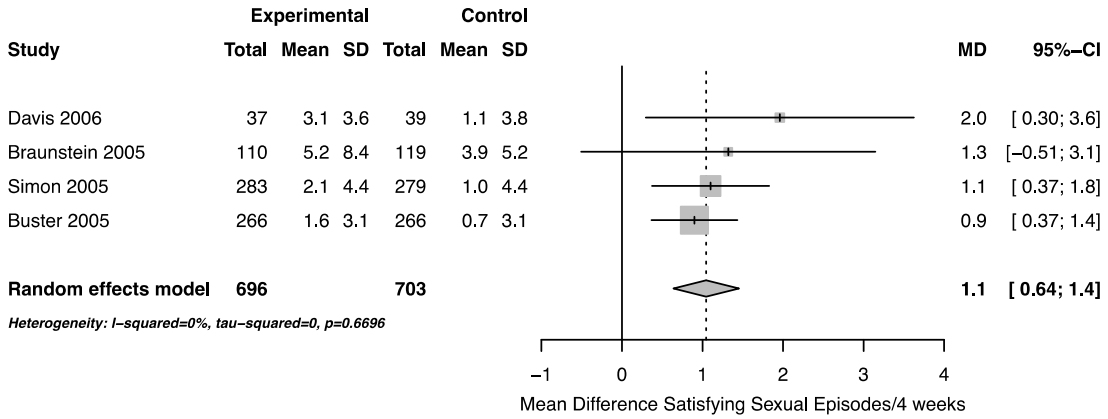


Figure I-11. Mean difference in satisfying sexual episodes over 4 weeks—testosterone compared with placebo in women with and without intact uteri/ovaries

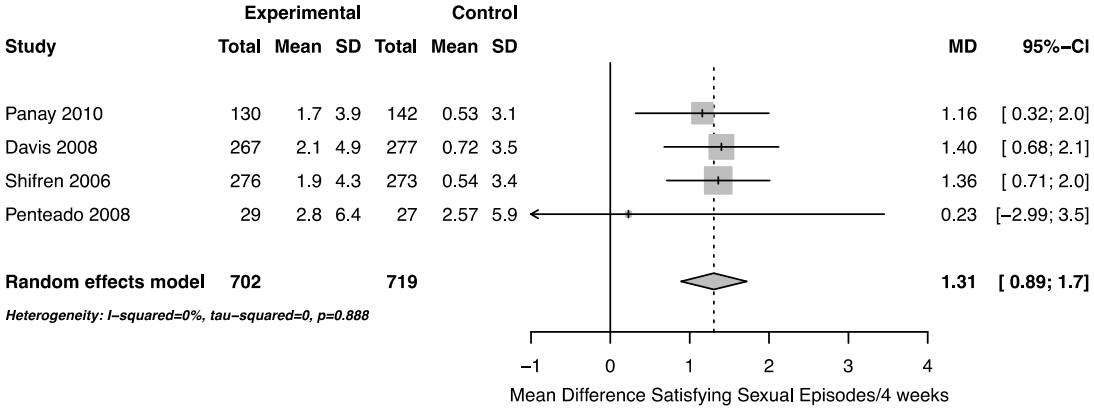
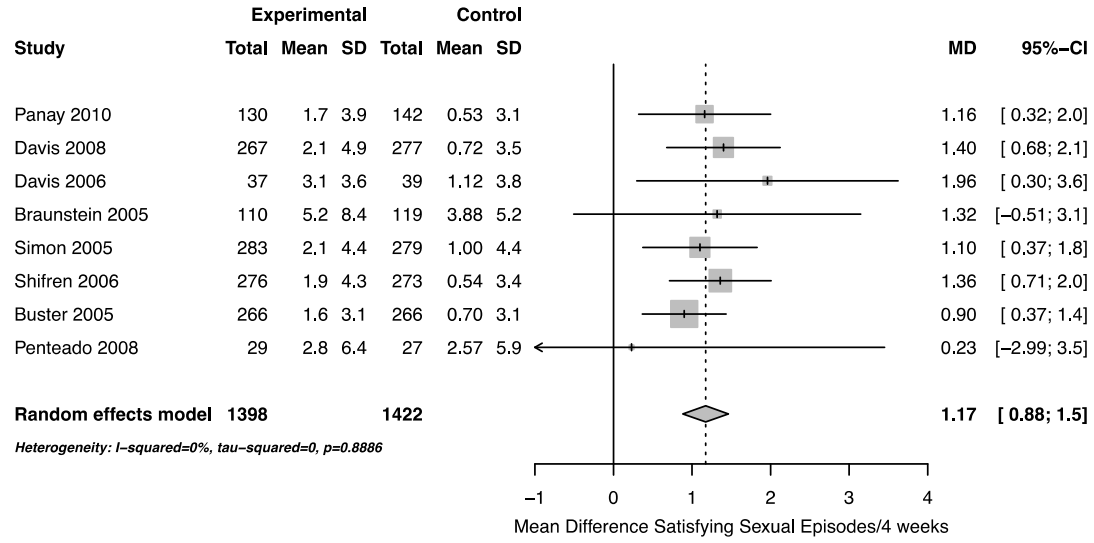


Figure I-12. Mean difference in satisfying sexual episodes over 4 weeks—testosterone compared with placebo (all trials)



Appendix J. Urogenital Atrophy Supplemental Plots

Figure J-1. Urogenital atrophy and symptoms forest plot of pairwise comparisons—vaginal estrogens compared with placebo (excludes Dessole 2004 as outlier)

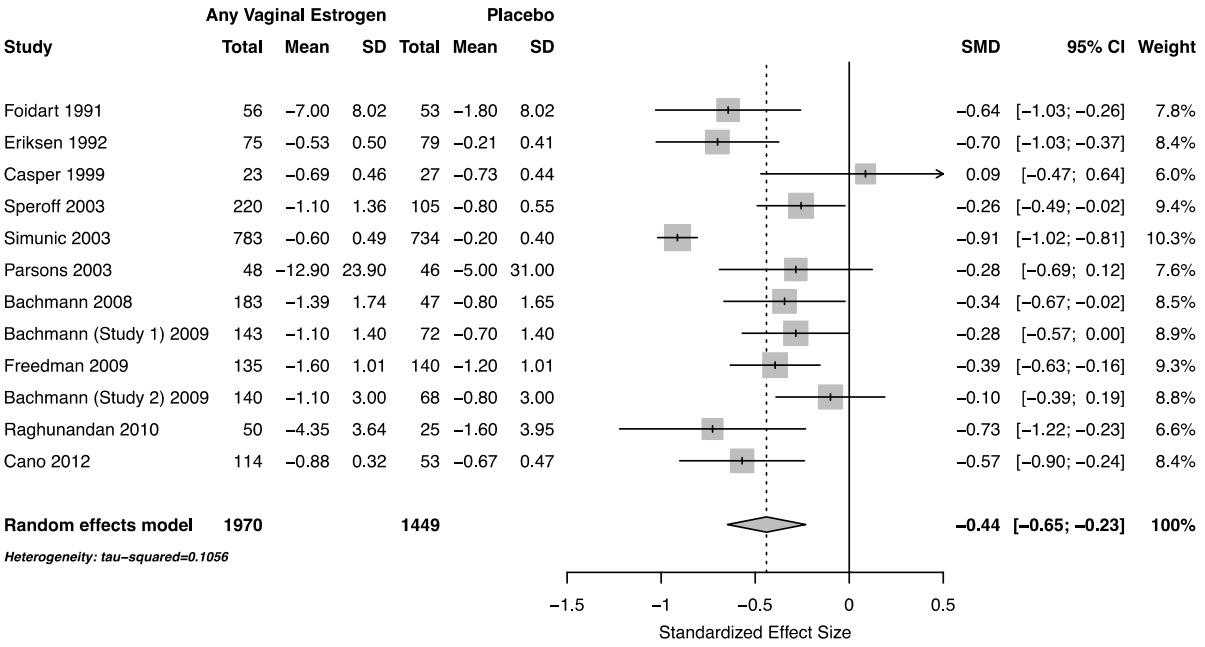


Figure J-2. Urogenital atrophy and symptoms forest plot of pairwise comparisons—vaginal estrogens compared with placebo (includes Dessole 2004)

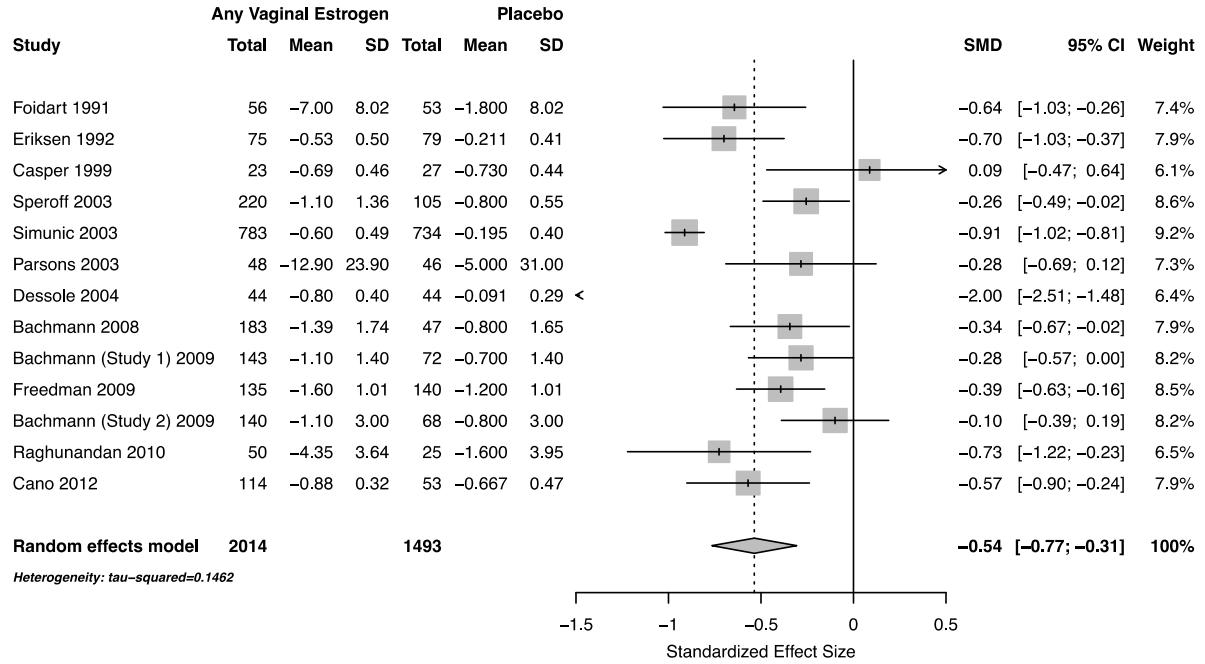


Figure J-3. Urogenital atrophy and symptoms forest plot of pairwise comparisons—ospemifene compared with placebo

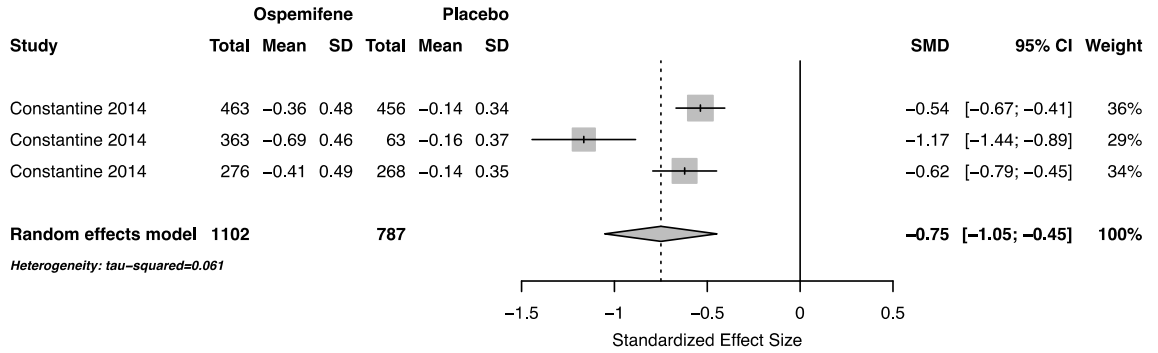


Figure J-4. Urogenital atrophy forest plot of pairwise comparisons—nonvaginal standard dose estrogens compared with placebo

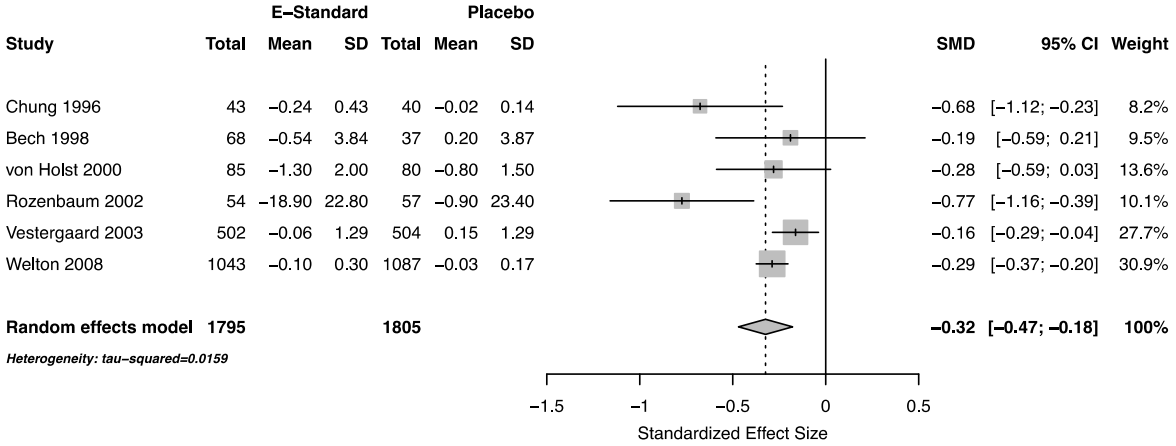


Figure J-5. Urogenital atrophy forest plot of pairwise comparisons—nonvaginal low/ultralow dose estrogens compared with placebo

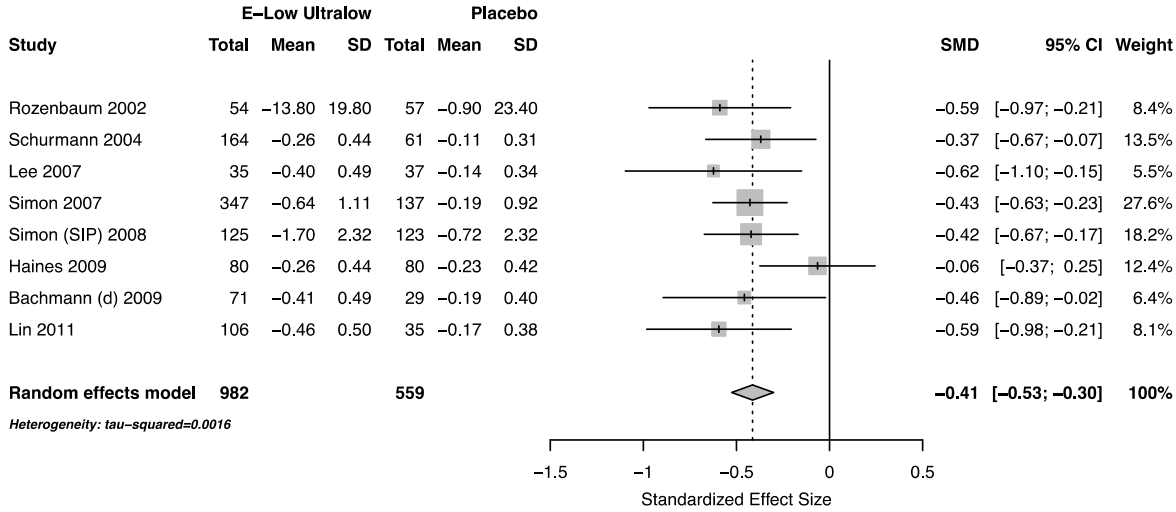
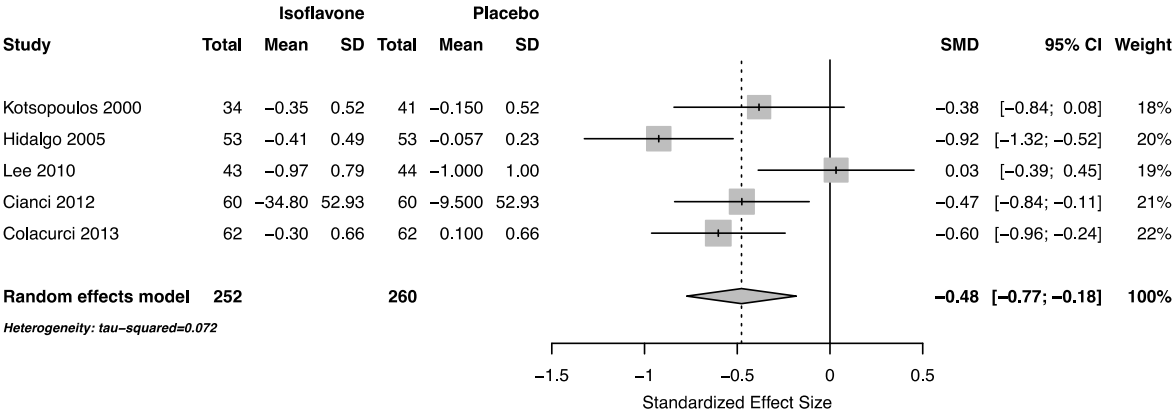


Figure J-6. Urogenital atrophy forest plot of pairwise comparisons—isoflavones with placebo



Appendix K. Sleep Disturbance Plots

Figure K-1. Sleep disturbance forest plot of pairwise comparisons—estrogen (standard dose) compared with placebo

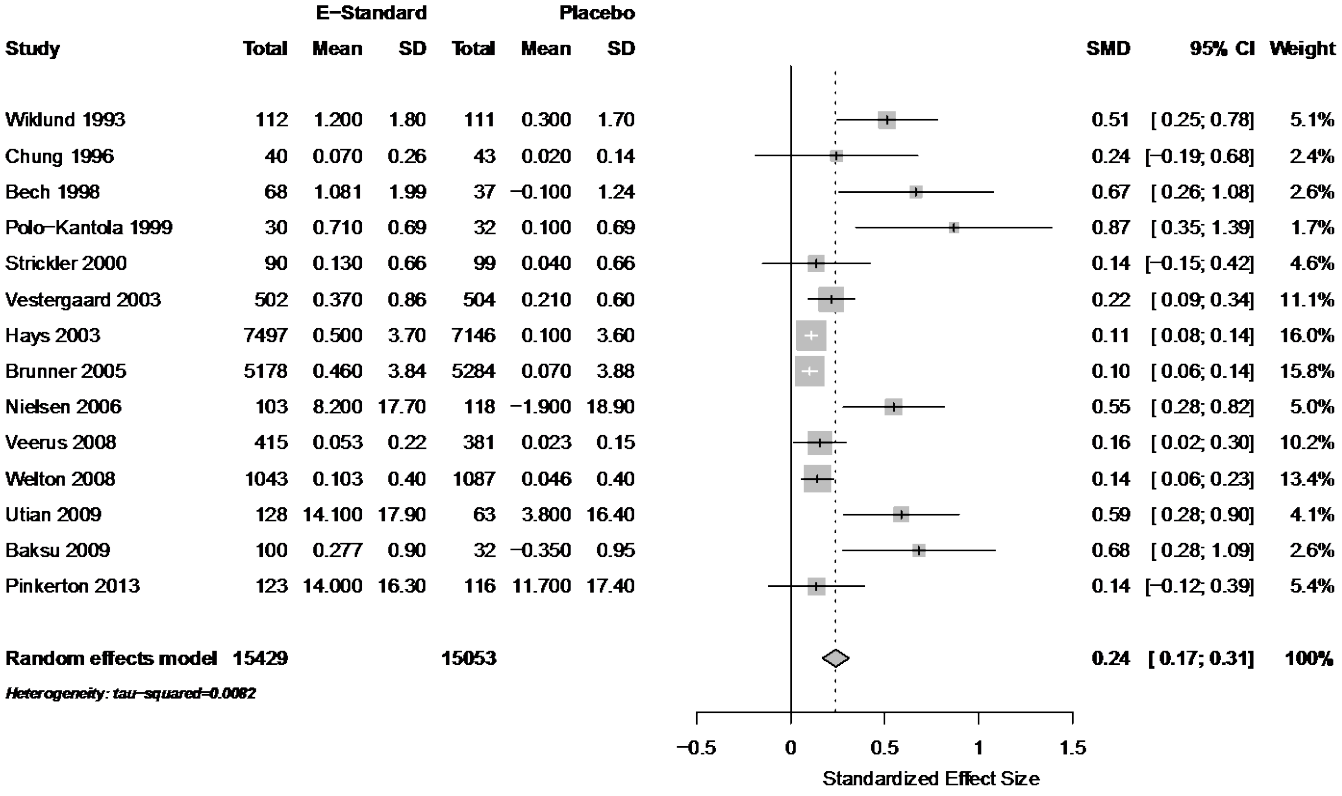


Figure K-2. Sleep disturbance forest plot of pairwise comparisons—estrogen (low and ultralow dose) compared with placebo

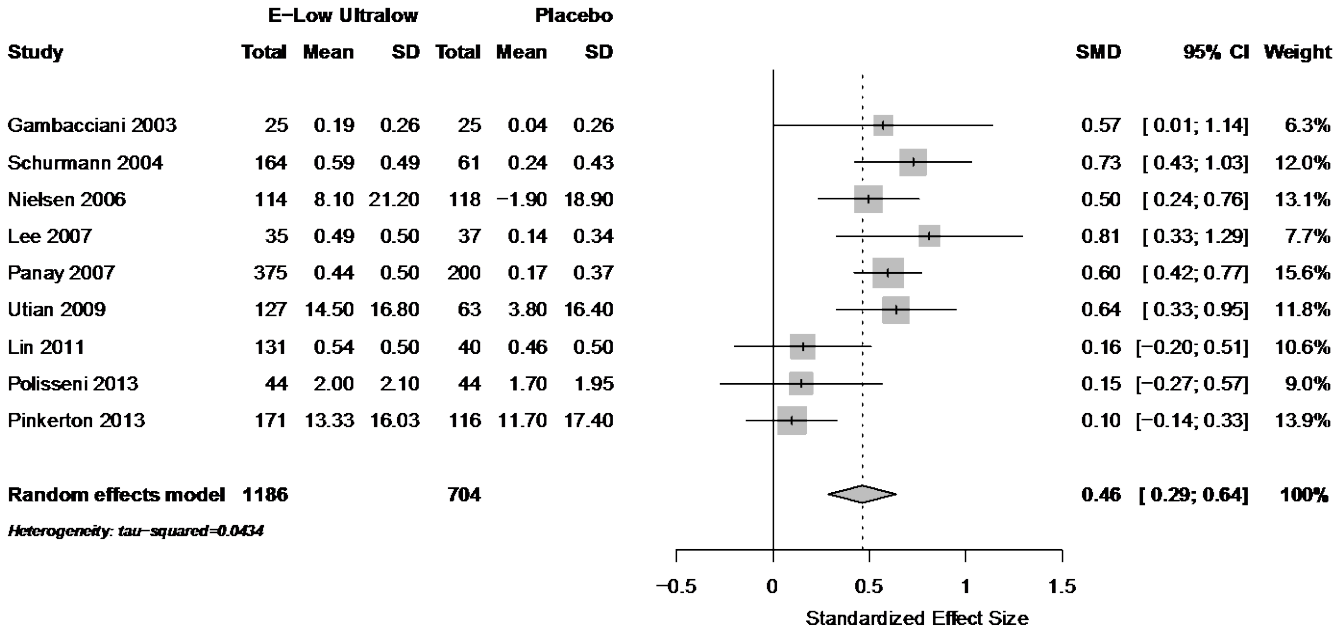


Figure K-3. Sleep disturbance forest plot of pairwise comparisons—standard and low/ultralow dose estrogen

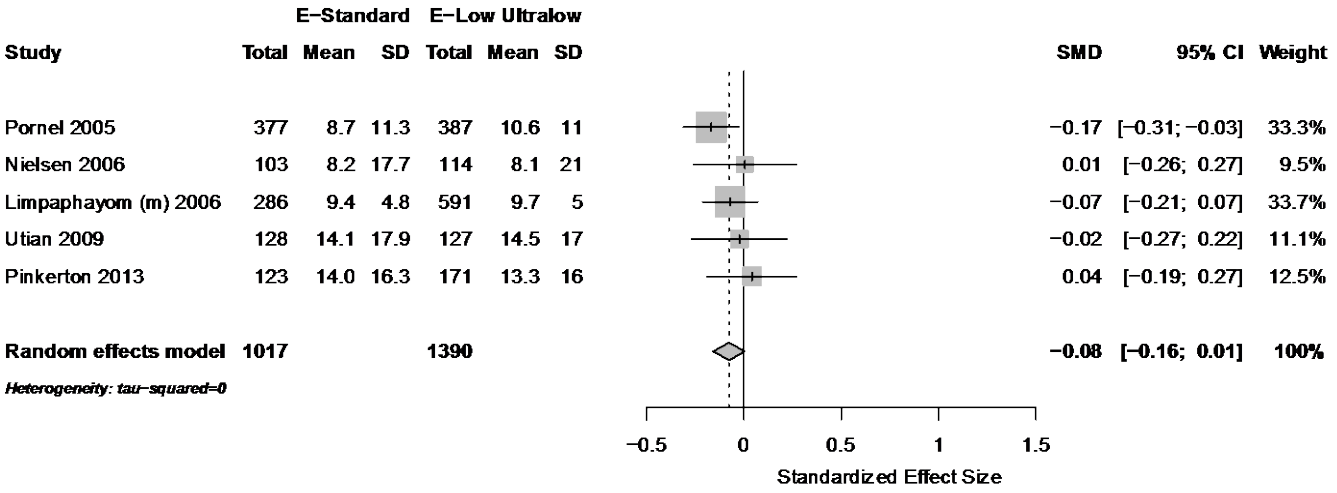


Figure K-4. Sleep disturbance forest plot of pairwise comparisons—SSRIs compared with placebo

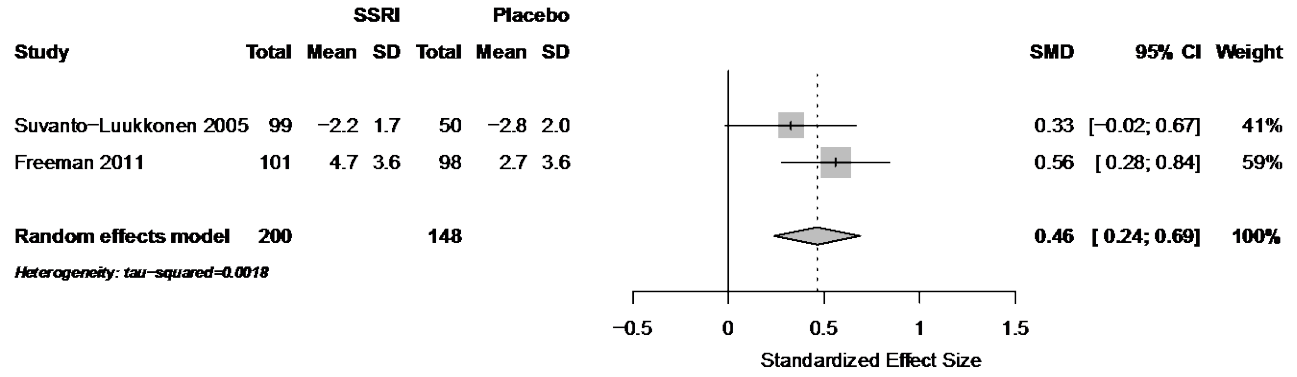


Figure K-5. Sleep disturbance forest plot of pairwise comparisons—gabapentin compared with placebo

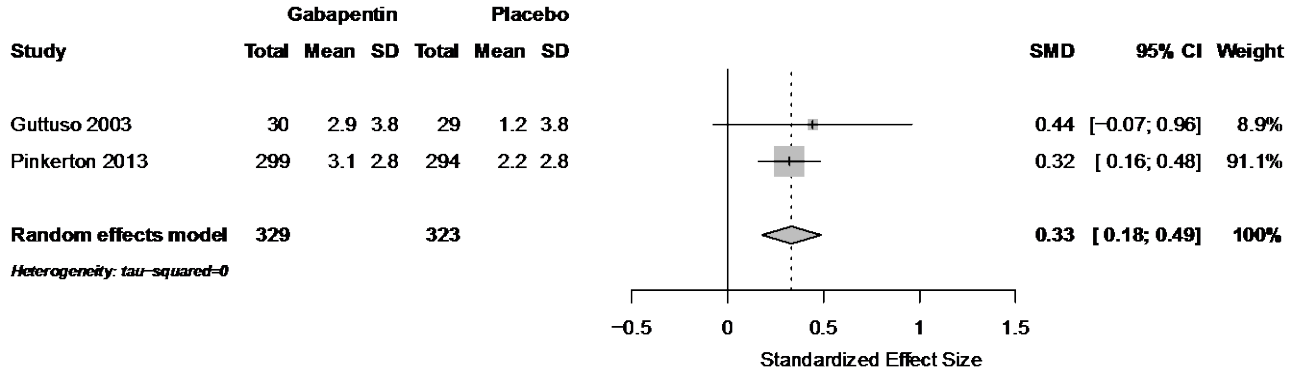


Figure K-6. Sleep disturbance forest plot of pairwise comparisons—isoflavones compared with placebo

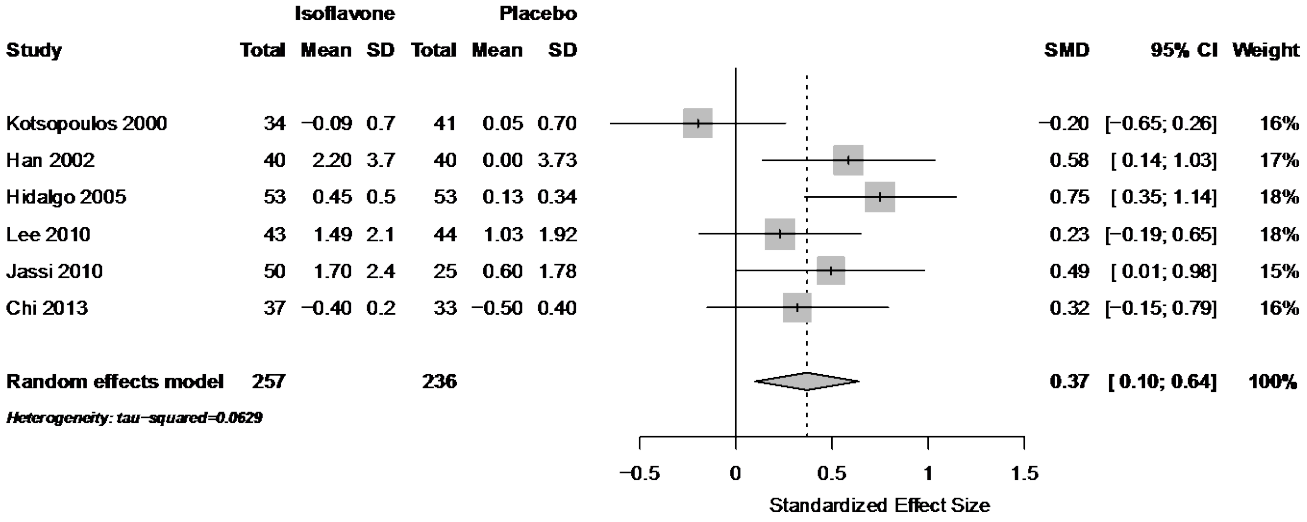
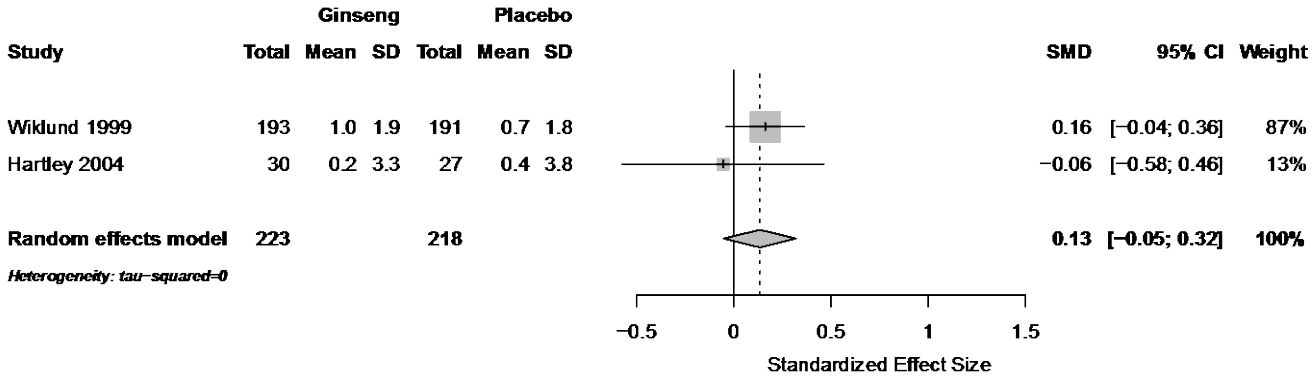


Figure K-7. Sleep disturbance forest plot of pairwise comparisons—ginseng compared with placebo



Appendix L. Quality Assessments From Nelson Report

Table L-1a. Quality assessment for articles reporting long term effects of hormone therapies

Study/Trial	Adequate randomization	Adequate concealment	Groups similar at baseline	Comparable groups maintained	Eligibility criteria specified	Outcome assessors masked	Care provider maskedHE	Patient masked
Anderson 2003}/WHI estrogen plus progestin	Y	Y	Y	Compliance similar	Y	Y	Y	Y
Anderson 2004 /WHI estrogen only	Y	Y	Y	Y	Y	Y	Y	Y
Cherry 2002/ESPRIT	Y	Y	Y	Greater noncompliance in treatment group	Y	Y	Y	Y
Chlebowski 2010/WHI estrogen plus progestin	Y	Y	Y	Y	Y	Y	Y	Y
Cirillo 2005/WHI estrogen plus progestin	Y	Y	Y	Y	Y	Y	Y	Y
Heiss 2008/WHI estrogen plus progestin	Y	Y	Y	Y	Y	Y	Y	Y
Hulley 2002/HERS and HERS II	Y	Y	Y	Y	Y	Y	Y	Y
LaCroix 2011/WHI estrogen only	Y	Y	Y	Y	Y	Y	Y	Y
Rossouw 2002/WHI estrogen plus progestin	Y	Y	Y	Y	Y	Y	Y	Y

Table L1-b1. Quality assessment for articles reporting long term effects of hormone therapies

Study/Trial	crossovers, adherence, and contamination	Differential loss to followup	Intention to treat analysis	Post-randomization exclusions	Outcomes prespecified	Funding source	External validity	Study Quality
Anderson 2003/WHI estrogen/ progestin	Y	N	Y	Not reported	Y	National Heart, Lung, and Blood Institute, US Dept of Health and Human Services	Good	Fair
Anderson 2004 /WHI estrogen only	Y	N	Y	N	Y	National Heart, Lung, and Blood Institute, US Dept of Health and Human Services	Good	Fair
Cherry 2002/ESPRIT	Unclear	Unclear	Y	Not reported	Y	Schering AG	Fair	Fair
Chlebowski 2010/WHI estrogen/ progestin	Y	N	Y	N	Y	National Heart, Lung, and Blood Institute, US Dept of Health and Human Services	Good	Fair
Cirillo 2005/WHI estrogen/ progestin	Y	N	Y	N	Y	National Heart, Lung, and Blood Institute, US Dept of Health and Human Services	Good	Fair
Heiss 2008/WHI estrogen/ progestin	Y	N	Y	N	Y	National Heart, Lung, and Blood Institute, US Dept of Health and	Good	Fair

						Human Services		
Hulley 2002/HERS and HERS II	Y	N	Y	Y	Y	Wyeth-Ayerst Research	Good/Fair	Fair
LaCroix 2011/WHI estrogen only	Y	N	Y	N	Y	National Heart, Lung, and Blood Institute, US Dept of Health and Human Services	Good	Fair
Rossouw 2002/WHI estrogen/ progestin	Y	N	Y	N	Y	National Heart, Lung, and Blood Institute, US Dept of Health and Human Services	Good	Fair

Appendix M. Short-Term Adverse Effects for Nonhormone Therapies

Table M-1a. Short-term adverse effects for prescription nonhormone therapies used to treat menopausal symptoms

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Blood and Lymphatic System	Cardiac	Congenital, Familial and Genetic Disorders	Labyrinth	Eye	Endocrine Disorders	Gastrointestinal	General Disorders and Administration Site Conditions	Hepatobiliary Disorders	Immune System	Infections and Infestations
Archer, 2009, United States	placebo	180						0.0% to 1.1%		1.7% to 8.3%	0.6% to 5.0%			
	desvenlafaxine (100mg)	182						1.6% to 2.2%		4.9% to 45.1%	3.8% to 11.5%			
	desvenlafaxine (150mg)	179						5.0% to 6.1%		7.8% to 44.1%	5.0% to 17.3%			
Archer, 2009, United States	placebo	151	105							0.7% to 7.3%	4.0%			
	desvenlafaxine (100mg)	150	125					5.3%		6.0% to 28.7%	12.7%			
	desvenlafaxine (150mg)	151	128					0.7%		3.3% to 21.9%	11.3%			
Speroff, 2008, United states	placebo	77	67					0.0% to 1.3%		0.0% to 10.4%	0.0% to 9.1%			
	desvenlafaxine (50mg)	149	134					0.7% to 3.4%		4.7% to 27.5%	3.4% to 7.4%			
	desvenlafaxine (100mg)	155	146					2.6% to 5.8%		5.8% to 38.7%	5.2% to 19.4%			
	desvenlafaxine (150mg)	157	149					6.4% to 8.9%		5.7% to 47.8%	3.8% to 17.2%			
	desvenlafaxine (200mg)	151	147					6.0% to 6.6%		9.3% to 45.0%	7.3% to 15.2%			
Oktem, 2007,	black cohosh	40	7							0.0% to	2.5%			

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Blood and Lymphatic System	Cardiac	Congenital, Familial and Genetic Disorders	Ear and Labyrinth Disorders	Eye	Endocrine Disorders	Gastrointestinal	General Disorders and Administration Site Conditions	Hepatobiliary Disorders	Immune System Disorders	Infections and Infestations
Turkey	(40mg)									5.0%				
	fluoxetine (20mg)	40	13							2.5% to 5.0%	5.0%			
Bouchard, 2012, Multinational	placebo	152	85		5.3%					2.6% to 4.6%	2.0%			
	desvenlafaxine (100mg)	158	116		4.4%			5.7%		10.1% to 31.0%	8.9%			
Depomed (c), 2012, United States	placebo	177	69		0.6%					0.6% to 4.0%	0.6% to 1.7%			4.0% to 5.6%
	gabapentin (1200mg)	174	150							0.6% to 6.9%	5.2%			6.3% to 8.0%
	gabapentin (1800mg)	181	173							3.9% to 8.8%	5.0%			0.6% to 6.1%
Depomed (c), 2012, United States	placebo	183	31							1.6%				
	gabapentin (1200mg)	186	85							3.2%				
	gabapentin (1800mg)	190	72							7.4%	0.5%			
Pinkerton, 2012, Mulitinational	placebo	1052	908	0.5% to 1.7%	0.1% to 3.2%	0.1% to 0.2%	0.9%	0.1% to 7.6%	1.5%	0.1% to 16.3%	0.7% to 17.0%	0.3%	3.5%	0.1% to 31.3%
	desvenlafaxine (100mg)	1066	984	0.8% to 1.0%	0.1% to 3.3%	0.3%	4.0%	0.2% to 15.7%	0.7%	0.1% to 26.2%	0.1% to 23.5%	0.1% to 0.3%	2.9%	0.1% to 38.5%
Freeman, 2011, United States	placebo	101	62							5.0% to 17.8%	9.9% to 13.9%			
	escitalopram	104	54							9.6% to	3.8% to			

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Blood and Lymphatic System	Cardiac	Congenital, Familial and Genetic Disorders	Ear and Labyrinth	Eye	Endocrine Disorders	Gastrointestinal	General Disorders and Administration Site Conditions	Hepatobiliary Disorders	Immune System	Infections and Infestations
	(10mg)									10.6%	13.5%			
Butt, 2008, Canada	placebo	98					1.0%				1.0%			
	gabapentin (300mg)	99					2.0%	4.0%			1.0% to 2.0%			
Clayden, 1974, United Kingdom	placebo	43			16.3%					11.6% to 20.9%				
	clonidine (0.05 to 0.15mg)	42			9.5%					26.2% to 28.6%				
Soares, 2010, Multinational	escitalopram (10 to 20mg)	299								7.0% to 20.4%				
	desvenlafaxine (100 to 200mg)	296								8.8% to 27.7%				

Blood and Lymphatic System: Anaemia **Cardiac:** Acute Myocardial Infarction, Angina Pectoris, Atrial Fibrillation, Coronary Artery Occlusion, Palpitation, Coronary Artery Disease **Congenital, Familial and Genetic Disorders:** Cerebrovascular Arteriovenous Malformation, Carotid artery occlusion **Ear and Labyrinth Disorders:** Vertigo **Eye:** Glaucoma, Narrow Anterior Chamber Angle, Retinal Haemorrhage, Abnormal vision, Mydriasis **Gastrointestinal:** Abdominal Pain, Colitis Ischaemic, Diverticular Perforation, Gastrooesophageal Reflux Disease, Ileus, Ileus Paralytic, Lower Gastrotintestinal Hemorrhage, Stomatitis, Swollen Tongue, Upper Gastrointestinal Hemorrhage, Flatulence, Abdominal Hernia, Gastroesophageal reflux disease exacerbation, Constipation, Diarrhea, Dry mouth, Nausea, Vomiting, Anorexia, Dyspeptic Problems **General Disorders:** Chest Pain, Drug Therapeutic Incompatibility, Fatigue, Non-Cardiac Chest Pain, Chills, Asthenia, Tiredness **Hepatobiliary Disorders:** Biliary Dyskinesia, Cholecystitis **Infections and Infestations:** Cellulitis, Diverticulitis, Enterocolitis Viral, Escherichia Sepsis, Herpes Zoster, Laryngitis, Pneumonia, Pyelonephrities, Subcutaneous Abscess, Urinary Tract Infection, Nasopharyngitis, Upper Respiratory Tract Infection

Note: Blank cells indicate 0 adverse events

Table M-1b. Short-term adverse effects for prescription nonhormone therapies used to treat menopausal symptoms

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Investigations	Injury, poisoning and procedural complications	Metabolism/ Nutritional	Musculoskeletal	benign, malignant and unspecified (incl cysts and	Nervous System	Psychiatric Disorders	Renal/ Urinary	Reproductive System and Breast	Respiratory, Thoracic and Mediastinal Disorders	Skin and Subcutaneous Tissue	Vascular
Archer, 2009, United States	placebo	180				3.9%			2.2% to 10.0%						3.9%
	desvenlafaxine (100mg)	182				7.1%			8.2% to 19.2%						7.1%
	desvenlafaxine (150mg)	179				2.8%			11.2% to 22.9%						2.8%
Archer, 2009, United States	placebo	151	105						0.7% to 7.3%						1.3%
	desvenlafaxine (100mg)	150	125						9.3% to 12.7%						5.3%
	desvenlafaxine (150mg)	151	128						9.3% to 11.9%						4.0%
Speroff, 2008, United states	placebo	77	67			0.0% to 3.9%			0.0% to 10.4%					0.0% to 2.6%	1.3%
	desvenlafaxine (50mg)	149	134			2.7% to 4.0%			0.7% to 15.4%					1.3% to 6.0%	4.0%
	desvenlafaxine (100mg)	155	146			5.2% to 5.8%			2.6% to 19.4%					1.9% to 2.6%	5.2%

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Investigations	Injury, poisoning and procedural complications	Metabolism/ Nutritional	Musculoskeletal	Benign, malignant and unspecified (incl cysts and	Nervous System	Psychiatric Disorders	Renal/ Urinary	Reproductive System and Breast Disorders	Respiratory, Thoracic and Mediastinal Disorders	Skin and Subcutaneous Tissue	Vascular
	desvenlafaxine (150mg)	157	149			2.5% to 7.6%			1.9% to 27.4%					1.3% to 2.5%	6.4%
	desvenlafaxine (200mg)	151	147			3.3% to 6.0%			1.3% to 27.2%					0.7% to 6.0%	7.9%
Oktem, 2007, Turkey	black cohosh (40mg)	40	7						0.0% to 2.5%					2.5%	
	fluoxetine (20mg)	40	13						2.5% to 7.5%					5.0%	
Bouchard, 2012, Multinational	placebo	152	85				0.7%		1.3% to 3.9%		0.7%				
	desvenlafaxine (100mg)	158	116				3.8%		7.0% to 10.8%		0.6%				
Depomed (c), 2012, United States	placebo	177	69	2.3%			5.1%		0.6% to 5.6%						
	gabapentin (1200mg)	174	150	2.9%			2.3%	0.6%	8.6% to 23.6%				0.6%		
	gabapentin (1800mg)	181	173	5.0%	0.6%		2.8%	0.6%	0.6% to 19.3%						
Depomed (c),	placebo	18	31		0.5%				0.5%						

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Investigations	Injury, poisoning and procedural complications	Metabolism/ Nutritional	Musculoskeletal	Benign, malignant and unspecified (incl cysts and	Nervous System	Psychiatric Disorders	Renal/ Urinary	Reproductive System and Breast Disorders	Respiratory, Thoracic and Mediastinal Disorders	Skin and Subcutaneous Tissue	Vascular
2012, United States		3							to 7.7%						
	gabapentin (1200mg)	186	85		0.5%			0.5%	4.8% to 17.2%						
	gabapentin (1800mg)	190	72		0.5%				1.6% to 18.9%						
Pinkerton, 2012, Mulitinational	placebo	1052	908	0.1 % to 9.7 %	0.1% to 20.2%	0.1% to 4.2%	0.2% to 34.2%	0.1% to 1.0%	0.1% to 24.9%	23.0%		0.1% to 11.8%	0.4% to 19.6%	0.1% to 11.5%	3.1% to 6.0%
	desvenlafaxine (100mg)	1066	984	0.1 % to 12.4 %	0.0% to 22.0%	0.2% to 7.1%	0.1% to 27.8%	0.1% to 1.4%	0.1% to 31.1%	0.2% to 43.8%	0.1 %	0.1% to 9.8%	0.1% to 25.3%	0.2% to 15.7%	3.6% to 10.1%
Freeman, 2011, United States	placebo	101	62	4.0 %					6.9% to 10.9%					8.9%	
	escitalopram (10mg)	104	54	5.8 %					2.9% to 8.7%					6.7%	
Butt, 2008, Canada	placebo	98							1.0% to 36.7%						
	gabapentin (300mg)	99							2.0% to 25.3%						

Study (Author, Year, Country)	Treatment (dose)	N	Total Adverse Events	Investigations	Injury, poisoning and procedural complications	Metabolism/ Nutritional	Musculoskeletal	Benign, malignant and unspecified (incl cysts and	Nervous System	Psychiatric Disorders	Renal/ Urinary	Reproductive System and Breast	Respiratory, Thoracic and Mediastinal Disorders	Skin and Subcutaneous Tissue	Vascular
Clayden, 1974, United Kingdom	placebo	43					11.6%		51.2%			2.3%		9.3%	
	clonidine (0.05 to 0.15mg)	42					11.9%		52.4%			2.4%		16.7%	
Soares, 2010, Multinational	escitalopram (10 to 20mg)	299							9.4% to 28.4%					11.0%	
	desvenlafaxine (100 to 200mg)	296							11.1% to 25.7%					14.5%	

Investigations: Weight Increased, Blood Creatine Phosphokinase MB Increased, Blood Pressure Increased, Cardiac Stress Test Abnormal, Electrocardiogram T Wave Abnormal, Electrocardiogram T Wave Inversion, Electrocardiogram Abnormal **Injury, poisoning and procedural complications:** Overdose; Attempted Suicide, Accidental Overdose, Road Traffic Accident, Meniscus Lesion, Rib Fracture, Drug Toxicity, Hand Fracture, Injury, Intentional Overdose, Limb Injury, Patella Fracture, Radius Fracture, Traumatic Intracranial Hemorrhage, Ulna Fracture **Metabolism/Nutritional:** Weight Gain, Hypercholesteremia, Hyperlipemia, Hypokalaemia **Musculoskeletal and Connective Tissue:** Arthralgia, Back Pain, Bunion, Flank Pain, Foot Deformity, Intervertebral Disc Protrusion, Knee Deformity, Musculoskeletal Chest Pain, Osteoarthritis, Pain in Extremity **Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Breast Cancer, Basal Cell Carcinoma, Carcinoid Tumor Pulmonary, Dermatofibrosarcoma, Lung Adenocarcinoma, Malignant Lung Neoplasm, Malignant Melanoma In Situ, Multiple Myeloma, Non-Small Cell Lung Cancer Stage III, Ovarian Cancer, Ovarian Cancer Recurrent, Pancreatic Carcinoma Metastatic, Squamous Cell Carcinoma of Skin, Thyroid Cancer, Transitional Cell Carcinoma, Uterine Leiomyoma **Nervous System**: Ageusia, Cerebral Hematoma, Cerebrovascular Disorder, Cervical Myelopathy, Confusion, Convulsion, Dizziness, Dysarthria, Headache, Hypoaesthesia, Insomnia, Irritability, Libido Decrease, Migraine, Nerve Compression, Nervousness, Paraesthesia, Presyncope, Sedation, Somnolence, Thinking Abnormal, Transient Ischemic Attack **Psychiatric Disorders:** Major Depression, Mental Status Changes **Reproductive System and Breast Disorders:** Endometrial Hyperplasia **Respiratory, Thoracic and Mediastinal Disorders:** Acute Resperatory Failure, Asthma, Chronic Obstructive Pulmonary Disease, Non-Cardiogenic Pulmonary Edema, Pulmonary Embolism, Pneumothorax **Renal/ Urinary:** Leukorrhea, Nephrolithiasis, Renal Failure Acute **Skin and Subcutaneous Tissue:** Sweating, Rash, Allergic Skin Reaction, Erythema, Pruritus **Vascular:** Hypertension

Note: Blank cells indicate 0 adverse events

Table M-2a. Short-term adverse effects for nonprescription nonhormone therapies used to treat menopausal symptoms

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events	Blood and Lymphatic System	Cardiac	Ear and Labyrinth	Endocrine	Eye	Gastrointestinal	General Disorders and Administration Site Conditions	Immune	Infections
Evans, 2011, Canada	Placebo	42	33	79						0.0% to 14.3%			
	Genistein (30mg)	41	29	72						0.0% to 9.8%			
Garcia, 2010, Multinational	Placebo	31	9	34						6.5%	6.5%		3.2%
	Nutrafem [multibotanical]	103	43	109			1.0%			9.7%	5.8%	1.9%	1.9%
Chandeying, 2007, Thailand	CEE + MPA (0.625mg E + 2.5mg P)	30		34		3.3%				0.0% to 6.7%			
	Pueraria mirifica (50 mg)	30		31		6.7%				0.0% to 10.0%	3.3%		
Newton, 2006, United States	Placebo	84		67						15.5%	9.5%		
	CEE + MPA (0.625mg E + 2.5mg P)	32		41						12.5%	18.8%		
	Black cohosh (160 mg)	80		57						15.0%	15.0%		
	ProGyne multibotanical w/ black cohosh (200 mg) + 9 other ingredients	76		44						14.5%	9.2%		
	ProGyne multibotanical + dietary soy counseling	79		57						10.1%	15.2%		

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events	Blood and Lymphatic System	Cardiac	Ear and Labyrinth	Endocrine	Eye	Gastrointestinal	General Disorders and Administration Site Conditions	Immune	Infections
Heger, 2006, Ukraine	Placebo	55	8										
	Phytoestrol N [rheum rhaponticum] (4 mg)	54	8			1.9 %				1.9%			
Tice, 2003, United States	Placebo	85		33						3.5% to 4.7%			
	Rimostil (57.2 mg)	83		28						3.6% to 9.6%			
	Promensil (82 mg)	84		31						2.4% to 4.8%			
Albertazzi, 1998, Italy	Placebo	53		45						1.9% to 50.9%			
	Isoflavones [soy protein] (76 mg)	51		35						0.0% to 49.0%			
de Sousa-Munoz, 2009, Brazil	Placebo	42	7	16	2.4%					0.0% to 7.1%			
	Isoflavones (120 mg)	42	12	22					2.4 %	0.0% to 4.8%			
Uebelhack, 2006, Germany	Placebo	150		32	0.7%		0.7 %		1.3 %	0.7%			10.7 %
	St. John's Wort (70 mg) + black cohosh (3.75 mg)	151		35					0.7 %	0.7%	0.7%		11.9 %
Kotsopoulos, 2000, Australia	Placebo	50		9						4.0%	12.0 %	2.0 %	
	Isoflavones [daidzein, genistein,	44		10							15.9 %		

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events	Blood and Lymphatic System	Cardiac	Ear and Labyrinth	Endocrine	Eye	Gastrointestinal	General Disorders and Administration Site Conditions	Immune	Infections
	glycitein] (118 mg)												
Panjari, 2009, Australia	Placebo	43		24									
	DHEA (50 mg)	46		31									
Ho, 2007, Hong Kong	Placebo	91	43	68			1.1 %	3.3 %		3.3% to 11.0%	3.3%		
	Isoflavones [soy] (80 mg)	85	58	103			1.2 %	2.4 %	2.4 %	3.5% to 16.5%	2.4%		
Osmers, 2005, Germany	Placebo	151		47	0.7%		0.7 %			4.6%	0.7%		12.6 %
	Remifemin [black cohosh] (40 mg)	153		50	0.7%	1.3 %				5.2%	0.7%		8.5%
Levis, 2011, United States	Placebo	126	121		0.8% to 15.1%					9.5% to 42.9%			
	Novasoy [soy protein] (200 mg)	122	122		0.8% to 15.6%					17.2% to 52.5%			
Radhakrishnan, 2009, India	Placebo	41		27						0.0% to 34.1%	2.4%		
	Isoflavones [soy protein] (75 mg)	44		33						2.3% to 34.1%	6.8%		
Plotnikoff, 2011, United States	placebo	59								1.7%			
	keishibukuryogab (7.5g)	62								22.6%			
	keishibukuryogab (12.5g)	57								19.3%			

Blood and Lymphatic System: Anemia, Leukemia, Leg Edema **Cardiac:** Palpitation, Cardiomyopathy **Ear and Labyrinth:** Hearing **Endocrine:** Thyroid Eye: Blurred Vision, Swollen Eye **Gastrointestinal:** Anorexia, Bloating, Heartburn, Constipation, Diarrhea, Dry mouth, Nausea, Vomiting, Nausea/ Vomiting, Epigastric Pain, Stomach/GI Ache or Upset, Duodenal Ulcer, Flatulence **General Disorders and Administration Site Conditions:** Drowsiness/Tiredness, Weakness, Unpalatable/intolerable

Note: Blank cells indicate 0 adverse events

Table M-2b. Short-term adverse effects for nonprescription nonhormone therapies used to treat menopausal symptoms

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events, Injury, Poisoning, or Procedural Complications	Investigations	Metabolism/Nutritional	Musculoskeletal	Neoplasms	Nervous System	Psychiatric	Renal/ Urinary	Reproductive System/Breast	Respiratory and Thoracic	Skin and Subcutaneous	Surgical and Medical Procedures	Vascular	Other
Evans, 2011, Canada	Placebo	42	33	79					2.4%	2.4%		0.0% to 7.1%					
	Genistein (30mg)	41	29	72					0.0% to 2.4%		2.4%	2.4% to 9.8%		2.4%			
Garcia, 2010, Multinational	Placebo	31	9	34			12.9%		9.7%			3.2%	12.9%	9.7%	3.2%		
	Nutrafem [multibotanical]	103	43	109	2.9%		9.7%		12.6%			1.0%	17.5%	1.9%	1.9%		
Chandeying, 2007, Thailand	CEE + MPA (0.625mg E + 2.5mg P)	30		34		10.0%			0.0% to 6.7%		3.3%	0.0% to 30.0%	10.0%	6.7%			3.3% to 6.7%
	Pueraria mirifica (50 mg)	30		31			3.3%		0.0% to 20.0%			6.7% to 16.7%	6.7%	3.3%			
Newton, 2006, United States	Placebo	84		67			11.9%		19.0%			3.6% to 20.2%					
	CEE + MPA (0.625mg E +	32		41			3.1%		18.8%			15.6% to 59.4%					

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events	Injury, Poisoning, or Procedural Complications	Investigations	Metabolism/Nutritional	Musculoskeletal	Neoplasms	Nervous System	Psychiatric	Renal/ Urinary	Reproductive System/Breast	Respiratory and Thoracic	Skin and Subcutaneous	Surgical and Medical Procedures	Vascular	Other
	2.5mg P)																	
	Black cohosh (160 mg)	80		57				13.8%		15.0%			0.0% to 12.5%					
	ProGyne multibotanical w/ black cohosh (200 mg) + 9 other ingredients	76		44				11.8%		10.5%			1.3% to 10.5%					
	ProGyne multibotanical + dietary soy counseling	79		57				11.4%		15.2%			2.5% to 17.7%					
Heger, 2006, Ukraine	Placebo	55	8				1.8%	1.8%				1.8%	0.0% to 3.6%	1.8%				1.8%
	Phytoestrol N [rheum rhapontic	54	8				1.9%	1.9%		1.9%			0.0% to 1.9%	1.9%				

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events	Injury, Poisoning, or Procedural Complications	Investigations	Metabolism/Nutritional	Musculoskeletal	Neoplasms	Nervous System	Psychiatric	Renal/ Urinary	Reproductive System/Breast	Respiratory and Thoracic	Skin and Subcutaneous	Surgical and Medical Procedures	Vascular	Other
	um] (4 mg)																	
Tice, 2003, United States	Placebo	85		33				15.3%		12.9%				16.5%				
	Rimostil (57.2 mg)	83		28				18.1%		4.8%				12.0%				
	Promensil (82 mg)	84		31				17.9%		6.0%				10.7%				
Albertazzi, 1998, Italy	Placebo	53		45														17.0%
	Isoflavones [soy protein] (76 mg)	51		35														5.9%
de Sousa-Munoz, 2009, Brazil	Placebo	42	7	16			4.8%	7.1%		0.0% to 4.8%								
	Isoflavones (120 mg)	42	12	22			2.4%	4.8%		2.4% to 4.8%			2.4%					7.1%
Uebelhack, 2006, Germany	Placebo	150		32	1.3%	2.0%		3.3%					0.7%					
	St. John's Wort (70 mg) + black cohosh	151		35	1.3%	2.0%	1.3%	4.0%		0.7%								

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events	Injury, Poisoning, or Procedural Complications	Investigations	Metabolism/Nutritional	Musculoskeletal	Neoplasms	Nervous System	Psychiatric	Renal/ Urinary	Reproductive System/Breast	Respiratory and Thoracic	Skin and Subcutaneous	Surgical and Medical Procedures	Vascular	Other
	(3.75 mg)																	
Kotsopoulos, 2000, Australia	Placebo	50		9														
	Isoflavones [daidzein, genistein, glycitein] (118 mg)	44		10			2.3%											2.3%
Panjari, 2009, Australia	Placebo	43		24														55.8%
	DHEA (50 mg)	46		31														4.3% to 56.5%
Ho, 2007, Hong Kong	Placebo	91	43	68			2.2% to 3.3%	4.4% to 8.8%	1.1%	4.4%			2.2%	2.2%	2.2%		1.1% to 2.2%	2.2% to 4.4%
	Isoflavones [soy] (80 mg)	85	58	103			3.5% to 7.1%	3.5% to 20.0%		1.2% to 9.4%			3.5% to 4.7%	2.4%	2.4%		1.2% to 4.7%	1.2% to 8.2%
Osmers, 2005, Germany	Placebo	151		47		3.3%		6.6%		3.3%	3.3%		2.6%	0.7%	2.0%		0.7%	
	Remifemin [black cohosh] (40 mg)	153		50	1.3%	3.9%	1.3%	9.8%		2.6%	1.3%	0.7%	2.6%		2.0%		0.7%	
Levis,	Placebo	1	1					0.8% to	0.	34.1%		4.	4.8% to	4.0			4.0%	7.1% to

Study (Author, Year, Country)	Treatment (dose), n	N	Individuals with adverse events	Total Adverse Events,	Investigations	Metabolism/Nutritional	Musculoskeletal	Neoplasms	Nervous System	Psychiatric	Renal/ Urinary	Reproductive System/Breast	Respiratory and Thoracic	Skin and Subcutaneous	Surgical and Medical Procedures	Vascular	Other
2011, United States		26	21				5.6%	8%			0%	23.8%	%				34.1%
	Novasoy [soy protein] (200 mg)	122	122				4.9% to 5.7%	0.8%	44.3%		5.7%	7.4% to 25.4%	5.7%			4.1%	2.5% to 32.0%
Radhakrishnan, 2009, India	Placebo	41		27										4.9%			
	Isoflavones [soy protein] (75 mg)	44		33										4.5%			
Plotnikoff, 2011, United States	placebo	59															
	keishibukuryogab (7.5g)	62															
	keishibukuryogab (12.5g)	57															

Immune: Immune Disorders, Allergies **Metabolism/Nutritional:** Appetite Increase, Weight Gain, Hunger **Musculoskeletal:** Musculoskeletal spasm/numbness, Fracture, Back Pain, Myalgia/ Arthralgia **Nervous System:** Dizziness, Insomnia, Headache, Nervous Disorders, Memory, Sole/Palm Numb, Intercostal Neuralgia, Tremors **Psychiatric:** Increased Emotionality **Renal/ Urinary:** Renal/ Urinary, UTI, Dysuria, Nocturia, Freq Urination **Reproductive System/Breast:** Breast soreness, Abnormal Mammogram, Reproductive System/Breast, Mastodynia, Cramps, Vaginal bleeding/Spotting, Vaginal Odor, Uterofibroma, Endometrium Dysplasia, Cervical Dysplasia, Pelvic Discomfort, Menstrual Disorder **Respiratory and Thoracic:** Upper RTI, Chest Discomfort **Skin and Subcutaneous Tissue:** Bruisability, Itching, Skin Disorders **Vascular:** Vascular Disorders, Hypertension, Hemorrhoids **Other:** Lower extremity weakness, Lower Extremity Tenderness, Abdominal pain, Acute Appendicitis, Sweating, Hand Sweats, Nonandrogeneic Aes, Increased Facial Hair, Hair Loss

Note: Blank cells indicate 0 adverse events

Appendix N. Effectiveness of Treatments for Menopausal Symptoms in Selected Subgroups

Vasomotor Symptoms

Table N-1. Vasomotor outcomes by age subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Hedrick, 2010, Multinational	Mean change in daily MSHFNS	Age < 50	Placebo	24	-6.4
			0.25 mg estradiol	21	-8.5
			0.50 mg estradiol	29	-6.7
			1.0 mg estradiol	36	-9.3
		Age 50-59	Placebo	77	-5.1
			0.25 mg estradiol	73	-8.0[a]
			0.50 mg estradiol	68	-7.9[a]
			1.0 mg estradiol	59	-8.3[a]
		Age ≥ 60	Placebo	23	-4.7
			0.25 mg estradiol	27	-6.7
			0.50 mg estradiol	22	-7.1
			1.0 mg estradiol	29	-9.7[a]
	Mean change in MSHFNS severity score	Age < 50	Placebo	24	-0.8
			0.25 mg estradiol	21	-1.0
			0.50 mg estradiol	29	-0.9
			1.0 mg estradiol	36	-1.2
		Age 50-59	Placebo	77	-0.4
			0.25 mg estradiol	73	-0.7
			0.50 mg estradiol	68	-1.0[b]
			1.0 mg estradiol	59	-1.4[b]
		Age ≥ 60	Placebo	23	-0.4
			0.25 mg	27	-1.2[a]

Trial	Outcome	Subgroup	Treatment	N	Results
			estradiol 0.50 mg estradiol 1.0 mg estradiol	22 29	-1.1[c] -1.6[b]
Davis, 2001, Australia	Difference in MENQOL vasomotor score from placebo	Age <55	Placebo Chinese herbs	NR NR	- -0.94 (95% CI: -1.7 to -0.14)
		Age ≥ 55	Placebo Chinese herbs	NR NR	- 0.51 (95% CI: -0.56 to 1.60)
Rigano, 2001, Italy	Percent with hot flashes	Age 48-50	Placebo 0.05 mg estradiol	75 88	86% 20%
		Age 51-53	Placebo 0.05 mg estradiol	61 52	39% 38%
		Age 54-56	Placebo 0.05 mg estradiol	55 31	83% 0%

MENQOL: Menopause-Specific Quality of Life; MSHFNS: moderate to severe hot flashes and night sweats; NR: not reported
[a] difference from placebo: p<0.01
[b] difference from placebo: p<0.001
[c] difference from placebo: p<0.05

Table N-2. Vasomotor outcomes by BMI subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Tice, 2003, United States	Percent reduction in THF	BMI < 25	Placebo 57.2 mg isoflavones 82.0 mg isoflavones	NR NR NR	40% (95% CI: 26 to 55%) 22% (95% CI: 7 to 37%) 30% (95% CI: 16 to 44%)
		BMI ≥ 25	Placebo 57.2 mg isoflavones 82.0 mg isoflavones	NR NR NR	32% (95% CI: 21 to 42%) 45% (95% CI: 32 to 59%) 49% (95% CI: 35 to 63%)
Davis, 2001, Australia	Difference in MENQOL vasomotor score from placebo	BMI ≤ 25	Placebo Chinese herbs	NR NR	- -0.85 (95% CI: -1.6 to -0.08)
		BMI > 25	Placebo Chinese	NR NR	- 0.42 (95% CI: -0.73 to

Trial	Outcome	Subgroup	Treatment	N	Results
			herbs		1.58)

MENQOL: Menopause-Specific Quality of Life; NR: not reported; THF: total hot flashes

Table N-3. Vasomotor outcomes by race subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Freeman, 2011, United States	Mean change in daily THFNS	White	10-20 mg escitalopram	53	-2.2 (95% CI: -3.5 to -0.87)
		African american	10-20 mg escitalopram	47	
		Other	10-20 mg escitalopram	4	-0.48 (95% CI: -3.0 to 2.0)
					-2.3 (95% CI: -7.8 to -3.2)

THFNS: total hot flashes and night sweats

Table N-4. Vasomotor outcomes by severity of symptoms subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Aso, 2012, Japan	Mean daily THF	< 3 hot flashes/day	Placebo	32	Base: 1.6 (SD:0.57); 12-wk: 0.70
			10 mg equol	32	Base: 1.5 (SD: 0.57); 12-wk: 0.59
		≥ 3 hot flashes/day	Placebo	34	Base: 4.4 (SD: 2.3); 12-wk change: -1.2 (SD:2.9)
			10 mg equol	28	Base: 4.9 (SD: 2.3); 12-wk change: -2.9 (SD: 2.0)[a]
Lee, 2010, Korea	Mean change in MSHF	> 20 Kupperman Index score	Placebo	28	-3.9 (SD: 3.0)
			350 mg isoflavone	29	-5.4 (SD: 3.1)[b]
Maki, 2007, United States	Mean change in Green vasomotor score	Asymptomatic (hot flash severity score < 1.2)	Placebo	57	-0.8
			0.625 mg CEE + 2.5 mg MPA	41	-1.0
		Symptomatic (hot flash score ≥ 1.2)	Placebo	45	-1.6
			0.625 mg CEE + 2.5 mg MPA	36	-2.8[c]
Pitkin, 2007, Multinational	Mean weekly MSHF	< 30 hotflashes/week	1 mg E2V + 2.5 mg MPA	NR NR NR	Base: 18.7; 12-wk: 1.1; last: 0.61[d]
			1 mg E2V + 5 mg MPA		Base: 21.8; 12-wk: 2.5; last: 1.4[d]
			2 mg E2V		Base: 16.7; 12-wk: 0.99; last: 0.61[d]

Trial	Outcome	Subgroup	Treatment	N	Results
			+ 5 mg MPA		
		≥ 30 HF/wk	1 mg E2V + 2.5 mg MPA	NR NR NR	Base: 53.7; 12-wk: 5.3; last: 2.6[e] Base: 51.3; 12-wk: 4.5; last: 4.9[e]
			1 mg E2V + 5 mg MPA		Base: 55.6; 12-wk: 3.2; last: 2.3[e]
			2 mg E2V + 5 mg MPA		
Limpaphayom, 2006, Multinational	Mean daily THF	≥ 3 HF/day	0.3 mg CEE + 1.5 mg MPA	37	Base: 5.0; 12-wk: 0.71[d]; last: 0.35[d]
			0.45 mg CEE + 1.5 mg MPA	31	Base: 5.4; 12-wk: 0.86[d,f]; last: 0.35[d,f]
			0.625 mg CEE + 2.5 mg MPA	25	Base: 4.8; 12-wk: 0.56[d,f]; last: 0.41[d,f]
Frei-Kleiner, 2005, Switzerland	Reduction in weekly THF	≥ 20 KI score	Placebo	18	25%
			42 mg black cohosh	35	53%[g]
Verhoeven, 2005, Netherlands	Reduction in daily THF	≥ 9 HF/day	Placebo	NR	34%
			isoflavone + black cohosh	NR	51%[f]
Crisafulli, 2004, Italy	Reduction in daily THF	> 5 HF score	Placebo	NR	12-wk: 12.6%; 1 yr: 18.4%
			54 mg isoflavone	NR	12-wk: 85.2%; 1 yr: 95.1%[h]
			1 mg estradiol + 0.5 mg NETA	NR	12-wk: 49.3%; 1 yr: 56.3%[h]
Burke, 2003, United States	Daily THFNS	≥ 4 THFNS	Placebo	34	Base: 7.4 (SD: 3.3); last: 1.8 (SD: 2.9)[i]
			42 mg isoflavone	27	Base: 6.5 (SD: 2.9); last: 2.0 (SD: 3.2)[i, f]
			58 mg isoflavone	28	Base: 9.0 (SD:3.6); last: 2.7 (SD: 3.8)[i, f]

CEE: conjugated equine estrogen; E2V: estradiol valerate; MPA: medroxyprogesterone acetate; MSHF: moderate to severe hot flashes; NETA: norethisterone acetate; NR: not reported; THF: total hot flashes; THFNS: total hot flashes and night sweats

[a] difference from placebo: $p<0.009$

[b] difference from placebo: p<0.05
[c] difference from placebo: p=0.001
[d] pre/post: p<0.05
[e] pre/post: p<0.001
[f] no difference between subgroups
[g] difference from placebo: p=0.018
[h] difference from placebo: p<0.01
[i] pre/post: p<0.0001

Table N-5. Vasomotor outcomes by time since menopause subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Lobo, 2009, Multinational	Difference in MENQOL vasomotor score	< 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	154 162 161	-0.6 (SD: 1.2) -1.6 (SD: 1.3)[a] -1.8 (SD: 1.3)[a]
		≥ 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	273 271 253	-0.4 (SD: 1.7) -1.0 (SD: 1.6)[a] -1.2 (SD: 1.6)[a]
Utian, 2009, United States	Difference in MENQOL vasomotor score	< 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	40 82 81	-1.8 (SD: 1.9) -3.4 (SD:1.8)[a] -3.7 (SD: 2.7)[a]
		≥ 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	23 45 47	-1.6 (SD: 2.4) -3.7 (SD: 2.0)[a] -4.4 (SD: 2.7)[a]
Osmers, 2005, Germany	Difference in MRS vasomotor score from placebo	Early climacteric	Placebo 40 mg black cohosh	NR NR	- -0.11 (95% CI: -0.17 to -0.04)[b]
		Late climacteric	Placebo 40 mg black cohosh	NR NR	- -0.07 (95% CI: -0.13 to -0.02)[c]
Davis, 2001, Australia	Difference in	< 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- -0.31 (95% CI: -

Trial	Outcome	Subgroup	Treatment	N	Results
	MENQOL				1.7 to 1.1)
	vasomotor score from placebo	≥ 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- -0.09 (95% CI: -0.61 to 0.42)
	Difference in reduction of THFNS from placebo	< 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- 4.8% (95% CI: -24.6 to 34.2%)
		> 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- 26.8% (95% CI: 3.8 to 49.9%)
Simon, 2001, United States	Reduction in daily MSHF	0 to ≤ 6 mos last menses	Placebo 0.625 mg CEE	15 18	-74.0% (SD: 31.0) -77.5 (SD: 27.6)[d]
		6 to ≤ 12 mos last menses	Placebo 0.625 mg CEE	1 6	-27.9% (SD: 0.0) -82.6 (SD: 32.1)[d]
		12 to ≤ 36 mos last menses	Placebo 0.625 mg CEE	6 13	-46.7 (SD: 40.9) -85.2 (SD: 29.6)[e]
		> 36 mos last menses	Placebo 0.625 mg CEE	25 33	-53.1 (SD: 44.0) -80.1 (SD: 32.7)[e]
Baerug, 1998, Norway	Weekly HFS	Late perimenopausal	Placebo 1 mg estradiol + 0.25 mg NETA 1 mg estradiol + 0.5 mg NETA	NR NR NR	Baseline: 100.2; 12-wk: 38.0 Baseline: 107.1; 12-wk: 1.4 Baseline: 105.3; 12-wk: 1.2
		Postmenopausal	Placebo 1 mg estradiol + 0.25 mg NETA 1 mg estradiol + 0.5 mg NETA	NR NR NR	Baseline: 124.5; 12-wk: 79.3 Baseline: 126.9; 12-wk: 10.8 Baseline: 127.5; 12-wk: 7.4

CEE: conjugated equine estrogen; HFS: hot flash score; MENQOL: Menopause Quality of Life scale; MRS: Menopause Rating Scale; MSHF: moderate to severe hot flashes; NR: not reported; SD: standard deviation

[a] difference from placebo: p≤0.001

[b] difference from placebo: p=0.002

[c] difference from placebo: p=0.006

[d] difference from placebo: NS

[e] difference from placebo: p<0.05

Table N-6. Vasomotor outcomes by uterus status subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Hedrick, 2010 Multinational	Mean change in daily MSHFNS	Absent uterus	Placebo	71	-5.9
			0.25 mg	58	-8.8[a]
			estradiol	62	-7.0
			0.50 mg	68	-9.7[b]

Trial	Outcome	Subgroup	Treatment	N	Results
			estradiol 1.0 mg estradiol		
		Intact uterus	Placebo	53	-4.4
			0.25 mg estradiol	63	-7.0
			0.50 mg estradiol	57	-8.0[c]
			1.0 mg estradiol	56	-8.0[c]
	Mean change in daily MSHFNS severity score	Absent uterus	Placebo	71	-0.5
			0.25 mg estradiol	58	-0.8
			0.50 mg estradiol	62	-0.8
			1.0 mg estradiol	68	-1.4[c]
		Intact uterus	Placebo	53	-0.4
			0.25 mg estradiol	63	-0.9[a]
			0.50 mg estradiol	57	-1.2[c]
			1.0 mg estradiol	56	-1.4[c]

MSHFNS: moderate-to-severe hot flashes and night sweats; N: number
[a] difference from placebo: p<0.05
[b] difference from placebo: p<0.001
[c] difference from placebo: p<0.01

Sexual Function

Table N-7. Sexual function outcomes by age subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Brunner, 2005, United States	Mean change in satisfaction score[a]	Age 50-54 with MSVS	Placebo	134	0.02 (SD: 1.2)
			0.625 mg CEE	140	-0.07 (SD: 1.1)[b]
Hays, 2003, United States	Mean change in satisfaction score[a]	Age 50-54 with MSVS	Placebo	201	-0.2 (SD: 1.3)
			0.625 mg CEE + 2.5 mg MPA	221	0.1 (SD: 1.2)[c]
Davis, 2001, Australia	Difference in MENQOL sex score	Age < 55	Placebo	NR	-
			Chinese herbs	NR	-0.72 (95% CI: -2.8 to 1.4)
		Age ≥ 55	Placebo	NR	-

Trial	Outcome	Subgroup	Treatment	N	Results
	from placebo		Chinese herbs	NR	-0.14 (95% CI: -1.3 to 1.0)
Rigano, 2001, Italy	Percent reporting decrease in sexual activity	Age 48-50	Placebo 0.05 mg estradiol	75 88	44% 48%
		Age 51-53	Placebo 0.05 mg estradiol	61 52	62% 75%
		Age 54-56	Placebo 0.05 mg estradiol	55 31	48% 84%

CEE: conjugated equine estrogen; MENQOL: Menopause-specific Quality of Life; MPA: medroxyprogesterone acetate; MSV: moderate to severe vasomotor symptoms; NR: not reported

[a] Satisfaction score from a single question: 1='very unsatisfied' to 4='very satisfied'

[b] difference between groups: p=0.50

[c] difference between groups: p=0.06

Table N-8. Sexual function outcomes by BMI subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Davis, 2001, Australia	Difference in MENQOL sex score from placebo	BMI $\leq$ 25	Placebo	NR	-
			Chinese herbs	NR	-1.0 95% CI: -2.7 to 0.65)
		BMI >25	Placebo	NR	-
			Chinese herbs	NR	0.18 (95% CI: -1.5 to 1.8)

MENQOL: Menopause-specific Quality of Life; NR: not reported

Table N-9. Sexual function outcomes by time since menopause subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Lobo, 2009, Multinational	Difference in MENQOL sexual score	< 5 yrs menopause	Placebo	154	-0.9 (SD: 1.2)
			0.45 CEE + 20 mg bazedoxifene	162	-0.7 (SD: 1.3)
			0.625 mg CEE + 20 mg bazedoxifene	161	-0.7 (SD: 1.3)
		$\geq$ 5 yrs menopause	Placebo	273	-0.4 (SD: 1.7)
			0.45 CEE + 20 mg bazedoxifene	271	-0.6 (SD: 1.6)[a]
			0.625 mg CEE + 20 mg bazedoxifene	253	-0.7 (SD: 1.6)[b]
Utian, 2009, United States	Difference in MENQOL sexual score	< 5 yrs menopause	Placebo	40	-1.1 (SD: 1.9)
			0.45 CEE + 20 mg bazedoxifene	82	-1.4 (SD: 1.8)
			0.625 mg CEE + 20 mg	81	-1.4 (SD: 1.8)

Trial	Outcome	Subgroup	Treatment	N	Results
			bazedoxifene		
		≥ 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	23 45 47	-0.3 (SD: 1.9) -1.1 (SD: 2.0) -1.5 (SD: 2.1)[b]
Davis, 2001, Australia	Difference in MENQOL sex score from placebo	< 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- 0.52 (95% CI: -1.6 to 2.6)
		≥ 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- -0.96 (95% CI: -2.1 to 0.16)

MENQOL: Menopause-specific Quality of Life; NR: not reported
[a] difference from placebo: p≤0.05
[b] difference from placebo: p<0.01

Table N-10. Sexual function outcomes by uterus status subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Davis, 2008, Multinational	Mean number satisfying sexual episodes per four weeks	Natural menopause	Placebo 0.15 mg testosterone 0.30 mg testosterone	196 187 189	Base: 2.4 (SD: 2.8); last: 3.0 (SD: 4.2) Base: 2.8 (SD: 2.7); last: 4.0 (SD: 4.1)[a] Base: 2.6 (SD: 2.8); last: 4.5 (SD: 5.5)[b]
		Surgical menopause	Placebo 0.15 mg testosterone 0.30 mg testosterone	69 65 65	Base: 2.6 (SD: 2.5); last: 4.1 (SD: 4.2) Base: 3.1 (SD: 4.0); last 4.0 (SD: 4.8) Base: 2.0 (SD: 2.4); last: 4.4 (SD:5.6)

[a] difference from placebo: p=0.02
[b] difference from placebo: p<0.001

Psychological Symptoms

Table N-11. Psychological outcomes by age subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Brunner, 2005, United States	Mean change in psychological score[a]	Age 50-54 with MSVS	Placebo	151	0.08 (SD: 2.59)
			0.625 mg CEE	159	-0.15 (SD: 2.63)[b]
Hays, 2003,	Mean change in	Age 50-54 with MSVS	Placebo	213	-0.4 (SD: 2.3)
			0.625 mg	255	-0.1 (SD: 2.4)[c]

Trial	Outcome	Subgroup	Treatment	N	Results
United States	psychological score[a]		CEE + 2.5 mg MPA		
Davis, 2001, Australia	Difference in MENQOL psychological score from placebo	Age < 55	Placebo	NR	-
			Chinese herbs	NR	-0.22 (95% CI: -1.0 to 0.57)
		Age ≥ 55	Placebo	NR	-
			Chinese herbs	NR	0.10 (95% CI: -0.77 to 0.96)

CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate; MSVS: moderate to severe vasomotor symptoms; NR: not reported

[a] Center for Epidemiological Studies Depression Scale (6 items) plus Diagnostic Interview Schedule (2 items): range -8.2 (best) to 4.0 (worst)

[b] difference from placebo: p=0.44

[c] difference from placebo: p=0.23

Table N-12. Psychological outcomes by BMI subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Davis, 2001, Australia	Difference in MENQOL psychological score from placebo	BMI ≤ 25	Placebo	NR	-
			Chinese herbs	NR	-0.17 (95% CI: -1.01 to 0.68)
		BMI > 25	Placebo	NR	-
			Chinese herbs	NR	0.13 (95% CI: -0.68 to 0.95)

MENQOL: Menopause-specific Quality of Life; NR: not reported

Table N-13. Psychological outcomes by time since menopause subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Kornstein, 2010, United States	Mean change in Hamilton Depression Scale	Perimenopausal	Placebo	37	-6.8 (SD: 4.5)
			10 mg desvenlafaxine	84	-10.9 (SD: 4.9)[a]
		Postmenopausal	Placebo	88	-7.8 (SD: 7.0)
			10 mg desvenlafaxine	163	-11.1 (SD: 6.8)[b]
Lobo, 2009, Multinational	Difference in MENQOL psychological score	< 5 yrs menopause	Placebo	154	-0.4 (SD: 1.2)
			0.45 CEE + 20 mg bazedoxifene	162	-0.6 (SD: 1.3)
			0.625 mg CEE + 20 mg bazedoxifene	161	-0.6 (SD: 1.3)
		≥ 5 yrs menopause	Placebo	273	-0.4 (SD: 1.7)
			0.45 CEE + 20 mg bazedoxifene	271	-0.4 (SD: 1.6)
			0.625 mg CEE + 20 mg	253	-0.5 (SD: 1.6)

Trial	Outcome	Subgroup	Treatment	N	Results
			bazedoxifene		
Utian, 2009, United States	Difference in MENQOL psychological score	< 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	40 82 81	-0.9 (SD: 1.3) -1.0 (SD: 1.8) -1.4 (SD: 1.8)
		≥ 5 yrs menopause	Placebo 0.45 CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	23 45 47	-0.4 (SD: 1.9) -0.8 (SD: 2.0) -0.9 (SD: 2.1)
Osmers, 2005, Germany	Difference in MRS psychological score from placebo	Early climacteric	Placebo 40 mg black cohosh	NR NR	- -0.04 (95% CI: -0.09 to 0.00)[c]
		Late climacteric	Placebo 40 mg black cohosh	NR NR	- -0.03 (95% CI: -0.06 to 0.00)[d]
Davis, 2001, Australia	Difference in MENQOL psychological score from placebo	< 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- 0.18 (95% CI: -0.81 to 1.2)
		≥ 4 yrs amenorrhea	Placebo Chinese herbs	NR NR	- -0.08 (95% CI: -0.70 to 0.54)
Strickler, 2000, United States	Mean change in WHQ anxiety score	< 4 yrs post menopause	Placebo 0.625 mg CEE	NR NR	-0.02 -0.01[e]
		≥ 4 yrs post menopause	Placebo 0.625 mg CEE	NR NR	0.06 -0.02[f]

CEE: conjugated equine estrogens; MENQOL: Menopause-specific Quality of Life; MRS: Menopause Rating Scale; NR: not reported; WHQ: Womens Health Questionnaire

[a] difference from placebo: -4.1 (95% CI: -6.8 to -1.4); p=0.003

[b] difference from placebo: -3.3 (95% CI: -5.1 to -1.5); p<0.001

[c] difference from placebo: p=0.048

[d] difference from placebo p=0.08

[e] difference from placebo: p=0.11

[f] difference from place bo: p=0.24

Table N-14. Psychological outcomes by comorbidity subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Strickler, 2000, United States	Mean change in WHQ anxiety score	< 3.5 baseline anxiety score	Placebo 0.625 mg CEE	NR NR	0.19 0.21[a]
		≥ 3.5 baseline anxiety score	Placebo 0.625 mg	NR NR	-0.05 -0.15[b]

Trial	Outcome	Subgroup	Treatment	N	Results
			CEE		

CEE: conjugated equine estrogens; NR: not reported; PMS: premenstrual syndrome; PND: postnatal depression; WHQ: Womens Health Questionnaire

[a] difference from placebo: p=0.67

[b] difference from placebo: p=0.02

Quality of Life

Table N-15. Quality of life outcomes for severity of symptom subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Lee, 2010, Korea	Mean change in KI total score	> 20 KI score	Placebo	28	-11.2 (SD: 6.8)
			350 mg isoflavone	29	-16.4 (SD: 8.8)[a]
Maki, 2007, United States	Mean change in Green total score	Asymptomatic	Placebo	45	-3.3
			0.625 mg CEE + 2.5 mg MPA	36	-1.6
		Symptomatic	Placebo	38	-3.6
			0.625 mg CEE + 2.5 mg MPA	41	-6.4[b]
	Mean change in Utian QOL score	Asymptomatic	Placebo	45	3.5
			0.625 mg CEE + 2.5 mg MPA	36	-1.3
		Symptomatic	Placebo	38	-0.65
			0.625 mg CEE + 2.5 mg MPA	41	5.7[c]
Frei-Kleiner, 2005, Switzerland	Median KI total score	> 20 KI score	Placebo	18	Base: 24.0 (95% CI: 21.0 to 28.1); 12 wk: 17.0 (95% CI: 15 to 21.0)
			42 mg black cohosh	35	Base: 27.0 (95% CI: 24.0 to 28.0); 12 wk: 14.0 (95% CI: 10 to 18.0)[d]
Lopes, 2001, France	Mean KI total score	> 7 hot flashes/day	0.05 mg estradiol patch	83	Base: 32.5 (SD: 5.6); 12-wk: 11.5 (SD:9.2)[e]
			0.3 mg estradiol spray	68	Base: 31.7 (SD:6.1); 12-wk: 12.3 (SD:9.1)[e, f]
Mattsson, 2000	Mean KI total score	> 7 hot flashes/day	2 mg estradiol + dydrogesterone oral	110	Base: 29.7 (SD: 4.8); 12-wk: 9.6 (SD: 8.9)
			0.3 mg estradiol +	102	Base: 29.9 (SD: 6.1); 12-wk: 10.7 (SD: 9.4)[f]

Trial	Outcome	Subgroup	Treatment	N	Results
			dydrogesterone spray		

CEE: conjugated equine estrogen; KI: Kupperman Index; QOL: quality of life
[a] difference between treatment groups: p<0.01
[b] difference from placebo: p=0.10
[c] difference from placebo: p=0.01
[d] difference from placebo group: p=0.018
[e] pre/post: p<0.05
[f] difference between treatment groups: p=NS

Table N-16. Quality of life outcomes for time since menopause subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Lobo, 2009, Multinational	Difference in MENQOL total score	< 5 yrs since menopause	Placebo 0.45 mg CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	154 162 161	-0.6 (SD: 1.2) -0.9 (SD: 1.3)[a] -0.9 (SD: 1.3)[a]
		≥ 5 yrs since menopause	Placebo 0.45 mg CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	273 271 253	-0.4 (SD: 1.7) -0.6 (SD: 1.6)[b] -0.7 (SD: 1.6)[b]
Utian, 2009, United States	Difference in MENQOL total score	< 5 yrs since menopause	Placebo 0.45 mg CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	40 82 81	-1.2 (SD: 1.3) -1.8 (SD: 1.8)[c] -2.0 (SD: 1.8)[a]
		≥ 5 yrs since menopause	Placebo 0.45 mg CEE + 20 mg bazedoxifene 0.625 mg CEE + 20 mg bazedoxifene	23 45 47	-0.9 (SD: 1.4) -1.6 (SD: 1.3)[c] -2.1 (SD: 1.4)[b]
Osmers, 2005, Germany	Difference in MRS total score from	Early climacteric	Placebo 40 mg black cohosh	NR NR	- -0.06 (95% CI: -0.10 to -0.03)[d]
		Late climacteric	Placebo 40 mg black	NR NR	- -0.04 (95% CI: -0.07 to

Trial	Outcome	Subgroup	Treatment	N	Results
	placebo		cohosh		-0.02)[e]
Loh, 2002, Singapore	Change in mean KI total score	< 3 yrs menopausal	1 mg estradiol + 0.5 mg NETA	NR NR	Baseline: 12.5 (SD: 7.4); change: -5.4 (SD: 7.1)
			2 mg estradiol + 1 mg NETA		Baseline: 15.2 (SD: 12.3); change: -6.8 (SD: 8.2)[f]
		≥ 3 yrs menopausal	1 mg estradiol + 0.5 mg NETA	NR NR	Baseline: 13.3 (SD: 10.7); change: -5.0 (SD: 7.1)
			2 mg estradiol + 1 mg NETA		Baseline: 13.2 (SD: 8.7); change: -3.3 (SD: 8.1)[g]

MRS: Menopausal Rating Scale; NETA: norethisterone acetate; NR: not reported
[a] difference from placebo: p<0.01
[b] difference from placebo: p≤0.001
[c] difference from placebo: p≤0.05
[d] difference from placebo: p<0.001
[e] difference from placebo: p=0.002
[f] difference between treatment groups: p=0.47
[g] difference between treatment groups: p=0.40

Sleep Disturbance

Table N-17. Sleep disturbance outcomes by age subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Brunner, 2005, United States	Mean change in WHI sleep score	Age 50-54 with MSVS	Placebo	157	0.53 (SD: 4.6)
			0.625 mg CEE	165	1.4 (SD: 4.6)[a]
Hays, 2003, United States	Mean change in WHI sleep score	Age 50-54 with MSVS	Placebo	216	0.8 (SD: 4.6)
			0.625 mg CEE + 2.5 mg MPA	255	1.8 (SD: 4.8)[b]
Rigano, 2001, Italy	Percent reporting no insomnia[a]	Age 48-50	Placebo	75	29%
			0.05 mg estradiol	88	80%
		Age 51-53	Placebo	61	46%
			0.05 mg estradiol	52	62%
		Age 54-56	Placebo	55	17%
			0.05 mg estradiol	31	100%

[a] Unclear whether 100% reported insomnia at baseline
CEE: conjugated equine estrogen; MPA: medroxyprogesterone acetate ; MSVS: moderate to severe vasomotor symptoms; WHI: Women's Health Initiative
[a] difference from placebo: p=0.11
[b] difference from placebo: p=0.02

Table N-18. Sleep disturbance outcomes by time since menopause

Trial	Outcome	Subgroup	Treatment	N	Results
Lobo, 2009, Multinational	Difference in mean Quality of Sleep Score	< 5 yrs since menopause	Placebo	154	0.2 (SD: 0.6)
			0.45 mg CEE + 20 mg bazedoxifene	162	0.3 (SD: 0.6)[a]
			0.625 mg CEE + 20 mg bazedoxifene	161	0.3 (SD: 0.6)[a]
		≥ 5 yrs since menopause	Placebo	273	0.1 (SD: 0.7)
			0.45 mg CEE + 20 mg bazedoxifene	271	0.2 (SD: 0.7)[a]
			0.625 mg CEE + 20 mg bazedoxifene	253	0.3 (SD: 0.6)[b]
Utian, 2009, United States	Difference in MOS sleep score	< 5 yrs since menopause	Placebo	40	-6.1 (SD: 18.3)
			0.45 mg CEE + 20 mg bazedoxifene	82	-17.7 (SD: 19.0)[c]
			0.625 mg CEE + 20 mg bazedoxifene	81	-15.9 (SD: 19.8)[b]
		≥ 5 yrs since menopause	Placebo	23	-4.0 (SD: 16.3)
			0.45 mg CEE + 20 mg bazedoxifene	45	-11.3 (SD: 16.1)[d]
			0.625 mg CEE + 20 mg bazedoxifene	47	-11.7 (SD: 16.5)[b]

CEE: conjugated equine estrogen; MOS: Medical Outcomes Survey
[a] difference from placebo: p=NS
[b] difference from placebo: p<0.01
[c] difference from placebo: p<0.001
[d] difference from placebo: p<.0.05

Urogenital Atrophy

Table N-19. Urogenital outcomes by time since menopause subgroups

Trial	Outcome	Subgroup	Treatment	N	Results
Osmers, 2005,	Difference in MRS	Early climacteric	Placebo	NR	-
			40 mg	NR	-0.07 (95% CI: -0.10 to -

Trial	Outcome	Subgroup	Treatment	N	Results
Germany	vaginal atrophy score from placebo		black cohosh		0.03)[a]
		Late climacteric	Placebo	NR	-
			40 mg black cohosh	NR	-0.05 (95% CI: -0.08 to -0.02)[b]

MRS: Menopausal Rating Scale; NR: not reported
[a] Difference from placebo: p<0.001
[b] Difference from placebo: p=0.001

Appendix O. Completed Clinical Trials From ClinicalTrials.gov

The following clinical trials are reported as complete, but no data or related publications could be found.

Table O. Completed clinical trials from ClinicalTrials.gov

Trial	Status	Last Updated	Posted Study Results	N	Treatments	Duration	Estimated Study Completion Date
NCT00010712	Completed	8/17/2006	No	-	black cohosh	52 weeks	Jul-05
NCT00775242	Completed	8/21/2009	No	103	estradiol and progesterone injection	26 weeks?	Nov-08
NCT00141570	Completed	1/29/2009	No	350	esterified estrogens and methyltestosterone	12 weeks	-
NCT00195455	Completed	12/17/2007	No	133	trimegestone estradiol	-	Mar-07
NCT00272935	Completed	1/8/2010	No	400	cenestin placebo	12 weeks	May-07
NCT00604825	Completed	10/13/2011	No	359	premarin placebo	12 weeks	Jul-08
NCT00141557	Terminated (lack of enrollment)	4/10/2008	No	133	esterified estrogens and methyltestosterone esterified estrogens	12 weeks	Mar-08
NCT00494208[a]	Completed	5/12/2010	No	270	testosterone	60 weeks	Dec-09
NCT00338312	Completed	3/22/2010	No	610	placebo testosterone	52 weeks	Jul-06
NCT00511953	Completed	6/6/2011	No	108	gabapentin placebo	13 weeks	Dec-07

[a] Results were published subsequent to our last literature search in January 2014.