Attachment C: Federal Register Notice

Billing Code: 4160-90-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Supplemental Evidence and Data Request on Improving the Management of Menopausal Symptoms in Perimenopausal and Early Postmenopausal Women: A Systematic Review

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Supplemental Evidence and Data Submission

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review on *Improving the Management of Menopausal Symptoms in Perimenopausal and Early Postmenopausal Women: A Systematic Review,* which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

DATES: *Submission Deadline* on or before **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].**

ADDRESSES:

E-mail submissions: epc@ahrq.hhs.gov

Print submissions:

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E53A

Rockville, MD 20857

Shipping Address (FedEx, UPS, etc.):

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E77D

Rockville, MD 20857

FOR FURTHER INFORMATION CONTACT:

Kelly Carper, Telephone: 301-427-1656 or Email: epc@ahrq.hhs.gov.

SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for *Improving the Management of Menopausal Symptoms in Perimenopausal and Early Postmenopausal Women: A Systematic Review.* AHRQ is conducting this review pursuant to Section 902 of the Public Health Service Act, 42 U.S.C. 299a.

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on

Improving the Management of Menopausal Symptoms in Perimenopausal and Early Postmenopausal Women: A Systematic Review. The entire research protocol is available online at: https://effectivehealthcare.ahrq.gov/products/menopausal-symptoms/protocol

This is to notify the public that the EPC Program would find the following information on

Improving the Management of Menopausal Symptoms in Perimenopausal and Early Postmenopausal Women: A Systematic Review helpful:

- A list of completed studies that your organization has sponsored for this topic. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, a summary, including the following elements, if relevant: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this topic*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including, if relevant, a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute *ALL Phase II and above clinical trials* sponsored by your organization for this topic and an index outlining the relevant information in each submitted file.

Your contribution is very beneficial to the Program. Materials submitted must be publicly available or able to be made public. Materials that are

considered confidential; marketing materials; study types not included in the review; or information on topics not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://effectivehealthcare.ahrq.gov/email-updates.

The review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.

Key Questions (KQ)

KQ 1: What are the effectiveness, comparative effectiveness, and harms of treatments for menopausal symptoms in perimenopausal and early postmenopausal women?

a. Do the effectiveness, comparative effectiveness, and harms of treatment vary by dose, delivery mode, formulations, or duration of treatment?
b. Do the effectiveness, comparative effectiveness, and harms of treatment vary by timing and type of menopause (early, average; iatrogenic, natural)?

c. Do the effectiveness, comparative effectiveness, and harms of treatment vary by individual- or system-level factors?

KQ 2: What is the impact of individual- or system-level factors on the receipt of treatment for perimenopausal and early postmenopausal women with symptoms?

a. Individual-level factors include but are not limited to educational attainment, patient engagement in healthcare, lifestyle factors, comorbidities.
b. System-level factors include but are not limited to racism, provider bias, access to care, and social determinants of health.

PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, and Setting)

Table 1. PICOTS for KQ 1

Criteria	Inclusions	Exclusions
Population	Perimenopausal and early postmenopausal women with menopausal symptoms (new onset or worsening of vasomotor symptoms, genitourinary symptoms of menopause, and other symptoms) Eligible women are <10 years since menopause for Black and Hispanic women and <5 years for other women or are age <60; Figure 3 offers a decision algorithm to account for variability in reporting of age and years since menopause and longer duration in vasomotor symptoms by race or ethnicity Vasomotor symptoms: Hot flashes Night sweats Genitourinary symptoms of menopause : Genital pain including vulvodynia/vestibulodynia/dyspareunia Vulvovaginal dryness Vulvovaginal itching/irritation/discomfort Urinary pain including dysuria Involuntary urine loss/urinary leakage or urinary frequency Skin thinning Pelvic floor dysfunction Other symptoms: Joint pain Mood lability Change in severity or persistence of mental health disorders Cognitive changes Sleep disturbances Subgroups of interest (preplanned only): Natural menopause Iatrogenic (e.g., surgical) menopause, premature menopause, early menopause Early perimenopausal women (prior to	Studies limited to specific populations such as breast cancer survivors or HIV carriers, women with pelvic organ prolapse Studies solely comprising women with existing disorders (e.g., mood, anxiety, sleep disturbances, sexual or urinary dysfunction, cognitive changes, endometriosis, fibroids, endometrial hyperplasia, polycystic ovarian syndrome)

	and through 1 year from the final menstrual period) Women with/without hysterectomy Women at increased risk for breast cancer, women at increased risk for heart disease Individual- and system-level factors (e.g., socioeconomic status, social determinants of health, race/ethnicity, sexual orientation, gender identity)	
Intervention[a]	<u>Systemic hormone therapy (Appendix A):</u> FDA-approved hormone therapies: estrogens alone, estrogens + progestin, estrogens + progesterone, estrogens + androgen, androgens (including testosterone), micronized progesterone, synthetic progestins, tissue-selective estrogen complex (e.g., CEE/bazedoxifene), compounded menopausal hormone therapy (compounded in 503B outsourcing facilities),[b] "bioidentical hormones" <u>Subgroups of interest (preplanned only):</u> Route of delivery: oral, transdermal, pellets (for cBHT), vaginal, intramuscular Specific nonhormone therapies: paroxetine or paroxetine mesylate (common brand names: Paxil, Paxil CR, Brisdelle) venlafaxine (common brand names: Effexor XR) desvenlafaxine (common brand names: Pristiq) escitalopram (common brand names: Lexapro) citalopram (common brand names: Celexa) duloxetine (common brand names: Drizalma, Cymbalta) sertraline (common brand names: Zoloft) fluoxetine (common brand names: Prozac, Symbyax) gabapentin (common brand names: Neurontin, Gralise, Horizant) fezolinetant/neurokinin-3 (NK-3) receptor antagonist (common brand names: Veozah) elinzanetant/neurokinin-1,3 (NK-1,3) receptor antagonist (common brand names: none)[d] oxybutynin (common brand names:	Anti-estrogen therapy Nonhormonal treatments such as vitamins and herbs Energy-based therapies (e.g., laser) Behavioral therapies (e.g., yoga, dance) Nonsystemic therapies[c]

	Ditropan, Oxytrol, Gelnique) clonidine (common brand names: Catapres, Duraclon, Iopidine, Nexiclon XR, Onyda XR) pregabalin (common brand names: Lyrica)	
Comparator	Benefits: Placebo or inactive control , alternate treatment (i.e., any other eligible intervention) Harms: No treatment, placebo or inactive control (e.g., vitamins), alternate treatment (i.e., any other eligible intervention)	Same as above
Outcomes[e]	<u>Benefits:</u> Validated measures of new or worsening symptoms (frequency, severity, distress/bother) of: Vasomotor symptoms o Hot flashes o Night sweats Genitourinary symptoms of menopause o Genital pain including vulvodynia/vestibulodynia/dyspareunia o Vulvovaginal dryness o Vulvovaginal itching/irritation/discomfort o Urinary pain including dysuria o Involuntary urine loss/urinary leakage or urinary frequency o Skin thinning o Pelvic floor dysfunction Other symptoms o Joint pain o Mood lability o Change in severity or persistence of mental health disorders o Cognitive changes o Sleep disturbances Treatment satisfaction Sexual function Quality of life Harms or health impact: Abnormal uterine bleeding Coronary heart disease Stroke	Intermediate or nonclinical outcomes such as vaginal pH, arterial intimal thickness, fracture scores

	Venous thromboembolism Breast cancer Endometrial cancer Colorectal cancer Ovarian cancer Osteopenia and osteoporosis Alzheimer's disease and other dementias, or cognitive decline Side effects of treatment including liver damage Multimorbidity (2 or more conditions) All-cause mortality	
Timing	Onset of treatment at or near menopause (through 5 years of the final menstrual period [10 years for Black and Hispanic women]) At least 12 weeks duration of treatment	Later onset of treatment Less than 12 weeks duration of treatment
Sample size	All for benefits >1,000 for harms from cohort studies	None for benefits Cohort studies with ≤1,000 participants
Setting	Any	None
Study design	Randomized clinical trials, controlled clinical trials, nonrandomized interventions (cohorts and case-control studies), systematic reviews as hand-search sources	Case series, narrative reviews, editorials, and commentaries; systematic reviews are not eligible but will be reviewed to determine whether any included studies are eligible
Years of publication	2002 and beyond to ensure relevance to current clinical practice	Prior to 2002
Language	English	Studies published in languages other than English

[a] With the exception of compounded bioidenticals, testosterone, and hormonal contraceptives, we will limit inclusion to FDA-approved medications to treat menopausal symptoms. For testosterone and hormonal contraceptives, we will limit to FDA-approved medications.

[b] Compounded in a 503A compounding pharmacy, 503B outsourcing facilities, government healthcare facilities, for academic research, or for certain studies that were produced to assess off-label outcomes of FDA-approved products. These facilities are likely to be "subject to an increased level of federal oversight, although not as strict as FDA oversight."[20]

[c] Local therapies for genitourinary syndrome of menopause have been previously reviewed by AHRQ[29]

[d] Will be included on receipt of FDA approval.

e The proposed list of outcomes integrates core outcome sets defined for genitourinary syndrome of menopause[30] and vasomotor symptoms.[31]

CEE = conjugated equine estrogen; FDA = Food and Drug Administration; KQ = Key Question; PICOTS = population, intervention, comparators, outcomes, timing, study design and setting.

Table 2. SPIDER Table for KQ 2

Criteria	Inclusions	Exclusions
Sample	Perimenopausal and early postmenopausal women with menopausal symptoms (new onset or worsening of vasomotor symptoms, genitourinary symptoms of menopause, and other symptoms) or their providers Eligible women are <10 years since menopause for Black and Hispanic women and <5 years for other women or are age <60; Figure 3 offers a decision algorithm to account for variability in reporting of age and years since menopause Vasomotor symptoms: Hot flashes Night sweats Genitourinary symptoms of menopause : Genital pain including vulvodynia/vestibulodynia/dyspareunia Vulvovaginal dryness Vulvovaginal itching/irritation/discomfort Urinary pain including dysuria Involuntary urine loss/urinary leakage or urinary frequency Skin thinning Pelvic floor dysfunction Other symptoms: Joint pain Mood lability Change in severity or persistence of mental health disorders Cognitive changes Sleep disturbances Subgroups of interest (preplanned only): Natural menopause Iatrogenic (e.g., surgical) menopause, premature menopause, early menopause Early perimenopausal women (prior to and through 1 year from the final menstrual period)	Studies limited to specific populations such as breast cancer survivors or HIV carriers, women with pelvic organ prolapse Studies solely comprising women with existing disorders (mood, anxiety, sleep disturbances, sexual or urinary dysfunction, cognitive changes, endometriosis or fibroids, endometrial hyperplasia, polycystic ovary syndrome) Perimenopausal women with menopausal symptoms in countries other than the United States

	Women with/without hysterectomy Women at increased risk for breast cancer, women at increased risk for heart disease Individual- and system-level factors (e.g., socioeconomic status, social determinants of health, race/ethnicity, sexual orientation, gender identity)	
Phenomenon of interest[a]	Receipt of systemic hormone therapy: FDA-approved hormone therapies: estrogens alone, estrogens + progestin, estrogens + progesterone, estrogens + androgen, androgens (including testosterone), micronized progesterone, synthetic progestins, tissue-selective estrogen complex (e.g., CEE/bazedoxifene), compounded menopausal hormone therapy (compounded in 503B outsourcing facilities),[b] "bioidentical hormones" Specific nonhormone therapies: paroxetine or paroxetine mesylate (common brand names: Paxil, Paxil CR, Brisdelle) venlafaxine (common brand names: Effexor XR) desvenlafaxine (common brand names: Pristiq) escitalopram (common brand names: Lexapro) citalopram (common brand names: Celexa) duloxetine (common brand names: Drizalma, Cymbalta) sertraline (common brand names: Zoloft) fluoxetine (common brand names: Prozac, Symbyax) gabapentin (common brand names: Neurontin, Gralise, Horizant) fezolinetant/neurokinin-3 (NK-3) receptor antagonist (common brand names: Veozah) elinzanetant/neurokinin-1,3 (NK-1,3) receptor antagonist (common brand names: none)[c] oxybutynin (common brand names: Ditropan, Oxytrol, Gelnique) clonidine (common brand names: Catapres, Duraclon, Iopidine, Nexiclon XR, Onyda XR)	Any other phenomenon (e.g., shared decision making) Receipt of any other therapy

	pregabalin (common brand names: Lyrica)	
Design	No treatment, placebo or inactive control, alternate treatment (i.e., any other eligible intervention) active	Same as above
Evaluation	Factors explaining receipt of treatment (defined as treatment offered by prescriber, treatment received by patient, and treatment initiated/used/adhered to by patient)	Any other evaluation (including evaluation of factors upstream from receipt such as shared decision making and access)
Years of publication	2009 and beyond	Prior to 2009
Research type	Qualitative, survey, mixed methods, original research	Case studies, narrative reviews, editorials, and commentaries; systematic reviews are not eligible but will be reviewed to determine whether any included studies are eligible
Language	English	Studies published in languages other than English
Geographic setting	United States	Any other country

[a] With the exception of compounded bioidenticals, testosterone, and hormonal contraceptives, we will limit inclusion to FDA-approved medications to treat menopausal symptoms. For testosterone and hormonal contraceptives, we will limit to FDA-approved medications.

[b] Compounded in a 503A compounding pharmacy, 503B outsourcing facilities, government healthcare facilities, for academic research, or for certain studies that were produced to assess off-label outcomes of FDA-approved products. These facilities are likely to be "subject to an increased level of federal oversight, although not as strict as FDA oversight."[20]

[c] Will be included on receipt of FDA approval.

CEE = conjugated equine estrogen; FDA = Food and Drug Administration; KQ = Key Question; SPIDER = sample, phenomenon, design, evaluation, and research.

Dated: March 10, 2025

Marquita Cullom,

Associate Director.