VA/DOD CLINICAL PRACTICE GUIDELINE FOR MENOPAUSE

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DOD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any clinical situation with a patient-centered approach.

These guidelines are not intended to represent VA or DOD policies. Further, the inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

Version 1.0 – 2026

Prepared by

The Menopause Work Group

With support from

Office of Quality and Patient Safety, Veterans Health Administration

And

Clinical Quality Improvement Program, Defense Health Agency

Version 1.0 – 2026[1]

Based on evidence reviewed through June 2025

[1] VA/DOD Clinical Practice Guideline. (2026). Menopause Work Group. Washington, DC: U.S. Government Printing Office.

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DOD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004. Its mission is to advise the "…Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration and Military Health System," by facilitating the development of clinical practice guidelines (CPGs) for the VA and DOD populations.(1) The development and update of VA/DOD CPGs is funded by the VA Evidence-Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In 2025, the VA and DOD initiated the creation of the Menopause CPG, based on evidence reviewed from January 1, 2015, to June 30, 2025. This CPG uses the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, reflecting a rigorous application of the methodology.(2) Therefore, the strength of some recommendations may have been modified based on the confidence in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

The VA/DOD EBPWG initiated the creation of the VA/DOD Menopause CPG in 2025. This CPG provides an evidence-based framework for evaluating and managing individuals with naturally occurring or surgically/iatrogenically induced menopause or perimenopause. Successful implementation of this CPG will result in:

- Accurate assessment of the patient's menopausal status and, in collaboration with the patient, determine the most appropriate treatment plan;
- Minimization of preventable complications and morbidity using early screening and risk assessments;
- Emphasis on the use of informed, patient-centered care;
- Optimization of daily functioning, functional independence, health outcomes, and quality of life

II. Background

A. Menopause and Perimenopause Description and Epidemiology

Perimenopause

Perimenopause is the transitional stage of reproductive aging that precedes menopause. Perimenopause typically begins in the mid- to late 40s, though the onset varies by individual and symptoms may begin in the mid- to late 30s. The duration of perimenopause averages about four years but can extend up to a decade before the final transition to menopause.(3) Perimenopause is a universal physiological process, yet its manifestations and impact on health and functioning vary widely.

Perimenopause begins with changes in menstrual cycle length or regularity due to declining ovarian function and ends with menopause.(4) Hormonal signals between the brain and ovaries

become less synchronized, resulting in Luteal Out-Of-Phase (LOOP) cycles with recruitment of a new follicle during the luteal phase of the current cycle. Simultaneously, ovulation becomes increasingly unpredictable. As a result, progesterone is oftentimes the first hormone to show consistent decline while estrogen widely fluctuates, leading to elevations followed by sharp declines. Although less pronounced, testosterone levels gradually decrease during the menopausal transition.

These hormonal changes ultimately produce a wide range of clinical manifestations. Common symptoms include vasomotor instability (hot flashes, night sweats), irregular or heavy menstrual bleeding, and urogenital symptoms.(5) Nearly 80% of individuals experience vasomotor symptoms during the transition, and up to one-third report vasomotor symptoms that are moderate to severe.(6) Sleep disturbances, depressive symptoms, anxiety, mood changes, and cognitive complaints (such as perceived memory difficulties) are also common and may exacerbate existing mental health conditions or impair occupational functioning.(7) Patients may present with a single or multiple symptoms, and when multiple systems are involved, symptoms can interact with and intensify one another. The unpredictability of menstrual cycles and associated symptoms can further adversely affect quality of life, relationships, and daily activities.(8)

Perimenopause is also considered a critical window of vulnerability for longer-term health risks, including bone loss, cardiovascular changes, and metabolic alterations.(9) Recognition and timely management of perimenopausal symptoms can therefore have both immediate and long-lasting benefits.

In the general population, the demographic effect is substantial. More than 50 million women in the United States (U.S.) are currently aged 45 years and older;(10) thus, a large proportion are experiencing or approaching perimenopause. Stigma and under-recognition of perimenopausal concerns may discourage patients from seeking care, leading to a lack of symptom management and the possibility of increased health care costs.(11)

Menopause

Natural menopause is defined as the cessation of ovarian function. Natural menopause is diagnosed retrospectively after one year of amenorrhea. Surgically induced menopause is caused by bilateral oophorectomies before the final menstrual period. (See Sections C and D for more information about menopause types and factors that impact menopause onset.)

In the U.S., the average age of menopause onset is 51 years old.(12) During peri- and post-menopause, patients may experience a variety of symptoms, including vasomotor symptoms, cognitive impairment, changes in hair and skin, musculoskeletal symptoms, vaginal changes, decreased libido, changes in bladder symptoms, sleep disturbances, metabolic changes, and weight gain. While mood changes may be experienced in menopause, there is no statistically significant increase compared to perimenopause. These symptoms can be mild, moderate, or severe, and may last on average between 7 and 12 years. For some patients, vasomotor symptoms may persist beyond 12 years.(7) Because menopause is defined retrospectively, patients may not know when they have transitioned to menopause. This determination can be further complicated in individuals who have undergone hysterectomy, uterine ablations, or are receiving hormonal treatments, making it difficult to pinpoint the onset of menopause. Clinicians

should reassure patients that symptom-based management is appropriate for most treatment decisions.

B. Menopause in the Department of Defense and the Department of Veterans Affairs Populations and Its Impact

DOD

Women comprise a growing proportion of the U.S. Armed Forces. In 2023, women represented 17.7% of active duty personnel (225,119 of 1,273,382) and 21.9% of the Reserve (167,762 of 767,238). The average age in the female population is 28.6 for active duty and 32 for Reservists, with a sizable number of officers older than 41 years (22.6%), after which age there is no further breakdown by the DOD.(13) As the force ages and retention of all Service members remains a priority, perimenopause and menopause are a consideration which may affect readiness, health, safety, and retention for thousands of female Service members.

The effect of perimenopausal and menopausal symptoms, such as impaired heat tolerance, sleep disturbance, impaired concentration, mood disturbances, and effects on physical performance, may be disruptive to a Service member's duties as well as having operational relevance, particularly in austere environments where the military serves. Unmanaged symptoms may contribute to decreased readiness, safety risks, profile limitations, and attrition. Menopausal hormone therapy (MHT) may be underutilized in the active duty population. A 2025 retrospective study of female active duty Service members aged 45 to 64 years in the U.S. Army, Air Force, Navy, and Marine Corps from 2018 to 2022 showed that the prevalence of MHT use among this population is lower than MHT use among the U.S. Veteran population of the same age, though it is higher than the U.S. general population age 45 and older.(14)

Unfortunately, more direct, peer-reviewed data on menopause among currently serving U.S. military women is sparse. There are no studies specifically on menopause in Service members, as most evidence in the U.S. comes from Veterans in the VA. There are limited quantitative data linking menopausal symptoms to duty performance, mishaps, or attrition. Evidence is needed on racial and ethnic differences in symptom duration and severity (well-documented in civilian cohorts) as they pertain to the military setting.

National surveys and mixed-methods studies of United Kingdom (U.K.) female active duty Service members reveal that menopausal symptoms are common, affect work, and are inconsistently managed. Themes from these studies included symptom effects on performance, fear of career consequences, and barriers to accessing knowledgeable clinicians or appropriate therapy.(15) In the absence of robust data in the U.S. DOD, the literature from the U.K. suggests that there is work to be done in supporting servicewomen during this transition.

VA

The U.S. Department of Veteran Affairs, Veterans Health Administration (VHA), provided healthcare to more than 700,000 women Veterans in FY 2024, of whom nearly half (41%) were between the ages of 45 and 64.(16) 45% of the women in this age cohort who used VA health services in Fiscal Year (FY) 2024 belonged to a racial or ethnic minority group (Table 1).(17) VHA provides comprehensive perimenopause and menopause care through an interdisciplinary

approach, starting with the Veterans' designated women's health primary care providers (WH PCPs) who are trained and experienced in the provision of women's health care. Care is tailored to the needs of the specific Veteran using a shared decision-making process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider the benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.

VHA offers a range of evidence-based treatment modalities to manage symptoms related to perimenopause and menopause, including hormone therapy, non-hormonal medications, mental health support and treatment, pelvic floor physical therapy, stress management, weight management, and whole health approaches. In addition, gynecologists and other trained providers, such as clinical pharmacists, are available to support complex medical management of symptoms related to perimenopause and menopause. Mental and behavioral health providers can provide evidence-based treatments for symptoms associated with perimenopause and menopause, including sleep disturbance, mood disorders, cognitive changes, sexual dysfunction, and vasomotor symptoms. Complementary and integrative health (CIH) offerings such as mindfulness, yoga, and clinical hypnosis are also offered for menopause-related symptoms.

These efforts include attention to the unique and complex care needs of the women Veteran population, including prevalent trauma history, chronic pain, other chronic health conditions, and possible military exposures, all of which may influence perimenopause and menopause symptom burden.(18)

Table 1: Women Veterans by Race and Ethnicity, between ages 45-64, FY24 (17)

Race and Ethnicity	Women Veterans 45-64 years old, FY24
American Indian or Alaska Native	2,635 (1%)
Asian	4,295 (1.5%)
Black or African American	98,192 (34%)
Hispanic or Latina	19,187 (7%)
Multi-Race	3,505 (1%)
Native Hawaiian or Other Pacific Islander	2,704 (1%)
White	140,456 (49%)
Unknown	18,408 (6%)
Total	289,382
Belong to a racial or Ethnic Minority Group	130,518 (45%)

Abbreviations: FY: fiscal year

C. Factors Affecting Menopause Onset

Natural menopause is a natural biological transition occurring in the second half of life, but the experience varies significantly amongst individuals, due to a variety of factors, including heredity, race and ethnicity, family history, gynecological, medical, and mental health history, lifestyle behaviors, toxin exposure, and military service. Early menopause occurs between the ages of 40 and 45, and premature menopause occurs before the age of 40.

Genetics and Heredity

A key component of menopause onset is driven by ovarian aging,(19) a complex process influenced by multiple factors, including genetics and family history. Genetics is a key driver of the age variation around menopause onset, accounting for up to 50% of this variation (20), and a patient's family history of female family members' age at menopause may provide clues to the potential timing of the menopause transition.(21)

Race, Ethnicity, and Socioeconomic Status

Women Veterans aged 45-64 years are a diverse group with 130,518 (48%) women identifying with a minority group. In FY 24, the composition is as follows: 140,456 (49%) White, 98,192 (34%) Black or African American, 19,187 (7%) Hispanic or Latina, 4,295 (1.5%) Asian, and American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, and multi-race each at 1%. Research is continuing to examine differences in menopause onset and experience for individuals from different racial and ethnic identities, including intersections with socioeconomic status. Initial analysis of the Study of Women's Health Across the Nation (SWAN) study, a multisite, multiracial/ethnic, prospective, longitudinal cohort study of 3,302 women aged 42 to 52 years with an intact uterus, at least one ovary, not on hormonal therapy, and not pregnant or lactating, did not find any difference in menopausal onset between Black and White women.(22) However, re-analysis in 2023 with adjustment for selection bias revealed that Black women were 13% more likely to experience early natural menopause and 3.2-fold more likely to have surgical menopause than White women.(23) Black women in the SWAN cohort also experienced a longer duration of menopause transition.(22) In a very large multiethnic cohort study, both U.S.-born and non-U.S.-born Latina experienced natural menopause earlier and Japanese Americans later than non-Latina women.(24) The influence of race and ethnicity on the timing of menopause onset for Asian Americans is less clear, as these may be bi-directionally impacted by additional factors, including socioeconomic and lifestyle factors.(22,25)

In the SWAN study, low socioeconomic status metrics, including limited education and unemployment, were independently associated with earlier natural menopause.(22,26) The negative impact of low socioeconomic status was corroborated in a study comparing women living in very high and very low vulnerability neighborhoods as defined by the Centers for Disease Control and Prevention (CDC)'s Social Vulnerability Index; the former experienced natural menopause approximately two years earlier than the latter.(27) A recent cross-sectional survey study of over 67,000 women found that after adjustment for socioeconomic status as determined by household income and structure, educational level, public assistance with

income and/or food stamps, and employment status, Black and Hispanic women experienced more severe menopausal symptoms than their White and Asian peers.(25)

Obstetric and Gynecologic History

The interplay between reproductive health history, life events, menopausal symptoms, and timing is complex and multifactorial, and the subject of diverse ongoing research.(28,29) Reproductive health life events that temporarily reduce ovulation, such as pregnancy and breastfeeding, have been associated with a delay in menopause onset.(28,29) Similarly, oral contraceptive use has been associated with later menopause onset.(22,29) A recent meta-analysis (MA) also identified an association between menarche after age 13 and later menopause onset.(29) In contrast, hysterectomy, even with ovarian conservation, may be associated with earlier ovarian failure and earlier menopause onset.(30) Infertility history may also influence both menopause symptom severity(31) and timing.(32) Elucidating the possible links between infertility history and menopause is complicated by the multifactorial nature of both infertility and its treatment, as well as menopause itself.

Autoimmune Disease

Some autoimmune diseases have been linked to early menopause. The prevalence of early menopause is increased in women with thyroiditis(33-36), Addison's disease (37), Type 1 diabetes(38-40), polyglandular autoimmune diseases, vasculitis, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, and inflammatory bowel disease.(41)

Pharmacotherapy and Radiation Therapy

Chemotherapeutic agents can increase the risk of premature menopause in a cumulative dose-dependent manner. The most common chemotherapeutic agents associated with premature menopause are alkylating agents, with cyclophosphamide being the most well-studied. Other alkylating agents associated with ovarian toxicity include busulfan, carmustine, chlorambucil, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine, and thiotepa, as well as the nonclassical alkylators dacarbazine and temozolomide. Platinum-based agents (cisplatin and carboplatin) also heighten the risk of premature ovarian insufficiency and reduced ovarian reserve. Additionally, anthracyclines (e.g., doxorubicin) cause ovarian damage through mitochondrial dysfunction and oxidative stress, and taxanes (e.g., paclitaxel) can interfere with oocyte meiotic spindle function. The dose, duration, and age at the time of use determine its impact on ovarian function. Pelvic and ovarian radiation therapy are another major cause of premature ovarian insufficiency (POI). Beyond chemotherapy, adjuvant endocrine treatments used in cancer care and management of uterine fibroids and endometriosis can also trigger menopausal symptoms, including aromatase inhibitors (AIs) (anastrozole, letrozole, and exemestane), selective estrogen receptor modulators (SERMs) (tamoxifen and toremifene), the selective estrogen receptor degrader fulvestrant, and gonadotropin-releasing hormone agonists (goserelin, leuprolide, and triptorelin). (42-44)

Stress

Chronic stress may play a role in early menopause onset. In a cohort of 3,176 Korean women participating in the 5th Korean National Health and Nutrition Examination Survey (NHANES), chronic stress was linked to an earlier onset of menopause by approximately five months.(45)

Lifestyle Behaviors

Although the relation between diet and menopause onset has been studied, current data do not definitively clarify the influence of diet types on menopausal timing.(46-48) Similarly, there are no conclusive temporal effects between weight and exercise intensity on menopause onset.(22,46,47,49-51)

Tobacco smoking is strongly linked with earlier menopause by 1.5 to 2 years.(22,24,26,46,49,52,53) This adverse impact is dependent on the magnitude of tobacco use.(54)(54)(54)(54) At the 14- and 21-year follow-up time points in one study, women who quit smoking experience a comparable onset of menopause to the nonsmoker group.(52) Alcohol consumption 5-7 days/week or ≥11 drinks/week is associated with delayed menopause by 1.3 to 5.5 years.(22,54) Caffeine intake does not affect menopause onset.(54)(54)(54)(54)

Toxic Chemical Exposures

Environmental chemicals and pollutants exposure is associated with 1.9-3.8 years of earlier onset of menopause compared to those without exposure. In the U.S. NHANES of 31,575 females, polychlorinated biphenyls (electric transformer equipment, industrial fluids, and building and construction materials), dioxins (combustion byproducts), phthalates (plasticizers), organophosphate pesticides, polycyclic aromatic hydrocarbons (combustion products), and organophosphate esters (flame retardants and plasticizers) are not only linked to earlier onset but also exhibit a dose-dependent effect.(55,56) Information on military service in this cohort of women is not available. For female Veterans, there is currently no conclusive evidence that hazardous materials exposure is directly linked to early menopause; however, an increased prevalence of infertility is noted in personnel with exposure to petrochemicals and polychlorinated biphenyls during military service compared to those without exposure, which suggests that toxic chemical exposure may play a role in ovarian dysfunction. This topic warrants further investigation.(57)

Military Service

Military sexual trauma is disproportionately high among female Veterans and is strongly linked to menopausal symptoms. There is a 2.4-fold higher risk of developing vasomotor symptoms and a 2.2-fold higher risk of experiencing vaginal symptoms (vaginal irritation and dryness and/or dyspareunia) among women Veterans with a history of military sexual trauma compared to those with no such history.(18) Another risk factor for menopausal symptoms is post-traumatic stress disorder (PTSD), which is more prevalent in Veteran women compared to non-Veteran women and can result from prolonged stress from recurrent exposure to life-threatening conditions and combat during military service.(58) Finally, in a study of women aged ≤ 45 years during the 1990-1991 Gulf War, similar proportions of deployed and non-deployed women reported experiencing

early menopause (14.8% vs. 15.9%, respectively, p=not significant [NS]). The determination of possible early menopause is limited by recall bias of self-reporting data, absence of menopause onset age, and lack of objective data on menopause status (unable to exclude menstrual suppression while using birth control, secondary amenorrhea, or bilateral oophorectomy with or without hysterectomy). Despite similar prevalence, within this Gulf War Era Cohort of 668 deployed women, the adjusted odds of reporting early menopause are higher in women who experienced Gulf War Illness (Odds Ratio (OR): 1.83, 95% Confidence Interval (CI): 1.14-2.95, p=0.01) and probable PTSD (OR 2.45, 95% CI 1.54-3.90, p<0.001).(59)

D. Primary Ovarian Insufficiency

Primary Ovarian Insufficiency (POI) resembles natural menopause in its clinical presentation, including hypoestrogenism, vasomotor symptoms, urogenital atrophy, increased risk of osteoporosis, and increased cardiovascular risk. The distinction is the age of onset: while menopause occurs around age 51, POI occurs before age 40. Unlike menopause, POI has an unpredictable course, with intermittent ovarian activity and spontaneous ovulation possible, resulting in conception in 5-10% of affected women.(60-62)

According to the 2024 American Society for Reproductive Medicine/European Society of Human Reproduction and Embryology (ASRM/ESHRE) Guideline, the diagnosis of POI requires menstrual disturbance (amenorrhea or oligomenorrhea) for at least 4 months, accompanied by elevated follicle-stimulating hormone (FSH >25 international units per liter [IU/L]) with simultaneous low estradiol (often <50 picograms per milliliter [pg/mL] is utilized) on at least one occasion.(60) The prevalence of POI is approximately 1-3.5% of women under 40 years.(60,63)

POI can be categorized as spontaneous, iatrogenic, or surgical. Spontaneous POI may be idiopathic or associated with genetic, autoimmune, or metabolic etiologies.(63) Iatrogenic POI commonly occurs after gonadotoxic therapies such as chemotherapy or pelvic radiation, while surgical POI results from bilateral oophorectomy.(60,63)

POI has major fertility implications. In spontaneous POI, although overall fertility is reduced, intermittent ovarian activity may result in spontaneous ovulation and pregnancy in a minority of cases.(62,64) In contrast, following bilateral oophorectomy, ovulation is not possible due to the absence of ovarian tissue, and natural conception cannot occur. In other forms of iatrogenic POI, particularly after highly gonadotoxic therapies, ovarian function is often absent, and natural conception is unlikely. Because ovarian activity may be intermittent in spontaneous POI and some forms of iatrogenic POI, patients should be counseled on effective contraceptive options if pregnancy is not desired. Fertility preservation, including oocyte or embryo cryopreservation, should be offered to those at risk before gonadotoxic therapy or planned surgical removal of ovaries. For individuals with established POI, donor oocyte in vitro fertilization provides the most effective path to pregnancy.(60,64)

If a patient is under the age of 40 and suspected to have spontaneous POI, referral to a reproductive endocrinologist or other specialist is preferred. If no reproductive endocrinologist is available, the next appropriate referral would be to a gynecologist for diagnostic evaluation and counseling.(60)

Pelvic radiation is a common cause of iatrogenic POI and may also result in significant vaginal, cervical, and uterine tissue changes. Management of patients with radiation-induced POI generally follows the same principles as management of other forms of POI, including hormone therapy when not otherwise contraindicated. Patients with an intact uterus receiving systemic estrogen therapy should also receive adequate progestogen for endometrial protection. Management should be individualized in collaboration with oncology specialists when there is a history of hormone-sensitive malignancy.(65-67)

MHT is strongly recommended, in the absence of contraindications, at least until the average age of natural menopause (approximately age 50-51 years). In contrast to treatment initiated after natural menopause, hormone therapy in POI is intended to replace ovarian hormone production and reduce the long-term risks associated with prolonged hypoestrogenism, including bone loss, cardiovascular disease, and genitourinary symptoms.(65,66)

Because intermittent ovarian function and spontaneous ovulation may still occur in some individuals with POI, contraception should be discussed when pregnancy is not desired despite the use of hormone therapy.(60) Estrogen therapy should be combined with a progestogen in women with an intact uterus. Replacement-dose estrogen therapy is generally recommended, such as oral estradiol 1–2 milligrams (mg) daily or transdermal estradiol 100 micrograms (mcg) daily, with appropriate endometrial protection in patients with an intact uterus. Because these replacement regimens do not provide contraception and intermittent ovarian activity may occur, patients who do not desire pregnancy should be counseled regarding effective contraceptive options. Combined hormonal contraceptives may be considered for those seeking both symptom management and contraception, although physiologic hormone replacement regimens may be preferable for optimizing bone health. If the patient is at risk for unintended pregnancy, contraceptive options should be considered. Management should also include bone density monitoring, cardiovascular risk reduction, and psychological support.(60,63,65,66)

E. Force Readiness

Effect on Military Readiness

Symptom management during perimenopause and menopause is not just a health and wellness issue for Service members; it is a critical component of military readiness. Untreated symptoms can substantially undermine physical, cognitive, and emotional capabilities in some women, which are fundamental for operational effectiveness. A failure to provide adequate care for these treatable symptoms carries significant consequences, not only for the individual Service member but for the force as a whole.(68)

Symptoms can directly threaten a Service member's ability to perform duties in multiple ways, including:

- Cognitive Impairment: "Brain fog", memory issues, and difficulty concentrating reduce focus, decision-making ability, and situational awareness, which are critical in high-stakes environments.

- Sleep Disruption: Night sweats, insomnia, and other symptoms can impact sleep quality, leading to delayed reaction time, impaired judgement, and degradation of overall physical and cognitive performance.
- Musculoskeletal Injuries: Decreasing bone density and muscle mass increase the risk of injury, directly compromising the ability to train, deploy, and perform core tasks.
- Genitourinary Symptoms: Hypoestrogenism is a risk factor for recurrent urinary tract infections. In addition, urinary symptoms can lead women to delay hydration and increase sick call visits, disrupting daily duties and field exercises.
- Mood Disturbances: Increased anxiety, irritability, and higher risk of depression can impact team cohesion, leadership effectiveness, and overall performance, while simultaneously risking an increase in medical profiles that limit a Service member's duties and deploy ability.
- Menstrual Irregularities: Unpredictable and heavy bleeding can impede execution in the field environment where hygiene supplies and sanitation may be limited.

The consequences can create a ripple effect that impacts career longevity, retention, and operational stamina. Furthermore, untreated menopausal symptoms also increase the risk of chronic diseases such as diabetes, cardiovascular disease (CVD), obesity, metabolic syndrome, and osteoarthritis, further influencing long-term fitness and increasing the healthcare burden within DOD and VA systems. (69-71)

III. Scope of This Guideline

This CPG is based on clinical evidence and related information published from January 1, 2015, to June 30, 2025. It is intended to provide general guidance on evidence-based best practices (see Appendix A for additional information on the evidence review methodology). Although the CPG is intended to improve the quality of care and clinical outcomes (see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

A. Guideline Audience

This CPG's intended audience is all clinical professionals who provide health care to individuals experiencing perimenopause or menopause.

B. Guideline Population

The target population for this CPG includes individuals with naturally occurring or surgically/iatrogenically induced perimenopause or menopause. Individuals under 40 with natural menopause should be evaluated by specialists.

IV. Highlighted Features of This Guideline

A. Highlights in This Guideline

This document is a new VA/DOD Clinical Practice Guide for Menopause. This CPG provides recommendations for providers on clinical assessment and care options for individuals with

perimenopause or menopause. The recommendations are based on the most current and clinically relevant scientific evidence available.

The major strength of this CPG is the coordination and collaboration among the members of the multidisciplinary CPG Development Work Group, ensuring a broad representation of providers engaged in direct clinical care, research, and healthcare administration.

Highlights in this CPG include the following:

- The Work Group developed a total of 43 evidence-based recommendations, including 5 strong recommendations, 25 weak recommendations, and 13 insufficient evidence recommendations focused on the management of menopausal symptoms and improving patient outcomes. The recommendation topics include:
    - Diagnosis of Perimenopause and Menopause
    - Management of Menopausal Symptoms
        - Vasomotor Symptoms
        - Sleep Symptoms
        - Depressive and Anxiety Symptoms
        - Cognitive Symptoms and Dementia
        - Genitourinary Syndrome of Menopause (GSM) and/or Sexual Dysfunction Symptoms
        - Bone Health
        - Overweight and Obesity Management
    - Safety
        - Cardiovascular Disease Risk
        - Breast Cancer Risk
- This CPG recognizes the complexities of perimenopause and menopause and common co-occurring conditions in military and Veteran populations. The recommendations are based on the most recent and practical scientific and clinical evidence.
- The Recommendations and the Algorithm are focused on reducing the negative effects of perimenopause and menopause and promoting wellness. They include patient education and counseling; use of pharmacological and non-pharmacological interventions to treat and/or manage a range of symptoms; and referrals to specialists as part of a multidisciplinary, patient-centered, holistic/whole health approach.

The methodology used in developing this CPG reflects a rigorous application of the GRADE methodology. The result is a refined CPG that includes methodologically rigorous, evidence-based recommendations for individuals experiencing perimenopause or menopause.

B. Components of This Guideline

This CPG provides clinical practice recommendations for the care of patients with perimenopause and menopause (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research. To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, a patient summary, and a quick reference guide, which can be found at: https://www.healthquality.va.gov/index.asp.

C. Demographic and Other Terminology in This Guideline

The demographic terms in this guideline are based on the published literature sources included in the systematic review (SR) and the evidence base. The Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and improve clarity and consistency. To accurately present the research evidence on which this CPG is based, the Work Group made every effort to use the same terminology as reported in the published literature base of SRs, clinical trials, and other studies. Consequently, the usage of demographic terms in this CPG may vary and appear inconsistent.

Precise and intentional language has been utilized in this document to describe the hormones involved in menopause. “Estrogen” is used to describe the endogenous 18-carbon chemical compounds that have varying affinities for estrogen receptors, of which 17β-estradiol is the most relevant and active. “Progesterone” is used to describe the endogenous 21-carbon chemical compounds that bind and activate progesterone receptors.

When referencing systemic MHT, estrogen, or “E” as shorthand, is used to describe the estrogenic component of a MHT regimen. Conjugated estrogen (CE) denotes compounds formulated with multiple active estrogens from either equine or synthetic sources. Estradiol references either endogenous 17β-estradiol produced by the ovary or the bio-identical synthetic 17β-estradiol. Systemic estradiol is available in various forms, including oral pills, transdermal gels, sprays, creams, patches, and systemic vaginal rings. Non-oral forms of estradiol bypass the liver and are thought to carry less risk of venous thromboembolism. Local vaginal estradiol, used to treat GSM, is not considered systemic and does not carry the same risks. Local preparations include vaginal creams, tablets, and a local vaginal ring (distinct from the systemic vaginal ring). Phytoestrogens are naturally occurring compounds with structural similarity to estrogens obtained and consumed in dietary sources.

When referencing systemic MHT, progestogen, or “P” as shorthand, is used as shorthand for the progestogenic component of an MHT regimen. “Progesterone” references either the endogenous hormone produced by the ovary or the bio-identical micronized progesterone (MP) available as a pill. “Progestin” denotes synthetic compounds with progesterone-like activity and includes medroxyprogesterone acetates, norethindrone, norethindrone acetate, and levonorgestrel. The class “progestogen” includes both progesterone and progestins. Progestogen is an important component of MHT if the woman has a uterus, as it protects the lining of the uterus. The progestogen can be taken daily or 12 days per month if the patient prefers having a monthly cycle.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Elizabeth W. Patton MD, MPhil, MSc, FACOG, MSCP and Melissa Shaughnessy, DO, MSCP from VA; and Erin A. Keyser, MD, FACOG, MSCP, COL, MC, USA and Kathleen Pombier, MD, FACOG, Maj, USAF, MC from DOD. The Work Group comprised individuals with the following areas of expertise: obstetrics and gynecology, women's and reproductive health, family medicine, internal medicine, dietetics, nursing, pharmacy, cardiovascular medicine, psychiatry, and research. Table 2 lists the Work Group and Guideline Development Team members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG;
- Crafting clinically relevant key questions (KQ) to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

The Sigma Team (Sigma Health Consulting and Duty First Consulting) was contracted by VA to help develop this CPG.

Table 2. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Elizabeth Patton, MD, MPhil, MSc, FACOG, MSCP (Champion)**
	Melissa Shaughnessy, DO, MSCP (Champion)
	Nancy Roberson Jasper, MD, FACOG, MSCP
	Karen M. Goldstein, MD, MSPH
	Bevanne Bean-Mayberry, MD, MHS, FACP
	Destiny Byrd, WHNP-BC, AGNP-C, MSCP
	Ana E. Reyna, RDN, CDCES, CLC
	Lisa Longo, PharmD, BCPS
	Jennifer Jennings, MD
	Dai-Trang E. Le, MD, FACC, FASE, FAHA
	Laura Miller, MD

Organization	Names*
Department of Defense	**Erin A. Keyser, MD, FACOG, MSCP, COL, MC, USA (Champion)**
	Kathleen Pombier, MD, FACOG, Maj, USAF, MC (Champion)
	Franchesca M. Desriviere, CNM, LTC, AN, USA (APRN)
	Allison A. Eubanks, MD, FACOG, LCDR, MC, USN
	Megan McDermott, MD, MSCP, CPT, MC, USA
	Meghan Raleigh, MD, MS, FAAFP, CAQSM, COL, MC, USA
	Larissa F. Weir, MD, FACOG, Col, USAF, MC
	Kara N. Wilson, Capt, USAF, BSC, RD, LDN
VA Evidence Based Practice, Office of Quality and Patient Safety Veterans Health Administration	James Sall, PhD, FNP-BC
	René M. Sutton, BS, HCA, FAC-COR II
	Jennifer Ballard-Hernandez, DNP, RN, FNP-BC
	Jessica M. Bingham, PhD-C, RN, NE-BC, EBP-C
	Kelly Gantt, DNP, MBA-HLM
Clinical Quality Improvement Program Defense Health Agency	Jenifer Meno, DNP, FNP-BC, AMB-BC, NEA-BC, FAANP
	Margaret Rincon, PharmD
	Lynn M. Young, BSN, RN, CIC
	Gwen Holland, MSN, RN

Organization	Names*
Sigma Health Consulting, LLC	Frances Murphy, MD, MPH
	James Smirniotopoulos, MD
	Janice Kaczmarek, MS
	William Wester, MLIS
	James Reston, PhD, MPH
	Joann Fontanarosa, PhD
	Zyna Egbe, MPH
	Ruth Bekele, MPP
	Deepti Ghimire, MPH
	Rachel McCausland, PhD
	Susan Connor, PhD
	Aggée Loblack, MPH
	Dan Sztubinski
	Sophie Roberts, BS
	Rebecca Rishar, MLIS
Duty First Consulting	Kate Johnson, BS
	Anita Ramanathan, BA

*Additional contributor contact information is available in Appendix C

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the Guideline for Guidelines, an internal document of the VA/DOD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DOD CPGs.(72) The Guideline for Guidelines is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(73) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction).(74)

1. Balance of desirable and undesirable outcomes
2. Confidence in the quality of the evidence
3. Patient or provider values and preferences

4. Other implications, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong or Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.(75) A Strong recommendation generally indicates High or Moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, little variability in patient values and preferences, and limited concerns about the influence of other implications (e.g., resource use, feasibility).

In some instances, insufficient evidence exists on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The way this finding is expressed in the CPG might vary. In such instances, the Work Group might include among its set of recommendations a statement of insufficient evidence for an intervention that might be in common practice, although it is unsupported by clinical evidence, and particularly if other risks of continuing its use might exist (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might decide to exclude this type of statement about an intervention. For example, the Work Group might remain silent where an absence of evidence occurs for a rarely used intervention. In other cases, an intervention might have a favorable balance of benefits and harms but might be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in Table 3.

Table 3. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend…
Weak for	We suggest…
Neither for nor against	There is insufficient evidence to recommend for or against…
Weak against	We suggest against…
Strong against	We recommend against...

It is important to note that a recommendation's strength (i.e., Strong versus Weak) is distinct from its clinical importance (e.g., a Weak recommendation is evidence based and still important to clinical care). The strength of each recommendation is shown in Recommendations.

This CPG's use of GRADE reflects a rigorous application of the methodology; the determination of the strength of the recommendation is directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of

the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies might be inherently more difficult (e.g., randomized controlled trials [RCT]) are typically supported by lower quality evidence and, in turn, Weak recommendations. Recommendations on topics for which rigorous studies can be designed and conducted might more often be Strong recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2,76) This strict standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled, subject to time-based expirations.(77) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(78)

Recommendation categories are used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(79,80) Table 4 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which a previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2026 CPG recommendation categories can be found in Recommendations.

Table 4. Recommendation Categories and Definitions*

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from previous CPG that has been removed based on review of the evidence

Evidence Reviewed*	Recommendation Category*	Definition*
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG, where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012)(79) and Martinez Garcia, et al. (2014)(80)
Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the Guideline for Guidelines.(72) Further, the Guideline for Guidelines refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care) (81) as well as to disclosure statements (i.e., standard disclosure form completed at least twice by CPG Work Group members and the guideline development team).(72) The disclosure form inquiries regarding relevant financial and intellectual interests or other relationships with, for example, manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments, ProPublica).

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(76) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DOD Leadership arranged a virtual patient focus group on April 25, 2025. The focus group aimed to gain insights into patient perspectives of adult patients with menopause who have received care in the VA and DOD healthcare systems and incorporate these insights into the CPG, as appropriate. Topics discussed included screening and management of menopause in the VA and DOD healthcare systems, including patients' menopause treatment history, preferences for care delivery setting and transitions, priorities, and treatment challenges, as well as the impact menopause has had on their lives.

The Patient Focus Group, which may include up to nine patients (i.e., subject to the Paperwork Reduction Act), was comprised of a convenience sample of thirteen women. The VA and DOD leadership overrecruited when seeking participants for the Patient Focus Group, with the expectation that some participants may not be able to attend. Participants were receiving care from the VA and DOD. The participants were primarily younger, ranging in age from 42 to 57 years old. Many of the participants were currently active duty military personnel, and others were

Veterans, military personnel, or dependents. Some participants shared other co-occurring conditions they have with their menopause, including ductal carcinoma in situ (DCIS), fibromyalgia, and Hashimoto's thyroiditis. For more information on the patient focus group methods and findings, see Appendix D. The patient focus group participants were provided with the opportunity to review the final draft of this CPG and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified experts from VA and DOD health care systems and outside organizations generally viewed as experts in the respective field to review it. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithms serve as a tool to prompt providers to consider key decision points in the care of patients who would benefit from menopause management. The Work Group submits suggested performance metrics for VA and DOD to use when assessing the implementation of this CPG. Robust implementation is outlined in VA and DOD internal implementation plans and policies. Additionally, implementation will entail wide dissemination through publication in the medical literature, online access to the final CPG, educational programs, and ideally, electronic medical record programming in the form of clinical decision support tools at the point-of-care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. Patient-Centered Care

VA and DOD encourage providers to be sensitive to demographic, cultural, and other differences that affect patients' values, needs, and preferences. Patient-centered care is aimed at treating the condition while also optimizing the individual's overall health and well-being. Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(82,83) A holistic whole-person health approach (https:/www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. Guideline recommendations should be applied in a holistic approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities.

B. Shared Decision Making

This CPG encourages providers to practice shared decision-making, a process in which providers, patients, and family/friend/caregiver consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(84) Shared decision making is emphasized in *Crossing the Quality Chasm*, an Institute of Medicine report from 2001 (85), and is a core component of a holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels or settings of care, or both, especially where patient heterogeneity in weighing risks and benefits might exist. The Veterans Health Administration and the Military Health System have embraced shared decision-making. Providers are encouraged to use shared decision-making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

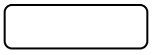
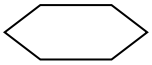
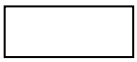
Co-occurring health conditions are important to recognize because they can contribute to the risk of early menopause, impact the management of menopause, influence patient or provider treatment priorities and clinical decisions, and affect the overall provider approach to the management of menopause. Providers should expect that many Veterans, Service members, and their families will have one or more co-occurring health condition(s). Because menopause is often accompanied by co-occurring conditions, collaborative management with other care providers is often best. Some co-occurring conditions may require early specialist consultation to determine necessary changes in treatment or establish a common understanding of how care should be coordinated.

VIII. Algorithm

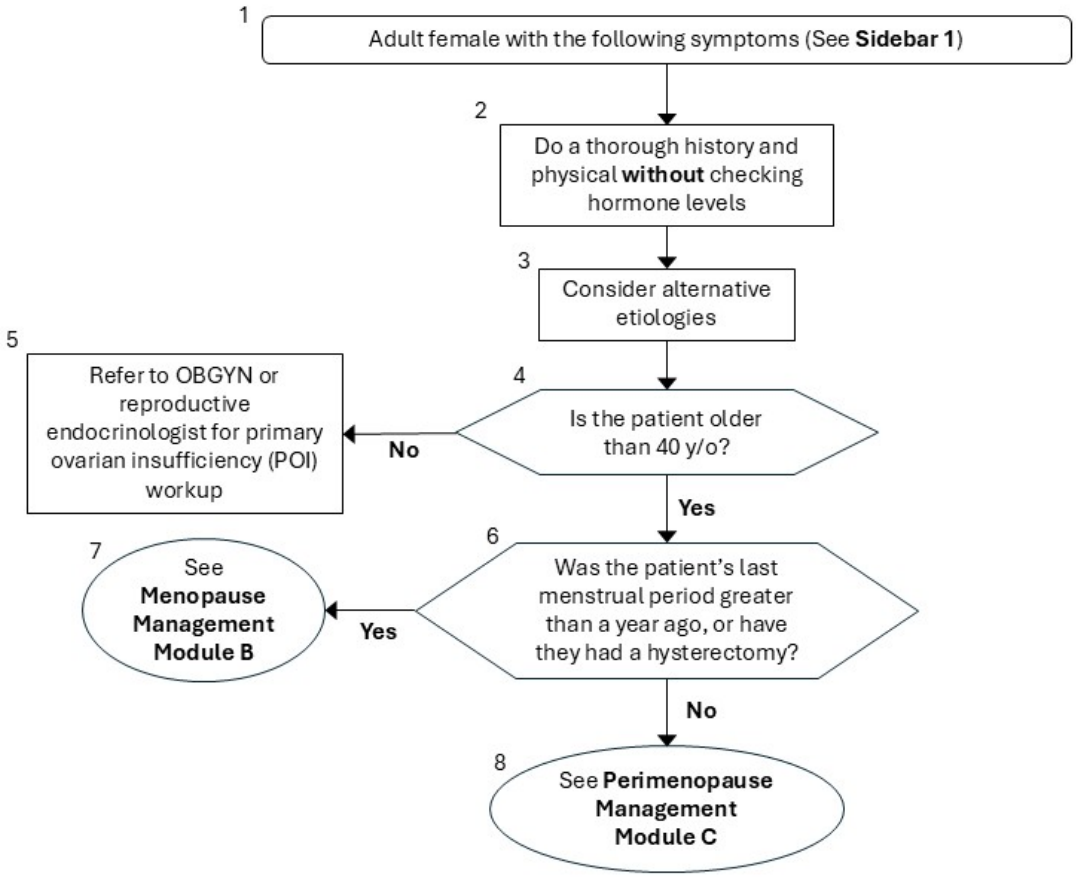
This CPG includes an algorithm that is designed to facilitate understanding of the clinical pathways and decision-making processes used in managing patients with menopause. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision making; it also has the potential to change patterns of resource use. Although the Work Group recognizes that not all clinical practices are linear, the simplified linear approach depicted through the algorithm and its format allows the provider to assess the critical information needed at the major decision points in the clinical process. It includes:

- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes, indicating the order in which the steps should be followed.(86) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

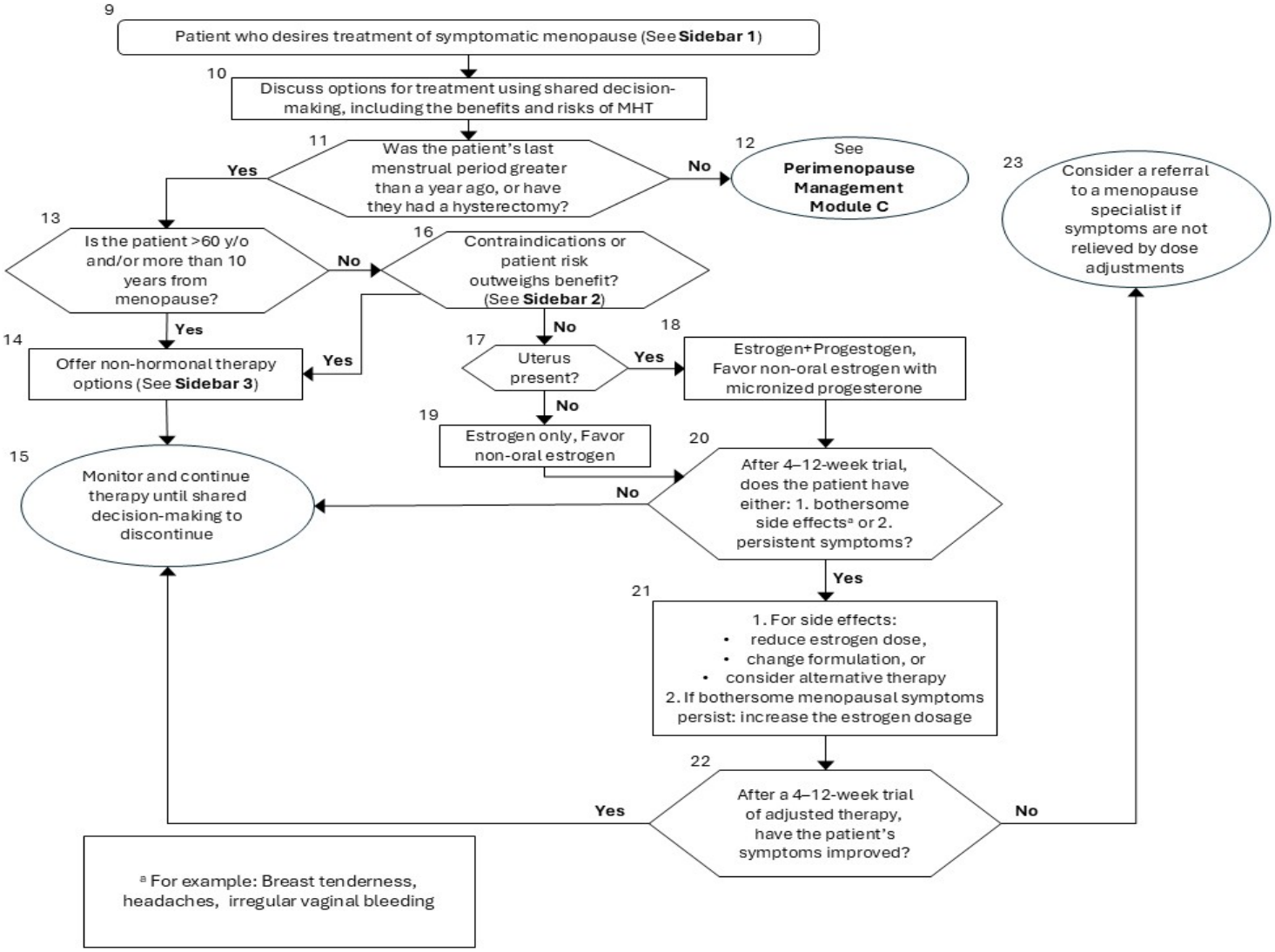
Shape	Description
	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered “Yes” or “No”.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the algorithm

Module A. Perimenopause and Menopause Diagnosis



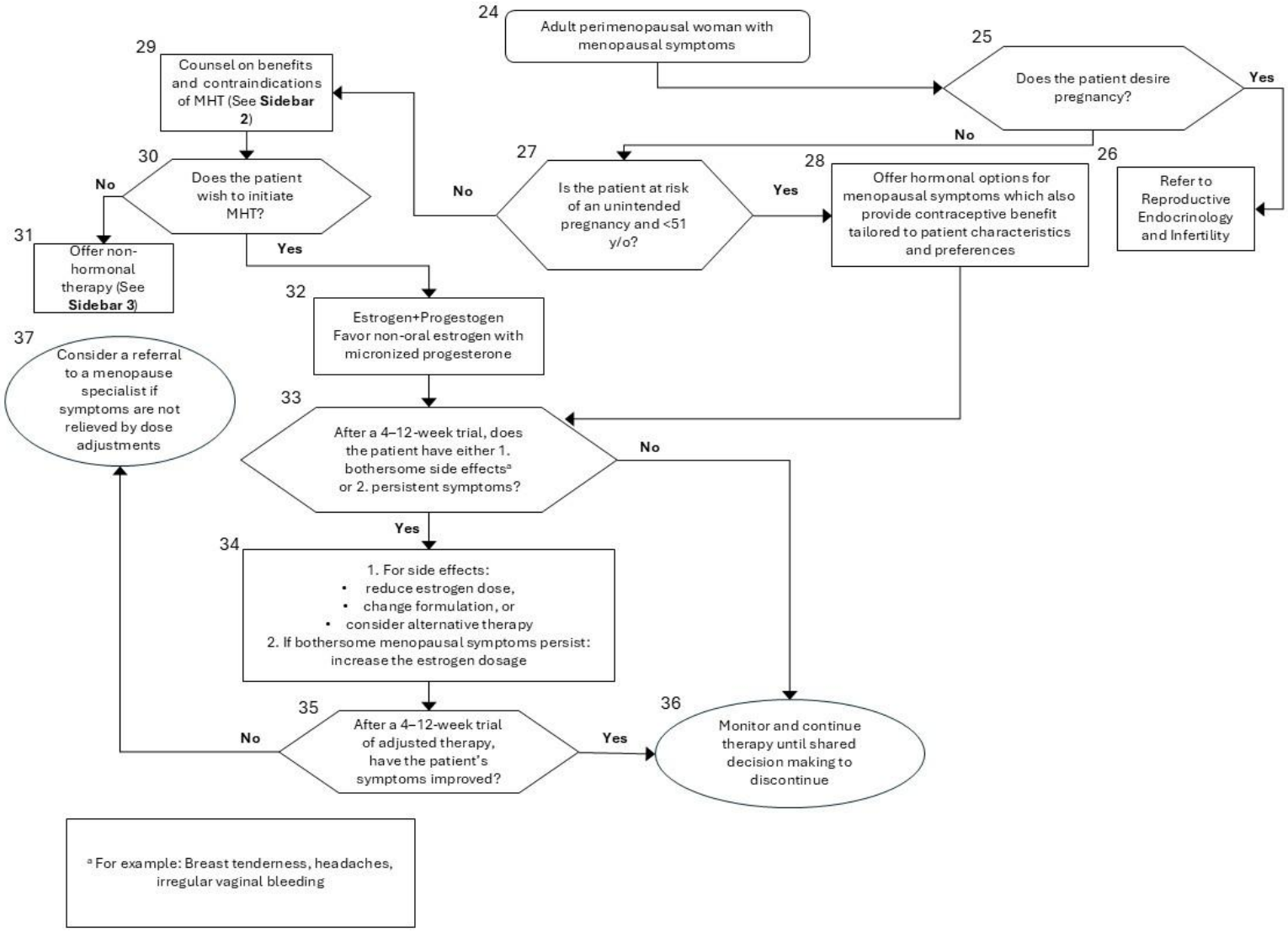
Abbreviations: OBGYN: obstetrician-gynecologist; POI: primary ovarian insufficiency; y/o: years old

Module B. Menopause Management



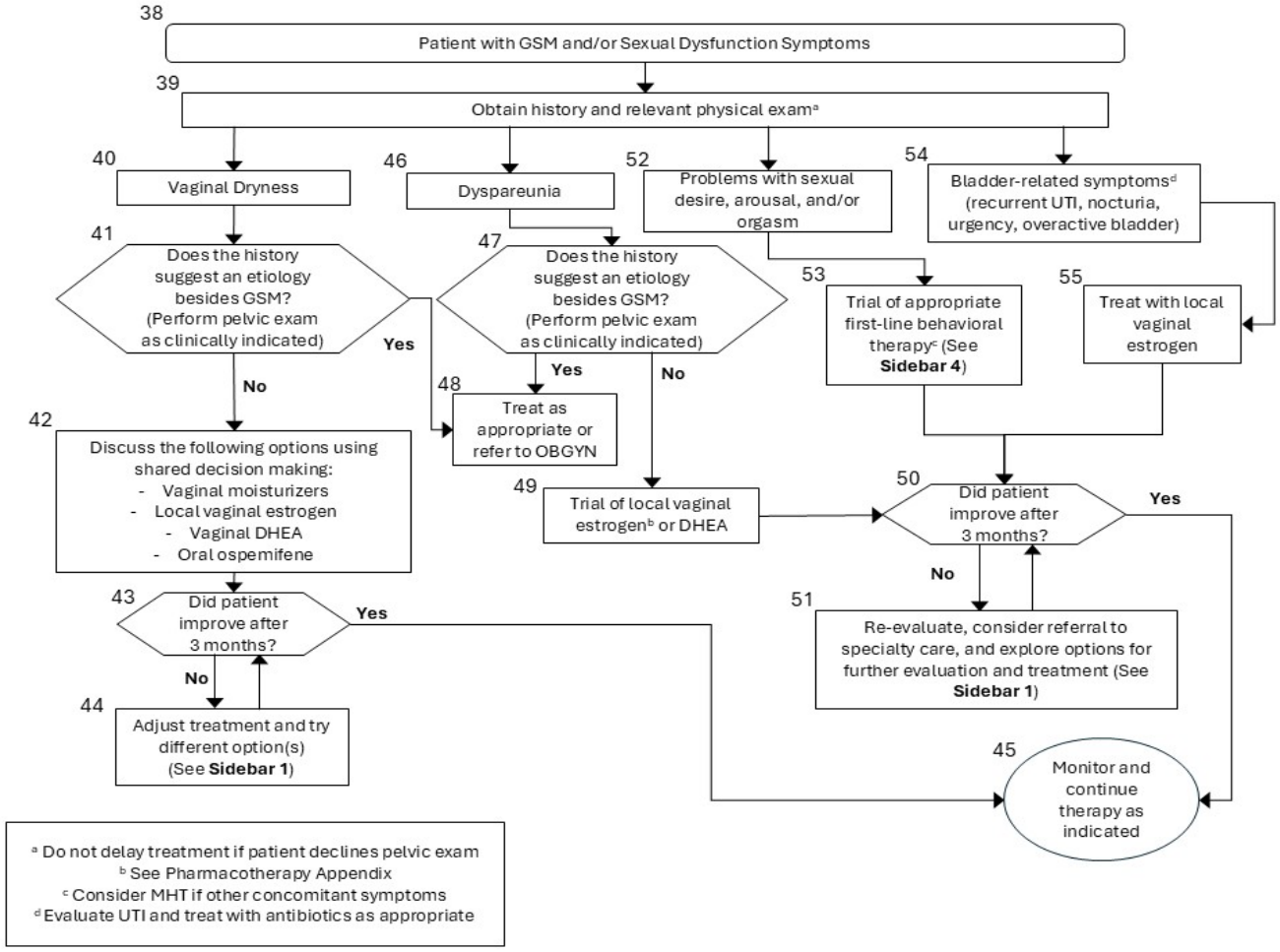
Abbreviations: MHT: menopausal hormonal therapy; y/o: years old

Module C. Perimenopause Management



Abbreviations: MHT: menopausal hormonal therapy; y/o: years old

Module D. Genitourinary Syndrome of Menopause (GSM) and/or Sexual Dysfunction Symptoms Treatment



Abbreviations: DHEA: dehydroepiandrosterone; GSM: genitourinary syndrome of menopause; MHT: menopausal hormonal therapy; OBGYN: obstetrician-gynecologist; UTI: urinary tract infection

Sidebar 1: Treatment Options for Menopausal Symptom Management							
Symptoms	**Behavioral Interventions**	**Dietary Interventions**	**Exercise & Physical Therapy**	**Local Hormonal Therapies**	**Systemic Menopausal Hormonal Therapy**	**Other Prescription Therapies**	**Over-The-Counter & Non-prescription Therapies**
Vasomotor Symptoms (hot flashes, night sweats)	✓				✓	✓	
	• Systemic Hormone Therapy: The most effective treatment for appropriately selected patients (**Recommendations 2-5, Appendix H, Section A**). • Behavioral Interventions: Includes provider-mediated therapies such as CBT, tobacco cessation, and mindfulness (**Recommendation 6**). Self-directed strategies, including trigger avoidance, cooling therapies, weight loss, and exercise, are common but not strictly evidence-based. • Other Prescription Therapies: Include NK3 antagonists (**Recommendation 7**), gabapentin, and SSRI/SNRI. See **Appendix H, Section C**.						
Urinary Symptoms (incontinence, overactive bladder, recurrent urinary tract infections)	✓	✓	✓	✓		✓	✓

	• Local Estrogen Therapy: Strong evidence supports its use in postmenopausal women for recurrent UTIs, non-infectious dysuria, urinary urgency/frequency, and urge incontinence. Evidence for stress urinary incontinence is mixed (**Appendix H, Section B**)
	• Behavioral & Physical Interventions: Pelvic floor muscle exercises, physical therapy, bladder training, weight loss, and avoidance of bladder irritants are recommended.
	• Pharmacologic, Dietary, & Surgical Interventions:
	  • OAB/Urge Incontinence: Outside the scope of this CPG; however, anticholinergics, antimuscarinics, and beta-3 agonists are options.
	  • Recurrent UTIs Prevention: Suppressive antibiotics used nightly or post-coital, vaginal estrogen, cranberry juice (100% pure unsweetened juice), Methenamine, D-mannose, and cranberry tablets (that contain proanthocyanidins have been shown to decrease recurrent UTIs. Prolapse and Stress Urinary Incontinence: Consider specialist evaluation and surgical management as appropriate.						

Sleep Disturbance or Insomnia	✓		✓			✓	✓
	• Behavioral Therapy: Cognitive behavioral therapy for insomnia (CBT-I) is the primary recommended treatment for menopause-related insomnia. • Other strategies that align with the standard of care for the general population include exercise, mindfulness and relaxation techniques, sleep hygiene, melatonin, and prescription sleep aids. See also VA/DOD CPG for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. • MHT may improve sleep if related to vasomotor symptoms. (**Recommendation 13**).						
Depressive/Anxiety Symptoms	✓		✓		✓*	✓	

Sidebar 1: Treatment Options for Menopausal Symptom Management							
Symptoms	**Behavioral Interventions**	**Dietary Interventions**	**Exercise & Physical Therapy**	**Local Hormonal Therapies**	**Systemic Menopausal Hormonal Therapy**	**Other Prescription Therapies**	**Over-The-Counter & Non-prescription Therapies**
	• Behavioral and Pharmacologic Therapy: Antidepressants and psychotherapy (e.g., CBT, mindfulness-based stress reduction [MBSR]) are the primary treatments for depression and anxiety (Recommendations **14-15**). In patients with a DSM diagnosis of Major Depressive Disorder, see also VA/DOD CPG for the Management of Major Depressive Disorder. • Systemic Hormone Therapy: Effective in treating depressive symptoms during perimenopause, not post menopause. (**Recommendation 16**) • Lifestyle: Physical exercise can improve depressive symptoms in both peri- and postmenopausal patients. (**Recommendation 17**)						
Altered Cognition ("Brain Fog", poor memory)	✓		✓				
	• Behavioral and Physical Interventions: Evidence is limited, though CBT and/or physical exercise may have a small, positive effect on menopause-related cognitive symptoms. Evidence does not support the use of estrogen/progestogen therapy solely for the treatment of cognitive symptoms (**Recommendation 20**).						
Dyspareunia	✓		✓	✓	✓		✓
	• Hormonal & OTC Therapies can improve lubrication and consequently reduce dyspareunia when related to poor lubrication. Interventions effective for vaginal dryness include systemic or local estrogen, DHEA, lubricants, and moisturizers. (Recommendations **21, 24, 28**) • Behavioral Interventions: Strategies to improve arousal may enhance natural lubrication and decrease discomfort (see **Sexual Concerns** below). • Physical Interventions: Pelvic floor physical therapy and dilator therapy can address pelvic floor myalgia and vaginodynia causing dyspareunia. • Dyspareunia is commonly secondary to vaginal dryness (see **Vaginal Dryness** below).						
Vaginal Dryness				✓	✓	✓	✓

	• Local vaginal and Systemic Hormone Therapies: Can effectively address vaginal dryness regardless of sexual activity.
	  • Local Estrogen: Preferred for isolated vaginal symptoms. May be used alone or as an adjunct to systemic estrogen.
	  • Vaginal DHEA: Demonstrated efficacy for vaginal dryness.
	  • Ospemifene: An oral SERM with estrogen agonism within vaginal tissue (**Appendix H, Sections A** and **B**).
	• OTC Therapies: Vaginal moisturizers and lubricants are effective for personal use and during sexual activity (**Recommendation 25**).						

Sidebar 1: Treatment Options for Menopausal Symptom Management							
Symptoms	**Behavioral Interventions**	**Dietary Interventions**	**Exercise & Physical Therapy**	**Local Hormonal Therapies**	**Systemic Menopausal Hormonal Therapy**	**Other Prescription Therapies**	**Over-The-Counter & Non-prescription Therapies**
Sexual Concerns (Difficulty with Arousal/Libido/Orgasm)	✓					✓	
	• Behavioral: Sexual skills training, CBT, mindfulness-based interventions, sex therapy, and couples therapy can address symptoms related to interest, arousal, and/or orgasm regardless of menopausal status. • Pharmacotherapy: Transdermal testosterone and flibanserin have demonstrated a modest but positive effect on total satisfying sexual encounters. (Recommendations **26-27**) Evidence for testosterone therapy is limited to postmenopausal women, and its use is considered off-label (**Appendix H, Section A**). Current evidence does not support the use of systemic estrogen and/or progestogen for improving sexual interest, arousal, or orgasm. Testosterone pellets should be avoided. • Treating conditions that cause sexual pain is likely to indirectly improve arousal and interest by reducing barriers to intimacy. See **Dyspareunia**.						
Loss of Bone Density/Fractures	✓	✓	✓		✓		✓
	• OTC and Dietary Interventions: Dietary or supplemental calcium is recommended as it may increase bone mineral density (**Recommendation 31**). Vitamin D is often recommended, although supporting evidence is limited (**Recommendation 32**). • Systemic Hormone Therapy: Estrogen-containing systemic hormone therapy is effective in decreasing bone resorption (**Recommendation 30**). • Lifestyle Interventions: Weight-bearing exercise and the avoidance of alcohol and tobacco are important behavioral interventions. • Pharmacotherapy: The choice of first-line prescription medication depends on the degree of bone loss and the patient's risk profile. While comprehensive osteoporosis management is outside the scope of this CPG, standard therapies include bisphosphonates, denosumab, and anabolic agents (Recommendations **33** and **34**).						
Weight Gain/Difficulty Losing Weight		✓	✓			✓	
	• Lifestyle Interventions: The management of obesity during menopause is similar to that in the general population. Exercise and a calorie-restricted diet have been shown to be effective (Recommendations **35** and **36**). • Pharmacotherapy: Medical therapies for obesity are outside the scope of this CPG, but standard options include GLP-1 receptor agonists and other weight-management medications. See also VA/DOD CPG for the Management of Adult Overweight and Obesity.						
Abnormal Uterine Bleeding					✓*	✓*	✓*

	Postmenopausal bleeding or undiagnosed AUB requires immediate evaluation (often including pelvic ultrasound and endometrial biopsy). Systemic estrogen therapy is contraindicated until the evaluation is complete. Irregular cycles and AUB are common in perimenopause and can be managed similarly to premenopausal women. Strategies tailored to perimenopause include: • LNG-IUD (52 mg): Provides endometrial protection when used with systemic estrogen, for up to 5 years, while also offering contraception and treating AUB. • Cyclic MHT (taking progestogen 14 days per month) induces scheduled withdrawal bleeding and limits unscheduled breakthrough bleeding. Synthetic progestins may offer better bleeding control than micronized progesterone, but may not prevent pregnancy. For patients who require birth control, we recommend validating that the selected progestin is an FDA-approved contraceptive. • Combined or Progestin-only Oral Contraceptives: Effective for regulating bleeding and preventing pregnancy, but may be less effective than MHT for treating severe vasomotor symptoms. • Non-Hormonal Therapies: NSAIDs and tranexamic acid (TXA) continue to offer benefit for AUB during perimenopause. • Consider referral to a provider privileged to perform endometrial sampling.

***For perimenopausal patients only**

Abbreviations: AUB: Abnormal Uterine Bleeding; CBT: Cognitive Behavioral Therapy; CBT-I: Cognitive Behavioral Therapy for Insomnia; CPG: Clinical Practice Guideline; DHEA: Dehydroepiandrosterone; DSM: Diagnostic and Statistical Manual of Mental Disorder; FDA: Food and Drug Administration; GLP-1: Glucagon-like peptide-1; LNG-IUD: Levonorgestrel-releasing Intrauterine Device; MBSR: Mindfulness-Based Stress Reduction; MHT: Menopausal Hormonal Therapy; NK3: Neurokinin-3; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; OAB: Overactive Bladder; OTC: Over The Counter; SERM: Selective Estrogen Receptor Modulator; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; SSRIs: Serotonin Reuptake Inhibitors; TXA: Tranexamic Acid; UTIs: Urinary Tract Infections; VA/DOD: Department of Veterans Affairs/Department of Defen

Sidebar 2: Contraindications to Systemic Menopausal Estrogen Therapy[†]

Absolute Contraindications:

- Active or recent arterial thromboembolic disease (e.g., stroke and MI)
- Active or recent DVT or PE
- Active or severe hepatic impairment or disease
- Known CVD and age > 60 years old and/or >10 years after menopause onset
- Breast cancer or history of breast cancer, except in appropriately selected patients being treated for metastatic diseases
- Estrogen-dependent neoplasia
- Known anaphylactic reaction or angioedema related to estrogen use
- Known or suspected pregnancy
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Undiagnosed abnormal genital bleeding

Exercise caution for:

- Patients at risk for but without CVD, and utilize a validated cardiovascular risk calculator (PREVENT[a], ASCVD, and/or VA Women CVD Risk Score[b])
- Patients on thyroid replacement therapy should have thyroid function monitored
- Patients with gallbladder disease (as estrogens increase the risk of gallbladder disease)
- Patients with history of DVT, PE, stroke, or MI
- The development of severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice (discontinue estrogen)

For patients with absolute contraindications or where caution should be exercised, refer to the appropriate specialist(s) for individualized counseling and shared decision-making.

[a]https://professional.heart.org/en/guidelines-and-statements/prevent-calculator

[b]https://www.vawomencvdriskcalculator.org/

[†]This sidebar incorporates a combination of FDA-approved language as well as evidence-based language within the CPG.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; DVT: deep vein thrombosis; MI: myocardial infarction; PE: pulmonary embolism; PREVENT: Predicting Risk of Cardiovascular Disease EVENTs; VA: Veterans Affairs

Sidebar 3: Non-hormonal Treatment Options for Vasomotor Symptoms

Generic Name	Brand	Mechanism	Usual Dosing	Comments
Fezolinetant	VEOZAH	NK3RA	45 mg daily	• Hepatic lab tests at baseline, 1, 2, 3, 6, and 9 months; do not initiate in patients with baseline enzyme elevations • Contraindicated in known cirrhosis, severe renal impairment
Elinzanetant	LYNKUET	NK1RA and NK3RA	120 mg daily at bedtime	• May cause somnolence and may be useful for nocturnal symptoms • Hepatic lab tests at baseline and 3 months; do not initiate in patients with baseline enzyme elevations • Avoid in patients with history of seizure disorder

Generic Name	Brand	Mechanism	Usual Dosing	Comments
				• Although indicated for menopausal hot flashes, if patient has risk of pregnancy, this drug is contraindicated.
Citalopram*	CELEXA	SSRI	10 to 20 mg daily (start with 10 mg daily)	
Escitalopram*	LEXAPRO		10 to 20 mg daily (start with 10 mg daily)	
Paroxetine*	PAXIL		10 to 25 mg daily	• Contraindicated with tamoxifen (reduced tamoxifen exposure) • If pregnancy is a concern, consider alternative SSRI
Paroxetine mesylate	BRISDELLE		7.5 mg daily	Contraindicated with tamoxifen (reduced tamoxifen exposure)
Desvenlafaxine*	PRISTIQ	SNRI	100 to 150 mg daily Start with 25 to 50 mg daily	
Venlafaxine*	EFFEXOR		37.5 mg to 150 mg daily Start with 37.5 mg daily	
Gabapentin*	NEURONTIN	Gabapentinoid	900 to 2400 mg daily Start with 100 to 300 mg daily at bedtime, increase to twice daily	May be useful for nocturnal symptoms

Note: Consult prescribing information for more details. Antidepressants may also be effective for co-occurring depression in addition to vasomotor symptoms.

*Off-label

Abbreviations: mg: milligram; NK1RA: Neurokinin-1 Receptor Antagonist; NK3RA: Neurokinin-3 Receptor Antagonist; SNRI: Serotonin-norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor

Sidebar 4: Treatments for Genitourinary Syndrome of Menopause and Sexual Dysfunction
Vaginal Dryness • Vaginal moisturizers/vaginal lubricants • Local vaginal and/or systemic estrogen • Vaginal DHEA • Oral ospemifene
Dyspareunia • Local Vaginal Estrogen • Vaginal DHEA • Vaginal moisturizers • Pelvic floor physical therapy
Diminished or Absent Desire, Arousal, and/or Orgasm • Behavioral Therapy (ACT, Couples Therapy, Sex Therapy, CBT) • Transdermal Testosterone • For patients meeting criteria of HSDD/FSIAD and <age 65, offer Flibanserin
Bladder-related Symptoms • Evaluate for active urinary tract infection and treat as appropriate • Local vaginal and/or systemic estrogen • Pelvic floor physical therapy • Bladder training

Abbreviations: ACT: Acceptance and Commitment Therapy; CBT: cognitive behavioral therapy; DHEA: dehydroepiandrosterone; FSIAD: Female Sexual Interest and Arousal Disorder; HSDD: hypoactive sexual desire disorder

Sidebar 5: Common Menopausal Hormone Therapies (Standard Dosing)

Hormone & Route	Brand	Components	Usual Dosing
Local therapies			
Estrogen (vaginal cream)	• ESTRACE • PREMARIN VAGINAL	• Estradiol 0.01% • Conjugated Equine Estrogen (0.625 mg/g)	0.5- 1 g vaginally daily for 2 weeks, then 1-3x per week
Estrogen (vaginal ring)	ESTRING	2 mg estradiol ring (7.5 mcg/day)	One ring every 90 days
Estrogen (vaginal insert)	• VAGIFEM • IMVEXXY	4 mcg or 10 mcg (Imvexxy only) estradiol insert	One insert daily for 2 weeks, then 1 insert 2x per week
Systemic therapies			
Estrogen only (oral)	• ESTRACE • MENEST • PREMARIN	• Estradiol • Esterified Estrogen • Conjugated Equine Estrogen (CEE)	One tablet daily (doses vary)
Estrogen only (patch)	• MINIVELL • VIVELLE-DOT • CLIMARA • MENOSTAR	Estradiol	One patch once or twice weekly (doses vary)

Sidebar 5: Common Menopausal Hormone Therapies (Standard Dosing)			
Hormone & Route	**Brand**	**Components**	**Usual Dosing**
Estrogen only (vaginal ring)	FEMRING	Estradiol	0.05 or 0.1 mg/day ring every 90 days
Progesterone/ Progestin only (oral)	• PROMETRIUM • PROVERA	• Micronized progesterone • Medroxyprogesterone acetate	One tablet daily or in cyclic fashion (doses vary)
Progestin only (intrauterine)	• MIRENA • LILETTA	Levonorgestrel 52 mg IUDs	One device for up to 5 yrs
Combination Estrogen and Progesterone/ Progestin (oral)	• BIJUVA • ANGELIQ • FEMHRT • PREMPRO • PREMPHASE • ACTIVELLA	• Estradiol/progesterone • Estradiol/Drospirenone • Ethinyl estradiol/ Norethindrone acetate • CEE/Medroxyprogesterone • CEE/Medroxyprogesterone • Estradiol/Norethindrone acetate	One tablet daily (doses vary)
Combination Estrogen and Progestin (patch)	• COMBIPATCH • CLIMARAPRO	• Estradiol/norethindrone • Estradiol/levonorgestrel	One patch once or twice weekly (doses vary)
Note: In women with a uterus, systemic (not local) estrogen therapy **must** be dosed in combination with a progestogen (progestin or progesterone), either as a combination product or estrogen only with a progestogen-only option. See Appendix H.			

Abbreviations: CEE: conjugated equine estrogen; IUD: intrauterine device

IX. Recommendations

The evidence-based clinical practice recommendations listed in the table below were developed using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Table 5. Evidence-Based Clinical Practice Recommendations with Strength and Category

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Diagnosis of Perimenopause and Menopause		1.	We suggest against using laboratory testing (e.g., anti-müllerian hormone and/or follicle-stimulating hormone) for the diagnosis of menopause and perimenopause.	Weak against	Reviewed, New-added
Management of Menopausal Symptoms	Vasomotor Symptoms	2.	In women with a uterus, we recommend systemic estradiol and progesterone for the treatment of vasomotor symptoms.	Strong for	Reviewed, New-added
		3.	In women with a uterus, we suggest the use of conjugated estrogen with bazedoxifene for the treatment of vasomotor symptoms.	Weak for	Reviewed, New-added
		4.	In women without a uterus, we suggest the use of systemic estradiol monotherapy for the treatment of vasomotor symptoms.	Weak for	Reviewed, New-added
		5.	For the treatment of vasomotor symptoms of menopause, we suggest against the use of progestogen monotherapy.	Weak against	Reviewed, New-added
		6.	We recommend cognitive behavioral therapy (CBT) to manage vasomotor symptoms related to menopause.	Strong for	Reviewed, New-added
		7.	We suggest elinzanetant or fezolinetant for vasomotor symptoms in menopausal women.	Weak for	Reviewed, New-added
		8.	There is insufficient evidence to favor fezolinetant or elinzanetant versus hormone therapy for vasomotor symptoms.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of Menopausal Symptoms (cont.)	Vasomotor Symptoms (cont.)	9.	We suggest selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin as non-hormonal options for menopausal vasomotor symptoms based on patient characteristics and preferences.	Weak for	Reviewed, New-added
		10.	For menopausal vasomotor symptoms, in patients without a contraindication to hormone therapy, we suggest hormone therapy over either venlafaxine or gabapentin.	Weak for	Reviewed, New-added
		11.	There is insufficient evidence to recommend for or against the following complementary and integrative health (CIH) interventions for menopausal vasomotor symptoms: • Acupressure • Acupuncture • Tai Chi/Qigong • Yoga	Neither for nor against	Reviewed, New-added
		12.	There is insufficient evidence to recommend for or against the following supplements and nutraceuticals for menopausal vasomotor symptoms: • Amino Acids • Black Cohosh • Danggwijagyaksan • Fenugreek • Giant Fennel • Ginseng • Kamishoyosan • Maca • Magnesium • Melatonin • Probiotics • Red Clover • Resveratrol + Equol • Salvia • Soy Supplements • Succinate	Neither for nor against	Reviewed, New-added
	Sleep Symptoms	13..	There is insufficient evidence to recommend for or against menopausal hormone therapy used solely for sleep symptoms.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of Menopausal Symptoms (cont.)	Depressive and Anxiety Symptoms	14.	We recommend cognitive behavioral therapy (CBT) to treat depressive and/or anxiety symptoms during perimenopause and menopause.	Strong for	Reviewed, New-added
		15.	We recommend mindfulness-based stress reduction (MBSR) for menopause-related depressive and/or anxiety symptoms (See VA/DOD CPG for Major Depressive Disorder [MDD]).	Strong for	Reviewed, New-added
		16.	In perimenopausal women, we suggest menopausal hormone therapy to treat depressive symptoms, depending on patient characteristics and preferences (For patients with Major Depressive Disorder [MDD], see VA/DOD CPG for MDD).	Weak for	Reviewed, New-added
		17.	For depressive symptoms during perimenopause or menopause, we suggest exercise (e.g., mind-body exercise, aerobic activity, or combination).	Weak for	Reviewed, New-added
		18.	For depressive symptoms during perimenopause or menopause, there is insufficient evidence to recommend for or against the use of phytoestrogens (e.g., soy supplements)	Neither for nor against	Reviewed, New-added
	Cognitive Symptoms and Dementia	19.	There is insufficient evidence to recommend for or against menopausal hormonal therapy (MHT) used solely for the prevention of dementia.	Neither for nor against	Reviewed, New-added
		20.	We suggest against the use of menopausal hormonal therapy (MHT) solely for treatment of cognitive symptoms in perimenopausal and menopausal women.	Weak against	Reviewed, New-added
	GSM and/or Sexual Dysfunction Symptoms	21.	We suggest local (non-systemic) vaginal and/or systemic estrogen therapy, for the management of sexual dysfunction in menopause, especially related to vaginal dryness and dyspareunia.	Weak for	Reviewed, New-added
		22.	For genitourinary syndrome of menopause (GSM), we suggest treatment with local (non-systemic) vaginal estrogen.	Weak for	Reviewed, New-added
		23.	For breast cancer survivors, we suggest local (non-systemic) vaginal estrogen therapy for the treatment of genitourinary syndrome of menopause (GSM).	Weak for	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
		24.	For dyspareunia, we suggest local (non-systemic) vaginal estrogen and/or vaginal dehydroepiandrosterone (DHEA).	Weak for	Reviewed, New-added
Management of Menopausal Symptoms (cont.)	GSM and/or Sexual Dysfunction Symptoms (cont.)	25.	For vaginal dryness, we suggest local (non-systemic) vaginal estrogen, vaginal DHEA, vaginal moisturizers, or ospemifene.	Weak for	Reviewed, New-added
		26.	We suggest transdermal testosterone for the treatment of sexual dysfunction in menopause, especially related to interest, desire, and/or arousal.	Weak for	Reviewed, New-added
		27.	For the treatment of Hypoactive Sexual Desire Disorder (reclassified in the DSM-5 as Female Sexual Interest/Arousal Disorder) in perimenopause and menopause, we suggest flibanserin.	Weak for	Reviewed, New-added
		28.	For dyspareunia, there is insufficient evidence to recommend for or against the use of vaginal moisturizers.	Neither for nor against	Reviewed, New-added
		29.	For genitourinary syndrome of menopause (GSM), we suggest against the use of vaginal lasers.	Weak against	Reviewed, New-added
	Bone Health	30.	In post-menopausal women with risk factors for osteoporosis, we suggest conjugated estrogen/bazedoxifene as an option to increase bone mineral density based on patient characteristics and preferences.	Weak for	Reviewed, New-added
		31.	In post-menopausal patients, we suggest dietary calcium and/or calcium supplementation to increase bone mineral density.	Weak for	Reviewed, New-added
		32.	In post-menopausal patients without osteoporosis, there is insufficient evidence to recommend for or against Vitamin D3 for primary improvement of decreased bone mineral density or fracture.	Neither for nor against	Reviewed, New-added
		33.	For primary prevention of fracture in post-menopausal patients without documentation of osteoporosis or osteopenia, there is insufficient evidence to recommend for or against bisphosphonates.	Neither for nor against	Reviewed, New-added
		34.	In post-menopausal patients with osteopenia, there is insufficient evidence to recommend for or against raloxifene to reduce fracture risk and improve bone mineral density.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Management of Menopausal Symptoms (cont.)	Overweight and Obesity Management	35.	In post-menopausal women with overweight or obesity, we suggest a calorie-restricted diet for weight management, depending on patient characteristics and preferences (see the VA/DOD CPG for the Management of Overweight and Obesity in Adults).	Weak for	Reviewed, New-added
		36.	We suggest exercise for peri-menopausal or post-menopausal women for reduction of weight and/or waist circumference (e.g., aerobic activity, resistance training, or combination).	Weak for	Reviewed, New-added
		37.	In post-menopausal women, there is insufficient evidence to recommend for or against any of the following dietary approaches for weight management: • High protein • Intermittent fasting • Low fat • Mediterranean • Paleolithic • Vegan (with soy supplementation)	Neither for nor against	Reviewed, New-added
Safety	Cardiovascular Disease Risk	38.	For the primary prevention of post-menopausal cerebrovascular events, we recommend against oral estrogen or estrogen and progestogen.	Strong against	Reviewed, New-added
		39.	For primary prevention of post-menopausal cardiovascular disease (CVD), we suggest against oral menopausal hormone therapy, whether it is estrogen alone or with progestogen, and whether it is low-dose or conventional dose.	Weak against	Reviewed, New-added
		40.	For women less than 60 years old and less than 10 years from the onset of menopause with established cardiovascular disease (CVD) and significant vasomotor symptoms, we suggest consideration of systemic estrogen-containing therapies based on the lack of evidence for increased cerebrovascular and cardiovascular morbidity and mortality.	Weak for	Reviewed, New-added
	Breast Cancer Risk	41.	For hormone-positive breast cancer survivors, we suggest against the use of systemic hormone therapy.	Weak against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Safety (cont.)	Breast Cancer Risk (cont.)	42.	For women with an intact uterus taking systemic estrogen, there is insufficient evidence to recommend for or against any one of the following progestogen formulations over another to modify breast cancer risk: • Oral Drospirenone • Transdermal, or 52 mg levonorgestrel intrauterine device (LNG IUD) • Oral micronized progesterone • Oral medroxyprogesterone acetate (MPA) • Oral or transdermal Norethindrone acetate	Neither for nor against	Reviewed, New-added
		43.	When selecting a progestogen in women with an intact uterus taking systemic estrogen, there is insufficient evidence to recommend any one of the following progestogen formulations over another for protection against endometrial cancer: • Oral Drospirenone • Transdermal, or 52 mg levonorgestrel intrauterine device (LNG IUD) • Oral micronized progesterone • Oral medroxyprogesterone acetate (MPA) • Oral or transdermal Norethindrone acetate	Neither for nor against	Reviewed, New-added

[a] For additional information, please refer to Determining Recommendation Strength and Direction
[b] For additional information, please refer to Recommendation Categorization

A. Diagnosis of Perimenopause and Menopause

Recommendation

1. We suggest against using laboratory testing (e.g., anti-müllerian hormone and/or follicle-stimulating hormone) for the diagnosis of menopause and perimenopause.
   (Weak against | Reviewed, New-added)

Discussion

Menopause is a natural biological process marking the end of a woman's reproductive years, defined as 12 consecutive months of amenorrhea in the absence of other pathological or physiological causes. Perimenopause refers to the transitional period preceding menopause, which can last several years and extends until 12 months after the final menstrual period.

Menopause remains a clinical diagnosis. The Work Group evaluated the available literature to assess the utility of laboratory markers in the diagnosis of menopause and perimenopause and found that laboratory testing adds limited clinical value and may, in fact, be misleading.

The SWAN(87) and the Stages of Reproductive Aging Workshop (STRAW)(12) have demonstrated significant day-to-day variability in hormone levels, particularly estradiol, progesterone, and FSH, during perimenopause. This variability makes it unreliable to use a single laboratory value for diagnosis or treatment decisions. Furthermore, hormone levels do not consistently correlate with the severity or presence of menopausal symptoms, and results that appear "normal" may provide false reassurance to patients experiencing significant symptoms.

Estradiol and Progesterone

During perimenopause, estradiol and progesterone levels fluctuate widely, often varying significantly from day to day. These fluctuations result in overlapping hormone levels between perimenopausal and reproductive-aged women, further complicating the interpretation of laboratory results.

FSH

FSH levels also vary considerably during the perimenopausal transition. While persistently elevated FSH levels over a four-month period have been proposed as a diagnostic tool for menopause (88), this approach is impractical in clinical settings and does not account for the influence of exogenous factors such as hormonal contraceptives or hormone therapy, which can significantly alter FSH levels.

Serum anti-Müllerian hormone (AMH)

AMH is produced by the granulosa cells of growing ovarian follicles and reflects the remaining ovarian follicular reserve. As ovarian function declines, AMH levels decrease, with a steep decline observed prior to the final menstrual period, making it a marker of interest in the diagnosis of menopause.

The Work Group evaluated the literature and identified one SR exploring the use of AMH as a diagnostic tool for menopause. The review did not support its clinical utility, and the overall

strength of evidence was rated as Very low. Notably, age was found to be a better predictor of menopause than any laboratory value. One included study examined AMH levels in women already clinically diagnosed with menopause and found AMH to be low, an unsurprising finding that does not support its diagnostic utility. Additional limitations of the available studies included the inclusion of non-randomized trials, reliance on non-standardized questionnaires, and variability in the assays used to measure AMH.

While the predictive value of AMH for menopause increases with age, particularly in late reproductive-aged women as the time to menopause shortens, its utility as a standalone diagnostic test remains unproven.

In recent years, marketing campaigns, cash-based practices, and social media have increasingly encouraged women to request hormone testing as part of their evaluation for menopausal symptoms. As a result, many patients present to their providers requesting hormone laboratory testing. However, the evidence clearly demonstrates that routine hormone testing has limited clinical value in the diagnosis and management of menopause and can be counterproductive. When laboratory results appear "normal" in the setting of significant menopausal symptoms, this disconnect can lead to confusion, delayed treatment, and false reassurance for both patients and providers.

The Work Group finds that laboratory testing, including FSH, AMH, estradiol, and progesterone, carries potential harm when used routinely for the diagnosis of menopause or perimenopause. Such testing is costly, subject to significant variability, and does not provide clinically relevant or actionable information in most cases.

Based on the available evidence, including the SWAN and STRAW data, the Work Group recommends against the routine use of laboratory testing for the diagnosis of menopause and perimenopause. Providers should prioritize a symptom-based, patient-centered approach to diagnosis and management, relying on clinical judgment rather than laboratory values.

Laboratory testing may have utility in the following select clinical scenarios: women who have undergone hysterectomy, desire fertility preservation, suspected POI, or have undergone chemotherapy or other gonadotoxic treatments. Outside of these specific circumstances, laboratory testing should not replace clinical judgment or patient-centered care.

The Work Group systematically reviewed evidence related to this recommendation.(89) It is categorized as Reviewed, New-added. The Work Group’s confidence in the quality of the evidence was Very low. The body of evidence had limitations, primarily due to the inclusion of non-RCTs, non-standardized questionnaires, and the use of different assays to measure AMH. The benefits of checking labs in attempts to diagnose menopause or perimenopause were outweighed by the inaccuracies and cost. Patient values and preferences varied largely because some patients would likely want to know the approximate time until menopause and may not care about cost. Thus, the Work Group decided upon a *Weak against* recommendation.

B. Management of Menopausal Symptoms

a. Vasomotor Symptoms

Introduction to 2026 Menopause Recommendations for the Management of Vasomotor Symptoms

MHT is widely recognized as the most effective treatment for vasomotor symptoms (VMS). Professional guidelines from the American College of Obstetricians and Gynecologists (ACOG), The Menopause Society, and the Endocrine Society consistently recommend hormone therapy as the first-line treatment for menopausal VMS. However, not all patients are candidates for MHT due to medical contraindications, coexisting conditions, comorbidities, or personal preference.

The Work Group acknowledges the importance of providing individualized care and offering a range of treatment options. In developing these guidelines, we reviewed the evidence to balance the benefits and risks of MHT while also addressing the need for effective non-hormonal alternatives. Additionally, the use of MHT is nuanced and must be tailored to the patient's specific circumstances, including the presence of a uterus, underlying medical conditions, and concurrent medications. "Bioidentical hormones" are products with the same chemical structure as endogenous hormones. In the U.S., several Food and Drug Administration (FDA)-approved bioidentical hormone products are available; these undergo rigorous evaluation for safety, efficacy, and quality. In contrast, compounded bioidentical hormones are custom-made formulations that are not FDA-tested or approved. These products are unregulated, and there is no reliable evidence supporting their safety or effectiveness. The literature search for this CPG did not identify any studies evaluating compounded bioidentical hormone therapy.

Consistent with recommendations from ACOG, the Menopause Society, and the Endocrine Society, the Work Group supports using FDA-approved products whenever they are available, rather than compounded alternatives.(90-92)

Additional considerations include access to knowledgeable and affordable care. Within the VA and DOD healthcare systems, variability in provider training, experience, and comfort with menopause management may affect patients' ability to receive timely, evidence-based counseling and treatment. Ensuring equitable access to appropriately trained clinicians is therefore an important implementation consideration that may influence patient preferences, treatment uptake, and overall outcomes.

This section outlines evidence-based recommendations for the management of vasomotor symptoms, including both hormonal and non-hormonal approaches, to ensure comprehensive and patient-centered care.

Recommendation

2. In women with a uterus, we recommend systemic estradiol and progesterone for the treatment of vasomotor symptoms.
   (Strong for | Reviewed, New-added)

Discussion

MHT is an effective treatment for VMS, with efficacy demonstrated across multiple RCTs. However, the safety profile of MHT varies by formulation, underscoring the importance of selecting regimens that provide symptom relief while maintaining uterine safety in women with an intact uterus. The 2026 VA/DOD Menopause Work Group's strong recommendation for estradiol and progesterone for the effective treatment of VMS in women with an intact uterus is supported by high-quality RCTs. The strength of evidence was Moderate based on Lobo et al. 2018 (93) and Black et al. 2021 (94). In the REPLENISH Trial(94), estradiol/progesterone significantly reduced both the frequency and severity of moderate to severe VMS compared to placebo. The 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone doses met all efficacy endpoints, with improvements observed as early as week 4 and sustained through week 12. These findings were further detailed by Lobo et al. 2018 (93), which demonstrated statistically significant reductions in VMS frequency and severity with the same dose combinations compared to placebo, confirming both consistency and dose responsiveness of effect. The REPLENISH Trial demonstrated that the incidence of endometrial hyperplasia was 0% at 12 months. Systemic estradiol options now available include an oral pill, transdermal gel, spray, or patch, and a systemic vaginal ring.

The benefits of therapy outweigh the potential harms/burden. The benefits of this treatment include a reduction in the frequency, severity, and unpredictability of VMS, including hot flashes and night sweats, which are among the most disruptive manifestations of menopause. Treatment is also associated with improvements in sleep quality, likely mediated through more effective control of nocturnal VMS. In addition to improving VMS, many patients report reductions in musculoskeletal discomfort, including arthralgias, which may contribute to overall functional improvement and quality of life. Additional benefits may include improvements in skin integrity, such as decreased dryness and pruritus, and preservation of bone mineral density (BMD), reflecting the known physiologic effects of estrogen on skeletal health. While short-term safety has been demonstrated in RCTs, long-term risks and uncommon adverse outcomes remain incompletely characterized, necessitating individualized risk-benefit assessment and ongoing surveillance. Importantly, in women with an intact uterus, the inclusion of progesterone (either daily or taken 12 days per month) provides adequate endometrial protection, mitigating the risk of estrogen-induced endometrial hyperplasia and supporting the safety of combined therapy in this population. When selecting systemic estrogen therapy, clinicians should consider the route of administration as part of individualized shared decision-making. Although the recommendation applies to systemic estradiol regardless of route, nonoral formulations (e.g., transdermal patches, gels, and sprays) may be associated with a lower risk of venous thromboembolism than oral estrogen. In addition, palpitations are a commonly reported symptom during menopause transition and may improve with treatment of vasomotor symptoms in some women; however, the current literature does not demonstrate a direct causal relationship between systemic estradiol therapy and palpitations. Patients presenting with new-onset, persistent, or concerning palpitations should undergo an appropriate cardiovascular evaluation to exclude underlying cardiac or other medical conditions.

The Work Group also reviewed evidence related to systemic conjugated equine estrogen (CEE), both alone and in combination with MPA. While CEE-based regimens have demonstrated benefit

for VMS, the evidence identified important safety concerns. Compared with placebo, CEE+MPA was associated with an increased risk of stroke and invasive breast cancer, while CEE alone was associated with an increased risk of stroke, ovarian cancer, and ovarian cancer mortality. These safety signals were observed in large randomized controlled trials and long-term follow-up analyses and were considered clinically meaningful despite relatively low absolute event rates.(95-97) Consequently, when systemic menopausal hormone therapy is indicated for the treatment of VMS, the Work Group favored estradiol-based therapy combined with micronized progesterone because the evidence demonstrated effective symptom relief, adequate endometrial protection in women with a uterus, and a more favorable overall benefit-risk profile than CEE-based regiments.(95-97)

Patient values and preferences regarding the use of combined estradiol and progesterone for the treatment of VMS in women with a uterus largely varied and play an important role in shared decision-making. Many patients experiencing moderate to severe symptoms prioritize timely access to MHT to achieve symptom relief and improve quality of life. Conversely, some patients prefer to avoid pharmacologic therapy altogether, reflecting concerns about medication use, perceived risks, or a desire for nonpharmacologic approaches. Preferences regarding (e.g., oral versus transdermal) differ among patients and are often influenced by convenience, prior experiences, and perceptions of safety. Risk tolerance varies substantially, particularly with respect to concerns about cancer, cardiovascular events, or other serious adverse outcomes. A subset of patients expresses a preference for “bioidentical” hormone therapies, defined as plant-derived hormones that are structurally identical to endogenous human hormones. However, there is considerable misinformation surrounding the term “bioidentical,” and clinicians should provide patient education to clarify that FDA-approved bioidentical hormone therapies are distinct from compounded bioidentical hormone preparations. There are FDA-approved formulations of MHT that are bioidentical. FDA-approved products should be preferred over compounded formulations when available.

The Work Group systematically reviewed evidence related to the use of combined estradiol and progesterone for the treatment of VMS, including data from RCTs such as the REPLENISH trial and associated analyses reported by Lobo et al. 2018 (93) and Black et al. 2021 (94) identified through the systematic evidence review. Therefore, it is categorized as Reviewed, New-added. Several studies included in the evidence review were conducted outside the United States and evaluated formulations that are not FDA-approved or commercially available in the U.S. The Work Group’s confidence in the quality of evidence was Moderate. The body of evidence had some limitations, including limited long-term follow-up and low event rates for rare but serious adverse outcomes, which reduced precision for estimating uncommon harms despite adequate sample size for efficacy outcomes.(93,94) The benefits of recommending estradiol and progesterone for effective treatment of VMS in women with a uterus outweigh the potential harm, which were generally infrequent and mild to moderate in severity in the reviewed trials. Patient values and preferences varied greatly; many patients prioritize effective symptom relief and quality of life improvement, while others express concern regarding hormone therapy risks or prefer nonhormonal options. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

3. In women with a uterus, we suggest the use of conjugated estrogen with bazedoxifene for the treatment of vasomotor symptoms.
   (Weak for | Reviewed, New-added)

Discussion

The VA/DOD Menopause Work Group endorses a weak suggestion for the use of systemic estrogen with bazedoxifene (BZA) for the treatment of VMS in women with a uterus. The strength of evidence is rated very low due to significant methodological limitations in the evidence base rather than an absence of treatment effect. In pooled analyses, BZA 20 mg/CE 0.45 mg reduced the daily number of hot flashes compared with placebo (standard mean difference [SMD] -5.89; 95% CI: -8.67 to -3.11), while BZA 20 mg/CE 0.625 mg demonstrated a similar or greater reduction (SMD -6.36; 95% CI: -9.36 to -3.36). Both doses also reduced moderate to severe hot flashes compared with placebo, although estimates demonstrated very high statistical heterogeneity (high I^2 ~98-98%). I^2 is a statistical measure used in meta-analyses to quantify how much the study results differ from each other. A high I^2 indicates that a large proportion of the variability in the study results is due to real differences between studies rather than chance.(98,99) The pooled studies (98,99) had considerable differences such as populations, estrogen doses, outcome definitions, and follow-up durations, which limited confidence in the precision and generalizability of effect estimates. In a SR of seven RCTs, Bi et al. 2022 (99) found that CE/BZA significantly reduced the daily number of hot flashes, including moderate to severe hot flashes, compared to placebo. Both approved doses (BZA 20 mg with CE 0.45 mg or 0.625 mg) demonstrated benefit, with greater symptom reduction observed at the higher estrogen dose. These findings are supported by individual Selective Estrogens, Menopause, and Response to Therapy (SMART) trials summarized by Archer et al. 2016 (98), which demonstrated significant reductions in VMS frequency and severity with CE/BZA compared to placebo, while showing no increase in endometrial hyperplasia. The benefits of therapy slightly outweigh harms/burden. While the therapeutic benefits observed were comparable to those described in the narrative supporting Recommendation 2, adverse events were infrequent across reviewed trials. Serious cardiovascular and cerebrovascular events were rare, though the low number of events limited statistical precision and precluded robust estimation of long-term risk. Consequently, despite an overall acceptable short-term safety profile, uncertainty remains regarding uncommon and longer-term adverse outcomes.

Patient values and preferences regarding the use of systemic estrogen with BZA for the treatment of VMS in women with a uterus are generally similar to those described for Recommendation 2, particularly the desire for effective symptom relief, avoidance of progestins, and consideration of individual risk tolerance. An important distinguishing factor for this therapy is the limited modes of delivery, as estrogen-bazedoxifene is currently available only in specific oral formulations, which may not align with the preferences of patients who favor transdermal or alternative routes of administration. Other implementation considerations are also largely similar to Recommendation 2 but include additional system-level constraints. In particular, availability within the VA and DOD pharmacy formularies may be limited, which can affect access, continuity of care, and patient willingness to initiate or continue therapy. As with other menopausal hormone therapies, variability

in provider familiarity with this formulation may further influence uptake and shared decision-making. From a subgroup perspective, estrogen with BZA may be particularly attractive to women with a uterus who have concerns about breast cancer risk or who prefer to avoid progestogen exposure, given BZA's role as an estrogen antagonist in breast and endometrial tissue. Additionally, this regimen may be valued by patients with osteopenia or concerns about bone health, as systemic estrogen and selective estrogen receptor modulators confer known skeletal benefits. These considerations highlight the importance of shared decision-making that incorporates symptom burden, comorbidities, access considerations, and patient preferences when selecting therapy.

The Work Group systematically reviewed evidence related to the suggested use of systemic CE/BZA for the treatment of VMS in women with a uterus, including an SR of seven RCTs (99) and the SMART trial (98) evidence summarized in the Menopause CPG Evidence Synthesis Report. Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low, because the body of evidence had very serious study limitations and serious inconsistency with very high heterogeneity (I^2 ~98-98%) in pooled VMS analyses. The benefits of CE/BZA slightly outweigh the potential harm because CE/BZA reduced the daily number of hot flushes and moderate-to-severe hot flashes compared with placebo and was associated with improvements in sleep-related outcomes and menopause-related quality of life (MENQOL).(99) Potential harms were infrequently reported in the VMS evidence synthesis, and key serious outcomes were not consistently reported, limiting precision and long-term risk estimation. Patient values and preferences varied largely as patients prioritize meaningful VMS relief and a progestin-free option, while others may be risk-averse given uncertainty in uncommon or longer-term adverse outcomes. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

4. In women without a uterus, we suggest the use of systemic estradiol monotherapy for the treatment of vasomotor symptoms.
   (Weak for | Reviewed, New-added)

Discussion

The VA/DOD Menopause Work Group endorses a *Weak for* recommendation for the use of systemic estradiol as an effective treatment for VMS in women without a uterus. For women without a uterus, the suggested use of systemic estradiol for moderate to severe VMS is primarily driven by the consistent evidence of symptom benefits versus placebo across multiple RCTs. Additionally, the ability to use estrogen without needing endometrial protection removes the uterus-specific risk that otherwise necessitates adding a progestogen. Gaudard et al. 2016,(100) provides a synthesized RCT evidence that showed estradiol (including transdermal patch and other systemic routes) reduces VMS frequency and intensity compared with placebo. For transdermal patch studies, pooled estimates showed a moderate to large reduction in hot flash frequency (e.g., SMD -0.68 [95% CI -0.83 to -0.53]) and a clinically meaningful reduction in hot flash intensity (e.g., MD -19.94 points on a 0-100 Visual Analogue Scale (VAS) [95% CI -24.86 to -15.02]). However, confidence is limited because pooled analyses demonstrated

inconsistency/heterogeneity (e.g., I^2 67% for patch frequency; I^2 54% for patch intensity) and the underlying trials were downgraded for study limitations (risk of bias/poor reporting) and imprecision, resulting in a low strength of evidence conclusion in the SR. The benefits of therapy outweigh harms/burden. While the therapeutic benefits observed were comparable to those described in the narrative supporting Recommendation 2, Gaudard et al. 2016 (100) notes that evidence regarding uncommon and long-term adverse outcomes remains limited, resulting in ongoing uncertainty about these risks.

Patient values and preferences related to the suggested use of systemic estradiol as an effective treatment for VMS in women without a uterus are generally similar to those described for Recommendation 2, particularly the desire for meaningful symptom relief, improvement in quality of life, and individualized risk-benefit assessment. As estrogen-only therapy does not require endometrial protection in this population, some patients may value the simplicity of treatment and avoidance of additional medications. Preferences regarding route of administration vary and may influence acceptability and adherence. For example, transdermal estrogen patches may be affected by perspiration and can detach prematurely or cause local skin irritation, while systemic estrogen gels may be perceived as inconvenient or cumbersome to apply. Intranasal estrogen preparations, although an alternative systemic option, may be non-formulary within the VA/DOD healthcare system, potentially limiting access. Additional considerations include access to appropriately trained providers and variability in clinician knowledge and comfort with menopause management, which may affect patient counseling, treatment selection, and continuity of care. These system-level factors, combined with individual preferences for route, convenience, and risk tolerance, underscore the importance of shared decision-making when considering systemic estradiol for VMS in women without a uterus.

One consideration regarding estrogen monotherapy in women post-hysterectomy should be the co-occurring diagnosis of endometriosis. Although outside the scope of the evidence review, some evidence suggests that an estrogen + progestogen (E+P) regimen is preferable to an E-only regimen in these patients for the suppression of endometriosis.(101)

The Work Group systematically reviewed evidence related to the suggested use of systemic estradiol for the treatment of VMS in women without a uterus, including the SR by Gaudard et al. 2016,(100) 23 RCTs evaluating multiple systemic estradiol routes compared with placebo. Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low, because the body of evidence had limitations including risk-of-bias/study reporting concerns, statistical heterogeneity in pooled estimates (e.g., patch trials with I^2 in the moderate-to-high range), and limited evidence for uncommon/long-term harms (e.g., no available data in this review for outcomes such as myocardial infarction [MI], stroke, or breast cancer). The benefits of systemic estradiol outweighed the potential harms for many appropriately selected patients because estradiol was associated with clinically meaningful reductions in hot-flush frequency and intensity versus placebo. In women without a uterus, estradiol can be used without a progestogen, avoiding the endometrial hyperplasia concern that applies to unopposed estrogen in women with a uterus.(100) Potential harms included a higher likelihood of treatment-emergent adverse events compared with placebo and ongoing uncertainty regarding rare or long-term adverse outcomes due to limited data. Patient values and preferences varied largely as many patients prioritize effective VMS relief and improved function, while others may prefer

nonhormonal options or place higher weight on uncertainty regarding uncommon or long-term harms. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

5. For the treatment of vasomotor symptoms of menopause, we suggest against the use of progestogen monotherapy.
   (Weak against | Reviewed, New-added)

Discussion

The VA/DOD evidence synthesis identified two RCTs evaluating micronized progesterone monotherapy versus placebo for VMS treatment, and both found no statistically significant difference in key VMS outcomes (frequency, score, and/or intensity). In Beinert et al. 2024 (102) reductions in moderate to severe VMS frequency were large in both progesterone and placebo groups, and differences between groups were not statistically significant, with interpretation limited by premature trial discontinuation, small sample size, and inadequate statistical power. In Prior et al. 2023,(103) the primary endpoint (3rd month VMS score) did not differ by therapy, and the trial also reported that variability and uncertainty limited confidence in the estimate. Due to the small body of evidence (only two RCTs), underpowered studies, and imprecise estimates, the VA/DOD Menopause Work Group rated the strength of evidence as low. The benefits and harms/burden are balanced. Potential benefits include mood stabilization with reductions in anxiety, decreased endometriosis-related pain, and uterine protection. Potential harms include ongoing vasomotor symptoms due to uncertain efficacy, irregular or breakthrough bleeding, breast pain, and additional adverse effects that remain insufficiently characterized.

Patient values and preferences relevant to the determination of a weak against recommendation of progestogen monotherapy for the treatment of VMS are generally consistent with those described for Recommendation 2, with important additional considerations. In particular, patients with contraindications to estrogen therapy may express interest in progestogen monotherapy as a potential alternative, despite the current uncertainty regarding its effectiveness for VMS. Other considerations include the relative ease of access and affordability of progestogen formulations, which may influence patient interest and utilization, especially in resource-constrained settings. However, access to appropriately trained providers remains a key factor, as counseling on uncertain benefits, potential harms, and alternative treatment options requires clinical expertise. Variability in provider knowledge and experience with menopause management may further affect patient understanding, shared decision-making, and consistency of care.

The Work Group systematically reviewed evidence related to micronized progesterone monotherapy for the treatment of VMS, including two RCTs: Prior et al. 2023 (103) and Beinert et al. 2024 (102), as summarized in the Menopause CPG evidence synthesis. Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low, because the body of evidence has important limitations, including a small number of trials, limited sample sizes, large placebo response, and imprecision/insufficient power to detect clinically meaningful differences (including premature trial discontinuation and underpowering in Effects of Progesterone on Vasomotor Symptoms in Postmenopausal Women [PROGEST]).(102) Benefits and harms are balanced. Potential harms were generally infrequent

but not absent; reported adverse effects included vaginal bleeding and breast pain in PROGEST. Patient values and preferences varied largely as some patients may prioritize potential sleep-related or perceived symptom benefits, while others prefer therapies with clearer efficacy and may be unwilling to accept uncertain benefit alongside possible bleeding or other adverse effects. Thus, the Work Group decided upon a *Weak against* recommendation for progestogen monotherapy for VMS.

Recommendation

6. We recommend cognitive behavioral therapy (CBT) to manage vasomotor symptoms related to menopause.
   (Strong for | Reviewed, New-added)

Discussion

CBT is a brief, structured psychotherapy that helps people strengthen adaptive thought patterns and behaviors. Some versions of CBT specifically target menopausal symptoms, including depression, anxiety, vasomotor symptoms, sleep disturbances, sexual dysfunction, and cognitive changes.

Women going through the menopausal transition often experience adverse physical changes such as hot flashes (vasomotor symptoms) that can significantly impact sleep, functioning, and overall quality of life. CBT has been proposed as a low-risk treatment for menopausal symptoms to be used as a stand-alone or an adjunct to hormonal therapy. Unlike hormone therapy, it works by changing the perception and response to symptoms rather than eliminating the physical occurrence itself.

This recommendation is based on one SR (104), and one RCT.(105) The RCT studied Cognitive Behavioral Therapy for Menopause (CBT-Meno), a manualized treatment specifically adapted to address menopausal symptoms. The SR covered a variety of CBT protocols, including but not limited to CBT-Meno. As there were no direct comparison studies of CBT-Meno and other forms of CBT, the recommendation encompasses all forms of CBT. There is evidence of improvement in coping with vasomotor symptoms related to menopause with CBT over waitlist control group. CBT reduces the bother, stress, and negative effects of hot flashes.

The overall strength of evidence is Moderate. The SR, which included 8 RCTs (104), was determined to be of fair quality based on risk of bias. Approximately 90% of the RCTs were judged to be at high risk of performance bias. The RCTs (105) overall quality of the included study is fair, as the study was not powered for beliefs outcomes.

The benefits of CBT outweigh the potential harm. Treatment burden, or the time and effort the patient would need to invest in CBT, would be the only potential harm.

Patient values and preferences regarding CBT for menopausal symptoms showed a large variation. While some patients value nonpharmacologic interventions, others prefer pharmacologic options. Some participants cited challenges with access to CBT for menopausal symptoms. Focus group participants disliked care fragmentation, and CBT integrates treatment of multiple menopausal symptoms in one intervention.

Even though CBT is considered an acceptable treatment by providers, the limited availability of CBT therapy for menopause within the VA/DOD may be a limiting factor in offering this treatment modality to patients.

The Work Group systematically reviewed evidence related to this recommendation in Ye et al. 2022 (104) and Donegan et al. 2022 (105). Therefore, it is categorized as Reviewed, New-Added. The Work Group's confidence in the quality of the evidence was Moderate. The benefits of CBT to treat or manage vasomotor symptoms related to menopause outweigh the potential harm, which only includes the treatment burden. Patient values and preferences varied largely, because overall, participants valued nonpharmacological interventions for the management of their menopausal symptoms but cited challenges with access and effectiveness. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

7. We suggest elinzanetant or fezolinetant for vasomotor symptoms in menopausal women. **(Weak for | Reviewed, New-added)**

Discussion

Elinzanetant and fezolinetant are newer non-hormonal agents that act as antagonists at neurokinin receptors in the hypothalamus (fezolinetant at NK3 receptors and elinzanetant at both NK1 and NK3 receptors). Evidence supporting fezolinetant was from an SR by Ismail et al. 2025 (106) which included 8 articles and 7 RCTs that compared this NK3 antagonist to placebo and found a beneficial effect across all critical outcomes. In particular, patients from 2 RCTs (n=570) had a mean reduction of 2.5 hot flashes per day and a modest improvement in severity of VMS compared to placebo at 12 weeks. Evidence in the study by Ismail et al. 2025 (106) was considered poor due to 4 of the included studies being found to be at high risk of bias due to issues with deviations from intended interventions and randomization; a majority of the studies included in the meta-analysis were at high risk of bias.(106) Similarly, benefit from elinzanetant vs. placebo was also found in an SR by Sobral et al. 2025 (107) which included 3 RCTS (OASIS 1 (108), OASIS 2 (108), SWITCH 1 (109)). Elinzanetant also showed a reduction in the frequency and severity of VMS. There was no statistically significant difference in adverse events with either fezolinetant or elinzanetant compared to placebo, but the follow-up only extended to 12 weeks. While not statistically significant, elinzanetant had more adverse events than placebo, most commonly headache, fatigue, somnolence, and diarrhea. While not considered in the strength of the recommendation, both agents had evidence supporting a beneficial effect on sleep.

For this recommendation, the Work Group only reviewed evidence to support the effectiveness of these agents. Literature to show the comparative effectiveness of these agents to MHT was not reviewed, and a recommendation was not made on this topic.

While evidence supporting the use of elinzanetant was deemed to be high, our enthusiasm was dampened due to the limited follow-up data available to date from which to judge long-term safety (FDA approval occurred in October 2025). Support for the use of fezolinetant was limited by the quality of existing data and the limited data to define potential long-term risks. Fezolinetant has potential for drug-drug interactions due to interaction via the cytochrome P450 family 1 subfamily,

a member 2 (CYP1A2) pathway (primary metabolism mechanism), and is thus contraindicated in those on CYP1A2 inhibitors. Potential drug interactions with elinzanetant may occur via the cytochrome P450 family 3 subfamily A member 4 (CYP3A4) pathway. Concerns for liver toxicity with fezolinetant require measuring liver enzymes prior to initiation, monthly for the first 3 months, then at 6 months and 9 months, or anytime patients have symptoms of acute liver injury, while elinzanetant requires baseline liver enzymes assessment. This additional testing could be burdensome to some patients, and the existence of baseline cirrhosis or markedly elevated liver enzymes is a contraindication to use. While these agents are likely appealing for those who cannot or who are not interested in the use of hormone-based therapy, the lack of long-term use and familiarity may make some patients less enthusiastic. Access to these agents may be limited due to cost, formulary restrictions, and availability. See Recommendation 11 for comparative effectiveness with hormone-based treatments.

While not within the scope of our review due to publication date and thus not considered in the strength of our recommendation, we are aware of a more recently published phase 3 trial comparing Elinzanetant for 52 weeks vs placebo for 12 weeks followed by elinzanetant for 40 weeks among women on endocrine therapy for a history of hormone receptor (HR)-positive breast cancer or its prevention (n=474; randomization at 2:1 ratio).(110) This trial reported a beneficial effect on VMS frequency and severity. During the first 12 weeks, similar proportions of participants in each arm experienced adverse events, most commonly headache, fatigue, and somnolence. Of note, this trial offered participants the opportunity to continue the intervention for an additional 2 years, and safety data will be collected on these individuals, though not available at the time of this publication.

The Work Group systematically reviewed evidence related to this recommendation from an SR by Sobral et al. 2025 (107) with 3 RCTs comparing elinzanetant to placebo and an SR by Ismail et al. 2025 (106) with 7 RCTs comparing fezolinetant to placebo. Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was High for elinzanetant and Low for fezolinetant. The body of evidence had some limitations, including concerns for risk of bias related to randomization, deviations from assigned interventions, and measurement of outcomes among RCTs evaluating fezolinetant.(106) A limitation in the body of evidence for elinzanetant was the limited follow-up in the currently published data. The benefits of neurokinin receptor antagonists included reductions in VMS frequency, VMS severity, and improvements in sleep, which were felt to outweigh the potential harms primarily due to the possible risk of liver injury. Patient values and preferences are suspected to be varied due to concerns about newer agents and the frequency of required lab monitoring, while for others, these agents offer a more effective non-hormonal treatment alternative for patients with significant symptoms and for whom hormone-based therapies are not a good option. Thus, the Work Group decided upon a *Weak for* recommendation for both agents.

Recommendation

8. There is insufficient evidence to favor fezolinetant or elinzanetant versus hormone therapy for vasomotor symptoms.
   (Neither for nor against | Reviewed, New-added)

Discussion

The Work Group reviewed evidence evaluating the comparative effectiveness of fezolinetant and hormone therapy for menopausal vasomotor symptoms. Evidence informing this recommendation consists of a single network meta-analysis including 26 RCTs, with only indirect comparisons between fezolinetant and various hormone therapy regimens. No direct head-to-head trials comparing NK3 receptor antagonists with hormone therapy were identified in the evidence base.(111) At the time of this publication, there were no studies comparing elinzanetant to hormone therapy.

Across indirect comparisons, no consistent differences were observed between fezolinetant 45 mg and most hormone therapy regimens for reduction in vasomotor symptom frequency or severity over short-term follow-up (approximately 12 weeks).(111) Notably, the only hormone therapy regimens that showed significantly greater efficacy than fezolinetant on any outcome (tibolone 2.5 mg and CE 0.625 mg/BZA 20 mg) are not available at those doses in the U.S.(111) Fezolinetant 45 mg was significantly more effective than non-hormone therapies, including paroxetine 7.5 mg, desvenlafaxine 50-200 mg, and gabapentin extended release (ER) 1800 mg, in reducing VMS frequency.(111) Comparative safety outcomes between fezolinetant and hormone therapy, including cardiovascular events, venous thromboembolism, and malignancy, were not reported in this evidence base.(111)

The certainty of evidence was downgraded to Very low due to very serious indirectness inherent to network comparisons, heterogeneity of hormone therapy regimens, and short duration of follow-up.(111)

Patient values and preferences were judged to vary somewhat. Some patients prefer nonhormonal therapies to avoid hormone exposure or due to contraindications, while others prioritize treatments with longer clinical experience and established efficacy, such as hormone therapy.

While not reviewed by the CPG evidence synthesis, MHT is generally recognized as the most effective treatment for vasomotor symptoms and recognizes nonhormonal agents, including NK1 and NK3-receptor antagonists, as alternatives when hormone therapy is contraindicated or declined.(90,112-114) This guidance reflects usual clinical practice but did not influence the strength of this recommendation.

Feasibility and access considerations include potential formulary restrictions and cost barriers for newer agents such as fezolinetant and elinzanetant within VA and DOD systems. Equity considerations include variability in access to specialty menopause care and laboratory monitoring requirements for fezolinetant.

The Work Group systematically reviewed evidence related to this recommendation, including a network meta-analysis with indirect comparisons between fezolinetant and/or elinzanetant and hormone therapy identified through the systematic evidence review.(111) Therefore, this recommendation is categorized as Reviewed, New-added. The Work Group's confidence in the

quality of the evidence was Very low. The body of evidence had limitations, including very serious indirectness, heterogeneity of comparators, and short follow-up duration.(111) The benefits and harms of fezolinetant relative to hormone therapy were balanced, and comparative safety outcomes were not available. Patient values and preferences varied somewhat, with some patients preferring nonhormonal therapies and others prioritizing established hormone therapy. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

9. We suggest selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin as non-hormonal options for menopausal vasomotor symptoms based on patient characteristics and preferences.
   (Weak for | Reviewed, New-added)

10. For menopausal vasomotor symptoms, in patients without a contraindication to hormone therapy, we suggest hormone therapy over either venlafaxine or gabapentin.
    (Weak for | Reviewed, New-added)

Discussion

Patients unable to receive or who are not interested in hormone-based treatments for menopausal VMS, may be considered for alternative pharmacologic options that demonstrate efficacy in treating VMS.

Serotonin reuptake inhibitors (SSRIs)/Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Evidence supporting this recommendation came primarily from a large 2015 Agency for Healthcare Research and Quality (AHRQ) SR by Grant et al which included data from 13 RCTs (n=4037) for this group of agents when compared to placebo.(115) As a group of pharmacologic agents, there was a small to moderate beneficial impact on vasomotor symptoms (SMD -0.35; 95% CI: -0.46 to -0.24) with duration measured up to 52 weeks.(115) Harms for this group of therapeutic agents were not well reported by studies included in this SR, but included adverse effects on metabolism, skin, and the nervous system, among others. Of note, numerous antidepressant agents were included within this analysis at dosages commonly used in practice for mood disorders (e.g., desvenlafaxine, escitalopram, fluoxetine) but were considered as a group rather than evaluated individually. Moreover, there was no evidence comparing individual agents in this category against each other; selection should be based on clinical judgement and consideration of individual patient characteristics.

For women who are unable to or not interested in taking hormone therapy, or for those with other indications for antidepressants, medications such as SSRIs/SNRIs may be an appealing, widely available, and low-cost option that could reduce polypharmacy and address multiple co-occurring symptoms simultaneously. Specifically, anxiety and/or depressive symptoms are commonly observed in perimenopause and menopause, and women Veterans have a high prevalence of mental health conditions such as major depressive disorder and post-traumatic stress disorder, which can be effectively treated with SSRI/SNRIs. Thus, if a patient has bothersome vasomotor symptoms and depression, selecting an SSRI or SNRI rather than the addition of MHT may allow

for treatment of both conditions with a single medication. Other considerations factored into this recommendation were known side effects of this class of therapeutic agents from extensive clinical experience with these agents and other literature. Specifically, these agents are known to have potential adverse effects, including weight gain and sexual dysfunction, which can vary across agents and which are often already concerns for peri- and post-menopausal women. We note that some of these agents, such as paroxetine, may be effective for VMS at lower dosages than are typically associated with unwelcome side effects like weight gain. Some women may be disinterested or unwilling to take medications well-known as mental health medications or may be reluctant to add an additional medication for a relatively small potential benefit. However, for example, if a patient has bothersome vasomotor symptoms and depression, selecting an SSRI or SNRI may allow for treatment of both conditions with a single medication. Of note, many conditions common among the Veteran and active duty Service member populations were excluded from trials contributing evidence to this recommendation, including those with preexisting conditions such as fibromyalgia, CVD, or prior use of similar agents.

Importantly, for women with a history of breast cancer on tamoxifen, the choice of agent should be undertaken carefully due to the potential effect of cytochrome P450 2D6 (CYP2D6) and the unintentional reduction in effective levels of tamoxifen (specifically caution with agents such as paroxetine and fluoxetine) (See Sidebar 3).

Venlafaxine

With respect to the use of SSRI/SNRI compared to MHT, we found evidence specific to estradiol versus venlafaxine from the pooled analyses from the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) trials. In these studies, estradiol was associated with greater improvement in menopause-related quality of life and vasomotor symptom outcomes compared with venlafaxine after 8 weeks. For total menopause-related quality of life measured by the MENQOL scale, estradiol showed a mean decrease of 0.3 to 0.5 points relative to control, while venlafaxine did not show significant improvement in total MENQOL scores in the pooled analysis.(116) While venlafaxine did demonstrate significant improvement in the psychosocial subscale, it did not significantly improve the vasomotor subscale, where estradiol showed the largest improvement at -1.2 points.(116) Notably, a reduction of ≥0.9 points in total MENQOL score and ≥2.0 points in the vasomotor domain are considered clinically meaningful thresholds; thus, while estradiol's improvements were statistically significant, they approached but did not clearly exceed these thresholds for clinically perceptible benefit. Comparative serious harms were not reported, and the trials were not designed to assess long-term safety outcomes. We found no other studies evaluating the use of other SSRIs/SNRIs vs MHT.

Gabapentin

Gabapentin is a gabapentinoid non-hormonal pharmacologic agent studied for the treatment of vasomotor symptoms in peri- and postmenopausal women that holds appeal for use among women who are not candidates, do not desire, or are intolerant to hormone-based treatments. Evidence for this recommendation came from 2 SRs with a total of 11 fair quality RCTs in one Shan et al. 2020 (117) and 5 fair quality RCTs in the other Grant et al. 2015.(115) In one analysis

with 447 patients across 2 RCTs, Shan et al reported a small beneficial effect on VMS frequency with an estimated reduction of 1.43 fewer daily hot flashes (95% CI: -2.56 to -0.29) after 24 weeks of treatment. Data at 12 weeks (7 RCTs, n=1913) found a larger reduction in hot flashes with 2.77 fewer daily hot flashes (95% CI: 4.29 to 1.24). A moderate to large effect on VMS severity was also reported, as well as a small to moderate benefit on sleep disturbances.

Enthusiasm for the use of gabapentin in this setting is dampened by the fact that the dosages of gabapentin studied ranged from 900 mg to 3000 mg daily, which often lead to intolerable side effects including somnolence, dizziness, peripheral edema, and cognitive impairment, which may be particularly unappealing in menopausal women experiencing brain fog and difficulty concentrating. In addition, gabapentin can be associated with weight gain, respiratory depression, and the potential for misuse. For women who are already taking gabapentin for other reasons (e.g., pain) or who have significant issues with sleep, leveraging its beneficial effects on vasomotor symptoms may be appealing without adding MHT and thereby limiting polypharmacy. In addition, it is a low-cost and readily available treatment option. Of note, this medication requires dose adjustment for renal impairment.

Of note, the Shan et al. 2020 (117) review also included comparisons between gabapentin and estrogen and antidepressants based on limited data from two small RCTs. Across these trials (total n=129; follow-up 4-12 weeks), estrogen therapy was more effective than gabapentin in reducing hot flash frequency (mean difference [MD] 2.26 per day; 95% CI: 0.15 to 4.38).(117) No statistically significant difference was found for hot flash severity between gabapentin and estrogen (SMD 0.29; 95% CI: -0.06 to 0.64), though estimates favored estrogen. Gabapentin improved symptoms compared with baseline but was consistently inferior to estrogen therapy.(117) Comparative adverse events, including discontinuation due to adverse effects and fatigue, were not clearly different between groups; however, estimates were imprecise due to small sample sizes. They reported some evidence that estrogen was more effective at reducing VMS frequency than gabapentin, and there was no statistically significant difference between gabapentin and antidepressants on VMS severity.

While not included in the CPG evidence review, professional society guidance from ACOG, the Menopause Society, and the Endocrine Society consistently identifies hormone therapy as the most effective treatment for menopausal vasomotor symptoms and recommends neurokinin receptor antagonists, SSRIs, SNRIs, and gabapentin as alternative options when hormone therapy is contraindicated or declined.(90,112-114) This guidance reflects usual clinical practice but did not influence the strength of this recommendation. While other guidelines discuss oxybutynin, the WG decided that the risks outweigh the benefits.

The Work Group systematically reviewed evidence related to Recommendation 9 from the fair quality AHRQ SR by Grant et al. 2015 (115) which included 13 RCTs and a total of 4037 participants, and Shan et al. 2020 (117). Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including concerns about allocation concealment, maintenance of comparable groups, and unclear use of intention-to-treat analysis. The benefits of antidepressants or gabapentin on vasomotor symptoms were felt to slightly outweigh the potential harm (e.g.,

weight gain, sexual dysfunction, or sedation with gabapentin. Findings from the patient focus groups suggested that some patients may be reluctant to use antidepressant medications because of the perceived stigma of these medications initially intended for treatment of other conditions, such as mental health diagnoses and potential unwillingness to add pill burden for relatively small benefit; however, they may be helpful for women with other indications for this class of agent and/or those who cannot or prefer to avoid hormone-based therapy. Thus, the Work Group decided upon a *Weak for* recommendation.

The Work Group systematically reviewed evidence related to Recommendation 10, including pooled analyses of RCTs comparing estradiol with venlafaxine and an SR and meta-analysis comparing gabapentin with estrogen therapy identified through the systematic evidence review.(116,117) Therefore, this recommendation is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low, with limitations including short follow-up duration, small sample sizes, and imprecision. The benefits of hormone therapy, reflected by greater reductions in VMS, slightly outweighed the potential harms, which were incompletely characterized in the available evidence. Patient values and preferences varied somewhat, with some patients prioritizing maximal symptom relief and others preferring nonhormonal options. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

11. There is insufficient evidence to recommend for or against the following complementary and integrative health (CIH) interventions for menopausal vasomotor symptoms:
    - Acupressure
    - Acupuncture
    - Tai Chi/Qigong
    - Yoga

    (Neither for nor against | Reviewed, New-added)

Discussion

Patients in the VA/DOD Menopause Patient Focus Group expressed the importance of holistic approaches in the treatment of menopause. The Menopause Work Group therefore felt it was important to review evidence related to CIH interventions for the management of menopausal VMS. The evidence review examined several studies on acupressure, acupuncture, qigong, yoga, and slow-paced guided respirations. Overall, the literature-based review was characterized as mostly very low strength of evidence by small sample sizes, high attrition rates, and lack of blinding.

Acupressure

Acupressure is an approach based on principles of traditional Chinese medicine that involves applying manual pressure to specific points on the body, similar to acupuncture, but without needles. This type of treatment stimulates the body's natural health abilities and restores balance to the body's energy pathways. The evidence review looked at two RCTs that showed possible improvement in menopausal VMS with acupressure compared to sham or no treatment.(118,119)

However, these studies were of poor quality due to a low number of participants, selective reporting, high attrition, and lack of blinding. Additionally, the studies utilized different acupressure point locations (auricular and extremities) and commercialized acupressure patch vs. provider-applied pressure.

Acupuncture

Acupuncture is a technique that involves inserting very thin metal needles into the skin at precise points on the body to balance energy channels, with the aim of restoring and maintaining health. The placement of insertion is chosen based on a complex network of lines of energy known as meridians. Acupuncture is a mainstay of traditional Chinese medicine, which has been practiced for thousands of years. Acupuncture stimulates the central nervous system, signaling the body to release various substances, including endorphins, immune system cells, neurotransmitters, and neurohormones. Acupuncture may also influence involuntary central nervous system functions, such as blood pressure, blood flow, and body temperature regulation. The evidence review looked at one RCT and one umbrella review, which included three SRs and four RCTs. These studies found possible improvements in the severity and frequency of VMS with acupuncture compared to waitlist, but not compared to sham.(120-122) The overall strength of evidence of the umbrella SR was fair.

Tai Chi/Qigong

Qigong comprises a diverse set of practices that coordinate body, breath, and mind. Practices include moving and still meditation, massage, chanting, sound meditation, and non-contact treatments performed in a broad array of body postures. The evidence review examined one RCT, which reported improvement in overall score on the Menopause Rating Scale (MRS) for qigong compared to no treatment. (123) This study was of poor quality due to low number of participants with no ethnic diversity, selective reporting, high attrition, and lack of blinding.

Yoga

Yoga is a mind-body practice that combines physical postures, breathing techniques, and meditation to promote overall well-being and self-discovery. There are many different styles of yoga, each with its unique focus and approach. More than just physical exercise, yoga is considered a holistic practice that encourages self-awareness, personal growth, and a deeper connection with oneself. The evidence review looked at an SR with three RCTs (124) comparing yoga interventions to waitlist, which found no difference in hot flash severity for yoga versus control, and an RCT (119) comparing laughter yoga intervention to no treatment, which found improvement in VMS for intervention compared to control. The strength of evidence of these trials was very low due to small sample sizes, selective reporting, high attrition, and lack of blinding.

Overall, the harms of some of these CIH interventions are minimal, including mild soreness, bruising, lightheadedness, tingling or heightened sensitivity, emotional release, headache or fatigue, with the most significant harms being infection and needle-related injuries. This results in a balance of possible benefits vs. harm.

Additionally, the Work Group searched for evidence on aromatherapy, biofeedback, chiropractic interventions, hypnosis, low-frequency sound-wave therapy, meditation, mindfulness, pharmacopuncture, and tai chi, which resulted in either no RCTs or SRs for the defined patient population or single RCTs that were of significantly poor quality.

Patients in the VA/DOD Menopause Patient Focus Group expressed the importance of holistic approaches in the treatment of menopause and may be willing to try CIH options with minimal evidence for improvement of their VMS of menopause given the minimal risks and harms of these interventions.

CIH interventions within the VA and DOD may have limited availability of trained providers, and access may be limited, especially in rural areas.

Underlying conditions, such as physical limitations, which are common in Veterans and active duty personnel, as well as cost to the healthcare system or patients should be taken into consideration.

The Work Group systematically reviewed evidence related to this recommendation, including three SRs and seven RCTs described in 11 publications.(118-124) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations including small sample sizes, selective reporting, high attrition, and lack of blinding. The benefits of CIH interventions showed some improvement in menopausal VMS and were balanced with some of the potential minimal harms including mild soreness, bruising, lightheadedness, tingling or heightened sensitivity, emotional release, headache or fatigue, with the most significant harms being infection and needle-related injuries. Patient values and preferences have some variation as some patients may be interested in trying holistic approaches including CIH options. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

12. There is insufficient evidence to recommend for or against the following supplements and nutraceuticals for menopausal vasomotor symptoms:
    - Amino Acids
    - Black Cohosh
    - Danggwijagyaksan
    - Fenugreek
    - Giant Fennel
    - Ginseng
    - Kamishoyosan
    - Maca
    - Magnesium
    - Melatonin
    - Probiotics
    - Red Clover
    - Resveratrol + Equol

- Salvia
- Soy Supplements
- Succinate

(Neither for nor against | Reviewed, New-added)

Discussion

A wide variety of supplements and nutraceuticals are available without prescription and are marketed directly to consumers as being useful for the management of menopausal VMS. In the United States, these supplements are not regulated by the FDA as long as they do not claim disease benefit. The evidence review examined 23 studies, including seven SRs and 16 RCTs, with methodological quality ranging from good to poor based on USPSTF criteria. 10 of the 16 RCTs were rated poor quality due to, in many cases, incomplete outcome data, and no clear reporting on allocation concealment nor assessor blinding, and selective reporting. All SRs and all but one RCT compared the supplement of interest to placebo; one RCT compared the supplement to no intervention. Black cohosh, ginseng and soy had the most developed evidence bases in terms of number of SRs and included RCTs, whereas many of the other supplements were examined in smaller SRs and RCTs. Overall, the literature base reviewed was characterized by small sample size, shorter duration of follow-up (often weeks rather than months or years), and a multitude of different scales and approaches to measure change in VMS, with a majority of studies conducted outside the United States. Studies frequently lacked consistency in supplement and nutraceutical formulation, format, and dosing, and included limited to no information regarding possible harms with use. Many of the supplements studied were proprietary blends that may not be available in the US, limiting applicability to VA and DOD populations. Furthermore, a majority of reviewed studies excluded individuals with many common comorbidities including CVD and mental health diagnoses, again limiting applicability to VA and DOD populations. Vasomotor symptom outcome measures varied widely across studies and few, if any, minimal clinically indicated difference thresholds were defined, making assessments of impact on VMS difficult. Additionally, a substantial number of studies included in the SRs and others reviewed individually were funded, at least in part, by manufacturers of the supplement under consideration (see, for example, Lee et al. 2022 (125) [ginseng]; Wilfried et al. 2021(126) [salvia]; and Kanadys et al. 2021(127) [red clover]). For these reasons, the Work Group determined that there was insufficient evidence to recommend for or against the reviewed supplements and nutraceuticals. We provide brief overviews of the literature for those supplements that are commonly available in the US as well as those whose evidence base was more substantial. We also include a brief summary statement on the remainder of the supplements reviewed.

Black Cohosh

Black cohosh is widely marketed as an over-the-counter supplement for menopausal VMS.(128) Although the literature reviewed did not directly address the mechanism of action, prior literature suggests possible interactions with serotonergic, dopaminergic, and adrenergic pathways.(129,130) The evidence review looked at one SR (131), which included 15 RCTs, and a much smaller RCT of only 50 participants in each arm.(132) While the SR had Moderate strength of evidence, and both the SR and stand-alone RCT showed an effect favoring intervention, included studies used varying doses of black cohosh, differing measures of change in VMS, and

contained scant information about harms. Importantly, case reports outside of the identified literature review described significant liver adverse events.

Ginseng

Ginseng (Panax ginseng) is a root native to the Far East that has been used in traditional medicine systems for various symptoms. The Work Group reviewed one SR and one RCT examining ginseng interventions on menopausal VMS; the overall strength of evidence was low. The SR (125) included three RCTs with 258 patients in the intervention arms and 257 patients in the placebo arm, with 12 weeks of follow-up. The meta-analysis of these three RCTs found a reduction in menopausal symptom score and in hot flashes in the ginseng intervention group. However, the RCTs were conducted outside the US, with varying formats and dosing of ginseng and minimal details of harms. Hyun et al. 2022 (133), a small RCT looking exclusively at the safety of using ginseng along with a combination herbal extract of multiple other herbs, found no serious adverse events over 12 weeks, but this formulation was distinct from the ginseng interventions reviewed in the SR.

Soy

Soybeans are a common part of dietary patterns in many cultures, particularly those in East Asia. Soy protein and soy isoflavones may have health effects. Soy isoflavones in particular have been marketed in various formats as menopausal symptom remedies.(134) The Work Group reviewed two SRs regarding soy supplementation. While the strength of evidence of the included two SRs was rated Moderate, the effect on VMS was mixed. In the Gençtürk et al. 2024 (135) SR, a meta-analysis of five RCTs found no difference in VMS between the intervention and placebo arms. A subset of four of the RCTs included in the SR by Kang et al. 2022 (136) noted an improvement in the overall Kupperman index score (a menopause symptom severity scale developed in the US in the 1950s).(137) However, a meta-analysis of six RCTs within the same SR found no difference in hot flash scores vs placebo.(136) Studies included in the reviewed SRs had widely varying doses of soy supplementation, used a multitude of soy formulations (for example, encapsulated soy, fermented soy, soy drinks, all of different dosing and strengths), and had minimal mentions of possible harms.(135,136)

Resveratrol + Equol

Resveratrol (polyphenolic phytoestrogen) + equol (end product of daidzein, a major soy isoflavone) is a nutraceutical combination marketed over the counter for menopause VMS. The Work Group reviewed one RCT (n=60) where participants took a combined soy + additional isoflavones plus resveratrol and equol proprietary blend (138) and a second pilot non-blinded efficacy study (139) of a different Italian proprietary blend that contained resveratrol + equol. While the RCT suggested a reduction in VMS greater than the reduction experienced in the placebo group, as did the pilot study, both studies were Low quality, had limited outcomes data details, and both utilized blends that contained other compounds that could themselves be the drivers of the VMS effects seen. No harms were noted. Strength of evidence was Low, and balance of harms and benefits could not be well ascertained.

Red Clover

Red clover is a member of the legume family that contains isoflavone compounds and in various cultures has been used for menstrual and menopausal concerns.(140) The Work Group reviewed two SRs. One, Kanadys et al. 2021 (127), examined the impact of red clover on VMS, and findings were mixed, with a decrease in hot flush daily frequency in seven RCTs looking at postmenopausal women, but without a significant difference on the same measure in the meta-analysis of three RCTs that included both perimenopausal and postmenopausal women. In the same SR, there was improvement in the Kupperman Index in three RCTs, but not in the Greene Climacteric Scale (GCS) in six RCTs. A second SR (141) looked at significant adverse events across four RCTs and found no difference between intervention and placebo groups, and no serious adverse events (SAEs) were reported with Red Clover use. Many of the RCTs included were funded by makers of red clover supplements.

Magnesium

Magnesium is a mineral relevant for multiple body functions, and various formulations of magnesium supplements are available over the counter marketed for various conditions including sleep disturbance. The Work Group reviewed one RCT (142) focusing on magnesium oxide for VMS in postmenopausal women with a history of breast cancer. The strength of evidence was rated Low. The small RCT (n=184) tested 800 mg and 1200 mg doses and assessed both hot flush frequency and severity at eight weeks for both doses and found no benefit in reduction of VMS vs placebo, with a noted side effect of diarrhea in the intervention group.

Melatonin

Melatonin is a hormone produced in the brain that can impact circadian rhythms.(143) The Work Group reviewed one SR (144) that attempted to review RCTs looking at melatonin supplementation of varying doses, both alone and combined with other supplements, as an intervention for menopausal VMS and sleep quality. One RCT from Iran contributed 75% of the participants to the meta-analysis of four RCTs. No difference between melatonin and placebo was noted for both VMS and sleep quality, and the overall strength of evidence was rated very Low.

Other Supplements

The Work Group reviewed literature on a number of other supplements including: amino acids (145), giant fennel (146), fenugreek (147), maca (148,149), probiotics (150), salvia (126), succinate (amberen) (151,152) as well as two herbal mixtures, danggwijagyaksan (153), and kamishoyosan (154). The literature base for these supplements was characterized by small sample size, Low quality for reasons including unclear recruitment, baseline differences, no reference to allocation concealment and unclear blinding, as well as a lack of clarity on the use of intention-to-treat analyses. Several of these small studies were sponsored by a manufacturer of the supplement under study. The literature included minimal information on harm, although in some instances, including giant fennel (bleeding,(155)) and kamoyishan (liver damage,(156)) there are case reports of adverse effects associated with use.

For all supplements reviewed, the strength of evidence reviewed by the Work Group was rated overall Very low due to multiple factors including limited generalizability due to use of varied formulations, doses and proprietary mixes, study populations from outside the U.S. with very strict eligibility criteria not applicable to U.S. populations, limited to no data on study concealment methodology, and almost no reporting on adverse events. Most studies demonstrated unclear to no benefit. For all of these reasons, the Work Group decided on an insufficient to recommend for or against recommendation.

The Work Group did consider other factors in addition to the literature reviewed. Patients in the VA and DOD focus group did note a preference for holistic management of menopause. For some patients, this may include a desire to use herbal or nutraceutical interventions to manage VMS. Other patients may be reluctant to use unregulated supplements with unclear benefits and harms. Clinicians counseling patients on menopausal symptoms and available treatments should thoughtfully solicit patient concerns and share information regarding the evidence basis for available menopause therapies. This discussion should include the robust evidence basis for prescription menopause pharmacotherapies and the paucity of high-quality evidence for the benefits and harms of most nutraceuticals. Furthermore, supplements may not be a covered benefit and may result in substantial out-of-pocket cost to patients. Additionally, many of the supplements reviewed were studied in other countries and may not be commercially available in the US, limiting applicability to VA and DOD populations. Many of the reviewed studies also included stringent exclusion criteria, excluding patients with many common comorbidities, including mental health diagnoses, which further limits the generalizability to VA and DOD populations. These factors contributed to the Work Group's decision for insufficient evidence to recommend for or against the reviewed supplements.

The Work Group systematically reviewed evidence related to this recommendation, including 23 studies (125-127,131-133,135,136,138,139,141,142,144-154), seven of which were SRs and 16 individual RCTs. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including small sample size and confounders in the analysis. Given the limitations of the evidence base, the Work Group was not able to effectively assess the balance of benefits and harms regarding the use of supplements for menopausal VMS and, in many cases, to ascertain a standard dose or formulation. Additionally, patient preferences for using such supplements with limited clarity on benefits and harms would also vary. Some patients seek out complementary and alternative treatment options for menopausal symptoms, and some may be interested in these supplements that are available over the counter and not FDA-regulated, despite the lack of quality evidence due to inconsistent dosing, outcome description, dosing, and study design. Other patients may be reluctant to consider unregulated supplements with unclear evidence basis, especially when other prescription therapeutic options with a well-established evidence base are available. For all of these reasons, the Work Group decided upon a *Neither for nor against* recommendation.

b. Sleep Symptoms

Recommendation

13. There is insufficient evidence to recommend for or against menopausal hormone therapy used solely for sleep symptoms.
(Neither for nor against | Reviewed, New-added)

Discussion

Sleep disturbance is one of the distinctive features of menopausal symptoms. Self-reported sleep problems are reported to increase by 2 to 3.5 times in women during the menopausal transition.(157) Sleep is essential for optimal health and functioning. Persistent sleep disturbances across menopause can negatively impact quality of life, including daytime functioning and productivity, and increase the risk for mental and physical health conditions.(158) The pathophysiology of menopause-related sleep disturbance appears to be complex. In particular, VMS such as hot flashes are known to adversely affect sleep quality and severe hot flashes are strongly associated with chronic insomnia in menopausal women.(159) Patients and providers are eager to find ways to improve sleep efficiency as long-term sleep disturbances in menopausal women are closely related to cardiovascular and metabolic disorders, as well as cognitive impairment.(157)

Overall, the evidence comparing MHT to placebo for improving sleep efficiency was limited to one SR containing five RCTs. The strength of evidence was Low. The evidence from the literature review found no difference in sleep efficiency measured by polysomnography. Sleep quality, assessed by subjective self-reported questionnaires, indicated improvement in the MHT group compared to the placebo group. Several MHTs were evaluated, including estrogen and estrogen-progestogen (157), as well as two of the more recently developed SERMs, raloxifene and BZA.(159) Additionally, a subgroup analysis favored MHT, in particular 17β-estradiol (E2) and CEE for estrogen as well as MP and MPA for progestogen. The results indicated that oral and transdermal regimens positively impacted sleep disturbance to some extent, and transdermal administration of both 17β-estradiol combined with MP for at least 6 months in menopausal women with sleep disturbance was more effective at improving sleep quality (important outcome). Future research priorities would benefit from more comparative effectiveness studies.

After discussing possible benefits in sleep quality but not efficiency (critical outcome) and how improvement in sleep quality can impact cardiovascular health as well as metabolic disorders, cognitive and immune function, the Work Group determined that the benefits and harms/burden were balanced. This determination was made after discussing usual harms for MHT, including but not limited to vaginal bleeding and breast tenderness.

In addition, patients with other indications for MHT, such as moderate to severe VMS, may wish to take MHT as it is associated with improvements in sleep quality, likely mediated through more effective control of nocturnal VMS. MHT may indirectly improve sleep in menopausal women when VMS are present, as a reduction in nocturnal hot flashes and night sweats can decrease nighttime awakening. See Recommendation 2 regarding MHT use for VMS.

Sleep disturbance during the menopausal transition is typically not an isolated symptom. Rather, it commonly occurs as part of a broader and more complex cluster of VMS associated with menopause. As such, sleep disturbance in this context is often secondary to, or exacerbated by, underlying VMS rather than representing a standalone sleep disorder. MHT may be beneficial for appropriately selected women, particularly where VMS are a primary driver of sleep disruption, by improving symptom control and thereby contributing to improved sleep quality.

Current practice guidelines recommend CBT as a low-risk treatment to manage VMS that can significantly impact sleep[1], functioning, and overall quality of life. See Recommendation 6 regarding CBT to manage VMS.

The Work Group recognizes that there is some variation in patient values and preferences. This includes patient willingness to take MHT without strong evidence to support benefits in sleep efficiency and also patient willingness to trial MHT due to potential side effects or personal beliefs. In terms of other implications, the Work Group looked at feasibility and resource use, including availability in VA/DOD formulary and cost.

The Work Group reviewed evidence related to this recommendation, and only two SRs that compared various MHTs to placebo for improving sleep symptoms due to menopause were identified. Pan et al. 2022 (157) was identified as the main source of evidence; however, it did not include the SERMs, so a second earlier network meta-analysis was solely reviewed to include the effects for the SERMs, BZA, and raloxifene (159) therefore there is insufficient evidence to recommend for or against the use of menopausal hormonal therapy solely for sleep symptoms.

The Work Group systematically reviewed evidence related to this recommendation.(157,159) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including small sample size and wide CIs.(157) The benefits of the use of MHT solely for sleep symptoms were balanced with the potential harms. Patient values and preferences varied somewhat because some patients may not be willing to take MHT without strong evidence to support the benefits in sleep efficiency and potential side effects or personal beliefs. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

c. Depressive and Anxiety Symptoms

Introduction to 2026 Menopause Recommendations for Depressive and Anxiety Symptoms

Perimenopause is a high-risk time for the development of depressive and anxiety symptoms. Compared to pre-menopause, women in perimenopause are about twice as likely to experience depressive symptoms, and symptoms are more severe on average.(160) The risk of new-onset anxiety symptoms or anxiety disorder increases.(87) Depression during perimenopause correlates with increased variability of estrogen, FSH, and luteinizing hormone (LH), but not with absolute

[1] See the VA/DOD Clinical Practice Guideline for the Management Chronic Insomnia Disorder and Obstructive Sleep Apnea. Available at: https://www.healthquality.va.gov/healthquality/guidelines/CD/insomnia/

levels.(161) Other influences on perimenopausal mental health include physical activity, chronic pain, comorbid medical illnesses, midlife stressors and role transitions, and social support.(162,163)

During perimenopause and menopause, physical and mental health conditions interact and need coordinated assessment and treatment. Depressive and anxiety symptoms, VMS, reduced physical activity, sleep disturbance, and sexual functioning influence one another.(164-167) Improvements in one domain can foster improvements in others.

Recommendation

14. We recommend cognitive behavioral therapy (CBT) to treat depressive and/or anxiety symptoms during perimenopause and menopause.
    (Strong for | Reviewed, New-added)

Discussion

CBT is a brief, structured psychotherapy that helps people strengthen adaptive thought patterns and behaviors. Some versions of CBT specifically target menopausal symptoms, including depression, anxiety, VMS, sleep disturbances, sexual dysfunction, and cognitive changes. Women going through the menopausal transition often experience adverse physical changes and mood disturbances such as anxiety and depressive symptoms that can significantly impact functioning and overall quality of life. CBT has been proposed as a low-risk treatment for menopausal symptoms to be used as a stand-alone or an adjunct to hormonal therapy.

This recommendation is based on one SR (104), and one RCT.(105) The RCT studied CBT-Meno, a manualized treatment specifically adapted to address menopausal symptoms. The SR covered a variety of CBT protocols, including but not limited to CBT-Meno. As there were no direct comparison studies of CBT-Meno and other forms of CBT, the recommendation encompasses all forms of CBT. There is evidence of improvement in menopause-related depressive and anxiety symptoms with CBT over a waitlist control group.

The overall strength of evidence is Moderate. The SR, which included eight RCTs (104), was determined to be of fair quality based on risk of bias. Approximately 90% of the RCTs were judged to be at high risk of performance bias. The quality of the included study(105) is fair, as the study was not powered for beliefs outcomes.

The benefits of CBT outweigh the potential harm. Treatment burden, or the time and effort the patient would need to invest in CBT, would be the only potential harm.

Patient values and preferences regarding CBT for menopausal symptoms showed a large variation. While some patients value nonpharmacologic interventions, others preferred pharmacologic options. Some participants cited challenges with access to CBT for menopausal symptoms. Focus group participants disliked care fragmentation, and CBT integrates treatment of multiple menopausal symptoms in one intervention.

Although CBT is considered an acceptable treatment by providers, limited availability of CBT therapy for menopause may be a limiting factor in offering this treatment modality to patients.

The Work Group systematically reviewed evidence related to this recommendation in Ye et al. 2022 (104) and Donegan et al. 2022.(105) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The benefits of CBT to treat depressive and/or anxiety symptoms related to menopause outweighed the potential harm, which only includes the treatment burden. Patient values and preferences varied largely, because overall, participants valued nonpharmacological interventions for the management of their menopausal symptoms but cited challenges with access. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

15. We recommend mindfulness-based stress reduction (MBSR) for menopause-related depressive and/or anxiety symptoms (See VA/DOD CPG for Major Depressive Disorder[1][MDD]).
    (Strong for | Reviewed, New-added)

Discussion

MBSR is a structured psychoeducational intervention using practices such as meditation, yoga, and body awareness in a systematic approach to reduce stress. The menopausal transition can manifest in a wide array of physical and psychological symptoms, collectively impacting a woman's overall well-being and quality of life. While hormone and other pharmacologic therapy can be used to address menopausal symptoms, many women are interested in non-pharmacologic therapy such as MBSR instead of or in conjunction with hormonal therapy. Mindfulness, specifically MBSR has been studied for efficacy in abating some menopausal symptoms. The evidence reviewed supports the use of MBSR in treating anxiety and depressive symptoms related to menopause. The theory behind MBSR suggests that stress is not solely a product of external circumstances but also arises from our internal responses to those circumstances, which may be impacted by the menopausal transition. Mindfulness may help women become more aware of their reaction to stimuli and temper their responses. It can help women acknowledge these experiences as temporary phenomena, reducing the tendency to ruminate or catastrophize. Unlike CBT, MBSR does not presently include a standardized menopause focused program.

This recommendation is based on a SR(104) and 2 RCTS.(168,169) There is evidence of improvement in menopause-related depressive and anxiety symptoms from in person group MBSR vs. waitlist.(104,168,169)

The overall strength of evidence is Moderate. The SR Ye et al. 2022(104) was determined to be of fair quality based on risk of bias. Approximately 90% of the RCTs were judged to be at high risk of performance bias. Of the RCTs, Gordon et al. 2021(169) had a good quality rating with consistent randomization and allocation concealment processes, Wong et al. 2018 (168) had a fair quality rating.

[1] See the VA/DOD Clinical Practice Guideline for the Management of Major Depressive Disorder. Available at: https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/mh/mdd/index.asp

The Work Group reviewed one other study by van Driel et al. 2019 (170), which only included a small sample size of post-oophorectomized patients. This was not used in the recommendation due to limitations of size and specificity of the subgroup population.

The benefits of MBSR outweigh the potential harm. Treatment burden, or the time and effort the patient would need to invest in the mindfulness program, would be the only potential harm.

Patient values and preferences regarding MBSR for menopausal symptoms showed a large variation. While some patients value non-pharmacologic interventions, others preferred pharmacologic options. Some participants cited challenges with access to MBSR for menopausal symptoms. Focus group participants were in favor of using a wide variety of CIH and lifestyle interventions for the management of menopausal symptoms. There was concern about being put on multiple pharmacotherapies that were not effective and valued non-pharmacologic intervention. However, others expressed concerns that non-hormonal or pharmacologic therapy may not be effective for their symptoms.

MBSR is considered to be an acceptable treatment by providers. Feasibility and equity could be a challenge, as the studies referenced had in-person sessions, not telehealth, and geographic barriers could be an issue. The number of MBSR therapy providers in the VA/DOD could be an additional limitation.

The Work Group systematically reviewed evidence related to this recommendation.(104,168,169) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The benefits outweighed the harms. Patient opinions had a large variation, as patients did express support for non-pharmacologic or hormonal therapies, especially in subgroup populations including those at higher risk for adverse side effects. However, some focus group participants felt that behavioral therapies may not be sufficient to treat "hormonal imbalance". Acceptance with providers was determined to be high, but availability may be limited. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

16. In perimenopausal women, we suggest menopausal hormone therapy to treat depressive symptoms, depending on patient characteristics and preferences (For patients with Major Depressive Disorder [MDD], see VA/DOD CPG for Major Depressive Disorder[1]).
    (Weak for | Reviewed, New-added)

Discussion

During perimenopause and menopause, as during other times of life, effective gold standard treatments for depression include antidepressant medications and psychotherapy (see VA/DOD CPG for MDD[1]). However, there are reasons to consider whether treatment of depressive symptoms with MHT is effective during perimenopause. Studies not included in this evidence review show that, compared to pre-menopause, the risk of depressive symptoms is significantly increased during perimenopause, but not during menopause.(160) During perimenopause,

[1] See the VA/DOD Clinical Practice Guideline for the Management of Major Depressive Disorder. Available at: https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/mh/mdd/index.asp

depressive symptoms have been found to be associated with increased variability of estradiol, rather than absolute levels of estradiol.(161) For these reasons, perimenopause is the relevant time frame to consider whether MHT could alleviate depressive symptoms. In addition, a bidirectional relationship has been found between depressive symptoms and VMS (167), suggesting that it would be clinically relevant to ascertain whether MHT could alleviate both of these frequently co-occurring symptoms.

This recommendation is based on a SR of 14 eligible RCTs (171) that included a subgroup analysis comparing the efficacy of MHT for depressive symptoms during perimenopause with its efficacy during menopause. The five included RCTs relevant to perimenopause found MHT in perimenopause was significantly superior to placebo for depressive symptoms. By contrast, the five included RCTs relevant to menopause found no difference between MHT and placebo during menopause.

The overall strength of evidence in this SR was Low. Concerns included small sample sizes of individual studies included in the SR, and risk of bias in some of the individual studies.

The Work Group reviewed one other SR that included data about MHT for depressive symptoms in perimenopausal and menopausal women.(172) That SR did not include a subgroup analysis of MHT's efficacy for depressive symptoms in perimenopause compared to menopause. Due to the absence of this crucial subgroup analysis, the Work Group did not directly incorporate the findings of this SR. The Work Group noted, however, that its findings were congruent with the recommendation, in that transdermal estradiol was found to be significantly more effective than placebo for depressive symptoms in perimenopausal women, but a significant difference was not found in menopausal women.

Depending on patient characteristics, the Work Group determined that the benefit of MHT for alleviation of depressive symptoms would exceed the harms. Although the studies reviewed did not address the harms of MHT, the Work Group considered potential harms of MHT known from other sources, such as risk of venous thromboembolism, other CVD, gall bladder disease, and breast cancer. Of note, this benefits/harms comparison only applies during perimenopause. If MHT were used solely for depressive symptoms in menopause, harms would exceed benefits because the reviewed evidence does not support benefits.

The SR by Tseng and colleagues (172), and one additional RCT (173), contained some data about the use of SERMs for depressive symptoms during perimenopause and menopause. Data were limited, and the strength of evidence was Very low. The Work Group determined that the evidence reviewed did not warrant any recommendation regarding the use of SERMs for depressive symptoms during perimenopause or menopause.

Focus group participants voiced that the effects of perimenopause and menopause on mental health were important. The Work Group determined that there would be some variation in patient values and preferences regarding the use of MHT for depressive symptoms. Some patients would prefer interventions with stronger evidence for efficacy, such as psychotherapy and/or antidepressants. However, some patients might prefer hormonal intervention as less stigmatizing than mental health interventions. In addition, patients with other indications for MHT may wish to reduce polypharmacy and integrate their care by seeing if MHT also alleviates their depressive symptoms.

There are clinically important subgroup considerations not fully addressed by the evidence reviewed. For example, available data do not adequately clarify whether MHT is best used to augment antidepressants, or whether it suffices as monotherapy. It is also not clear whether MHT is best used for subsyndromal depressive symptoms or whether it suffices for MDD. For those with MDD, interventions with robust evidence for efficacy, such as CBT or antidepressants, can be considered (see VA/DOD CPG for MDD[1]).

In summary, the Work Group systematically reviewed evidence related to this recommendation.(171) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, such as small sample size and potential risk of bias in some of the included individual studies. Depending on patient characteristics, the benefits of MHT (reduced depressive symptoms) outweigh the potential harm of adverse events. Patient values and preferences vary somewhat, because some patients might prefer better-studied options while others might prefer hormonal interventions to mental health interventions, and/or might prefer to reduce polypharmacy if they are using MHT for other indications. Thus, the Work Group decided on a *Weak for* recommendation.

Recommendation

17. For depressive symptoms during perimenopause or menopause, we suggest exercise (e.g., mind-body exercise, aerobic activity, or combination).
    (Weak for | Reviewed, New-added)

Discussion

We suggest exercise for improving depression based on one SR (174) with pairwise meta-analysis with Low strength of evidence. Outcomes were compiled from 22 RCTs comprising 1,564 participants, where overall exercise versus control significantly improved depression, subgroup analyses supported these findings, and network meta-analysis showed specific types of exercise were more effective for reducing depression: mind-body exercise (MBE), aerobic exercise (AE), and multicomponent exercise (ME). In descending order (MBE, AE, ME), each performed better than control.

For assessing the efficacy of exercise interventions on depression, the pairwise meta-analysis by Han et al. 2024 (174) demonstrated a clinically significant positive effect on depression in postmenopausal women (SMD -0.71, 95% CI: -0.94 to 0.48, p<0.001). Subgroup analyses showed that exercise significantly reduced depression levels in postmenopausal women even with differing durations of exercise (<six months, >six months), age (<60 years, >60 years), and health status (healthy, with depressive symptoms or other conditions), but the effect size varied by group. In particular, short-term interventions were more effective than long-term interventions (data not shown). Those with depressive symptoms achieved more health benefits (SMD -0.95, 95% CI: -1.44 to -0.45; I^2 78%). Moreover, those in both early post-menopause (n=7, SMD -0.70,

[1] See the VA/DOD Clinical Practice Guideline for the Management of Major Depressive Disorder. Available at: https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/mh/mdd/index.asp

95% CI: -1.24 to -0.16; I^2 85%) and late post-menopause (n=18, SMD -0.71, 95% CI: -0.97 to -0.45; I^2 75%) achieved similar benefits.

Within the same SR, a network meta-analysis was performed with 26 RCTs and 2,170 patients, showing no significant global or local inconsistency.(174) Pairwise comparisons of exercise outcomes revealed significantly reduced depression versus control for MBE (SMD -0.97, 95% CI: -1.28 to -0.67), AE (SMD -0.58, 95% CI: -0.88 to -0.27), and ME (SMD -0.57, 95% CI: -1.15 to -0.002). Thus, MBE and AE had the greatest benefits in reducing depression. In this SR/meta-analysis (174), MBE involved practicing a series of controlled movements and focusing on interactions among the brain, body, mind, and behavior, such as Tai Chi, yoga, qigong, Pilates, baduanjin, and dance. Separately, AE focused on improving cardiovascular fitness and included walking, running, swimming, or cycling.

Similar positive effects were seen for exercise on the secondary outcome of anxiety using 13 RCTs with 1,076 patients, and network meta-analyses (174) revealed similar findings of MBE and AE, each having a significant effect and improving anxiety levels.

The benefits of exercise outweigh harms by reducing depression symptoms directly, in addition to improving cardiovascular risk reduction through improved cardiometabolic risks, reduced or stable weight, improved musculoskeletal function, cognition, and sleep all allowing for overall health improvements through health behavior change (i.e., physical activity component of lifestyle change) and allowing for improved military readiness among active duty personnel and reduction of chronic health risks among Veterans. Moreover, for Veterans, exercise programs have the potential to increase social connections among mid-life adults. The major burden, for active duty personnel as well as Veterans, is the time and consistency required for exercise to become a disciplined activity so that outcomes can be achieved and sustained.

The Work Group systematically reviewed evidence related to this recommendation.(174) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including small sample size in the individual RCTs of the SR/meta-analyses, confounders in the analysis, lack of any patients with common co-morbidities (i.e., overweight/obesity, diabetes, pre-diabetes), numerical information on drop-outs in each arm and reason for study attrition, and potential bias related to inadequate reporting of allocation concealment and blinding of assessors.(174) Benefits outweighed harms for participating in exercise for depression in this recommendation. The potential for adverse events was small (separate from potential injury) or not reported. Patient values include the desire to reduce depression symptoms or severity during the peri- and post-menopausal periods of life, as per findings from the focus group, and many women (across the age spectrum) struggle with both mood disorders and body image as well as physical body composition changes, difficulties with initiation, motivation, or adherence to physical activity regimens, and preferences to have non-pharmacologic interventions. These current findings provide evidence to advocate for lifestyle change through initiating physical activity with exercise programs during the peri- and post-menopause period. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

18. For depressive symptoms during perimenopause or menopause, there is insufficient evidence to recommend for or against the use of phytoestrogens (e.g., soy supplements). **(Neither for nor against | Reviewed, New-added)**

Discussion

A SR (175) included three RCTs of soy products for depressive symptoms during perimenopause and menopause. None of the included RCTs found a difference between soy products and placebo. The overall strength of evidence in this SR was Very low. Concerns included small sample sizes, inadequate descriptions of treatment allocation and concealment, lack of relevant subgroup analysis, and blinding. Each of the RCTs studied a different type of soy product, which further limits generalizability and clinical applicability.

The Work Group determined that the benefit of phytoestrogens, if more robust evidence were to demonstrate that phytoestrogens alleviate depressive symptoms, would outweigh the harms. The studies reviewed did not address the harms of phytoestrogens. The Work Group considered potential harms of phytoestrogens from other sources, though adverse effects are not well studied in general. Side effects appear to be minimal, but some patients may experience allergic reactions, and an increased risk of breast cancer has not been fully ruled out. (176)

The SR also included RCTs comparing hops, kava, and red clover to placebo for depressive symptoms during perimenopause and menopause. Data were limited, the strength of evidence was Low, and results were mixed. The Work Group determined that the evidence reviewed did not warrant any recommendation regarding the use of hops, kava, or red clover for depressive symptoms during perimenopause or menopause.

Focus group participants voiced that the effects of perimenopause and menopause on mental health were important. The Work Group determined that there would be some variation in patient values and preferences regarding the use of phytoestrogens for depressive symptoms. Some patients might prefer an intervention they perceive as natural. However, some patients would prefer interventions with stronger evidence for efficacy, such as psychotherapy and/or antidepressants. Similarly, clinicians may find it less acceptable to recommend an intervention with no substantive evidence for efficacy. There are also feasibility and equity concerns, since phytoestrogen supplements could incur out-of-pocket costs. In addition, since phytoestrogen supplements are not regulated by the FDA as medications, quality may vary.

There are clinically important subgroup considerations not addressed by the evidence reviewed. These include comparisons of the effect of phytoestrogens during perimenopause vs menopause, as monotherapy vs augmentation of antidepressants, and/or for subsyndromal depressive symptoms versus MDD. Also not addressed by the evidence reviewed is whether phytoestrogens ingested in food differ from phytoestrogen supplements in their effects on depressive symptoms.

In summary, the Work Group systematically reviewed evidence related to this recommendation.(175) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, such as small sample sizes, inadequate descriptions of treatment allocation and concealment, lack of relevant subgroup analysis, blinding, and use of different soy products.

Depending on patient characteristics, the benefit of phytoestrogens, if they were to alleviate depressive symptoms, would slightly outweigh the harms. Patient values and preferences vary somewhat because some patients might prefer an intervention they perceive as natural, while some patients would prefer interventions with stronger evidence for efficacy. Thus, the Work Group decided on a *Neither for nor against* recommendation.

d. Cognitive Symptoms and Dementia

Introduction to 2026 Menopause Recommendations for the Management of Cognitive Symptoms and Dementia

During the menopause transition, up to two-thirds of women will experience cognitive symptoms, including memory problems and/or attention and language deficits.(177) Women will often describe these symptoms as forgetfulness, difficulty with word finding, or a general sense of "brain fog." While these symptoms are typically transient during the menopause transition, they can be very distressing to individuals experiencing them.

Dementia is a disease of substantial public health significance, with recent studies demonstrating that women have an approximate 48% lifetime risk of developing dementia (compared to 35% for men).(178) While substantial biologic evidence supports the importance of estrogen to cognitive function and there is mounting observational evidence that MHT initiated in midlife (within five years of menopause), the role of menopausal hormone therapy in the management and/or prevention of cognitive symptoms and/or dementia has not yet been established.(179)

Recommendation

19. There is insufficient evidence to recommend for or against menopausal hormonal therapy (MHT) used solely for the prevention of dementia.
    (Neither for nor against | Reviewed, New-added)

Discussion

Our evidence review identified one SR (97) which examined the evidence addressing the impact of MHT, both estrogen-progestogen and estrogen monotherapy, on the prevention of dementia in perimenopausal and menopausal women. Most RCTs examined in this SR did not demonstrate a benefit to the prevention of dementia with the use of MHT (compared to placebo). One study, however, favored the use of estrogen monotherapy (over placebo) in the prevention of Alzheimer's or other dementia related mortality in the post intervention follow up (mean of 10.8 years from onset of therapy).

The overall lack of evidence supporting direct benefit in the prevention of dementia with the use of MHT, compared with the standard, potential harms of MHT initially led to the consideration of a suggestion against the use of MHT solely for the prevention of dementia. However, one study comparing 5,310 women using estrogen monotherapy to 5,429 women on placebo showed the potential benefit of estrogen monotherapy on dementia associated mortality when evaluated at a mean of 10.8 years after initiation of therapy (post-intervention follow-up, Hazard Ratio [HR]: 0.73; 95% CI: 0.58 to 0.92; p=0.008). For this reason, the final recommendation regarding MHT for the prevention of dementia is that there is insufficient evidence to recommend for or against MHT

solely for the prevention of dementia. Patients value taking medications that clearly demonstrate efficacy, and given the majority of evidence demonstrating no difference between MHT and placebo, would direct patients away from MHT solely for prevention of dementia. However, there is a paucity of other options for the prevention of dementia, and it has a significant impact on future quality of life. These factors, along with a single study demonstrating benefit to estrogen monotherapy, may lead patients to consider MHT if they have significant concerns regarding prevention of dementia related mortality.

The Work Group systematically reviewed evidence related to this recommendation (97). Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including studies with large CIs and one in which no events were recorded, impacting the precision of the results. The benefits of utilizing MHT for the prevention of dementia were balanced with the potential harms (standard harms) associated with this treatment. Patient values and preferences demonstrated some variation because patients desire to use therapies that clearly demonstrate efficacy; however, there are very limited options for prevention of dementia or dementia related mortality, which can have a significant impact on future quality of life. Thus, the Work Group decided upon a *Neither for nor against* recommendation for the use of MHT solely for the prevention of dementia.

Recommendation

20. We suggest against the use of menopausal hormonal therapy (MHT) solely for the treatment of cognitive symptoms in perimenopausal and menopausal women. **(Weak against | Reviewed, New-added)**

Discussion

Our evidence review identified three SRs ***(***97**,**180**,**181***)*** and one RCT (182) which examined the evidence addressing the impact of MHT, both estrogen-progesterone and estrogen monotherapy, on cognitive symptoms in perimenopausal and menopausal women. No RCTs examined in these SRs demonstrated a benefit to a variety of cognitive symptoms with the use of MHT (compared to placebo). Some studies revealed superior cognitive function in the placebo group compared to those study subjects using MHT; however, this finding was limited to those over the age of 60 years or greater than five years since the menopause transition.

Due to the lack of evidence supporting a direct benefit of MHT for cognitive symptoms, along with its potential harms, the Work Group was led to suggest against its use solely for cognitive symptoms. Patients value taking medications that clearly demonstrate efficacy, and so MHT would not be suggested in those patients solely seeking improvement in cognition. While no studies directly identified improved cognitive symptoms with the use of MHT, we recognize that there is likely a significant interplay between other menopausal/perimenopausal symptoms (such as VMS, mood changes, and sleep disturbances) and cognitive symptoms. To this end, women using menopausal hormone therapy for these symptoms may also note improvement in cognition, such as memory and attention, thereby further improving quality of life. Additionally, while CBT has been shown to improve cognitive symptoms associated with menopause, we are otherwise very limited in options for managing cognitive concerns in women experiencing the perimenopausal transition. So, while the evidence does not support utilizing MHT solely for the

management of cognitive symptoms in perimenopausal or menopausal women, ensuring co-occurring symptoms are addressed may indirectly improve cognitive concerns.

One important caveat to the findings regarding the impact of MHT on cognitive symptoms is related to those women over the age of 60 years or >five years since menopause. The RCTs that found superior cognitive function in the placebo cohort compared to those using MHT did so only in this subgroup (either through the population included in the study or in subgroup analysis). To that end, utilization of MHT in this older cohort of menopausal women should take into consideration the potential negative impact on cognitive symptoms.

Disruption of cognitive symptoms such as memory, attention, and word finding can have significant implications for military readiness, and inadequate treatment can negatively impact a Service member's ability to most effectively perform their duties. Service members managing other perimenopausal/menopausal symptoms with MHT may note an improvement in cognitive symptoms when other symptoms are addressed. Those solely experiencing menopause-related cognitive concerns, or those who have persistent menopause related cognitive concerns despite treatment of other menopausal symptoms (particularly if over the age of 60 years or >five years from menopause) should consider CBT as a means of addressing these concerns.

The Work Group systematically reviewed evidence related to this recommendation.*(*97*,*180-182*)*Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including several studies with small sample sizes and large CIs, impacting the precision of the evidence. The benefits of MHT solely for the management of cognitive symptoms did not outweigh the standard harms of menopausal hormone therapy, and in patients over the age of 60 years or greater than five years since menopause, there was an additional negative impact on cognitive symptoms with the use of MHT compared to placebo. Patient values and preferences demonstrated some variation because patients desire to use therapies that clearly demonstrate efficacy; however, there are very limited options for management of cognitive symptoms, and disruptions to cognition can have a significant impact on quality of life. Thus, the Work Group decided upon a *Weak against* recommendation for the use of MHT solely for the management of cognitive symptoms in perimenopausal and postmenopausal women.

e. Genitourinary Syndrome of Menopause (GSM) and/or Sexual Dysfunction Symptoms

Introduction to 2026 Menopause Recommendations for the Management of GSM and Sexual Dysfunction

For most midlife women (67%), sex remains moderately to extremely important, and they wish to remain sexually active.(183) However, this period is often marked by a decline in sexual function. Significant hormonal shifts occur alongside a higher incidence of comorbid conditions (such as obesity, hypertension, diabetes, anxiety, and depression), increased medication use, genital atrophy, and an evolving personal identity, all of which can impact sexuality. There is an increased prevalence of sexual dysfunction during and after the menopausal transition, with over half of women acknowledging at least one sexual concern, though these issues are often underreported to healthcare providers.(184,185) Despite these challenges, most women between the ages of 57

and 64 remain sexually active, with one-third engaging in partnered sexual activity at least annually.(186)

Sexual dysfunction is a complex condition affected by psychosocial, hormonal, physiological, and anatomic factors.(184,187) The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 classifies distressing sexual symptoms related to interest, arousal, orgasm, or pain into specific disorders, such as female sexual interest/arousal disorder (FSIAD), female orgasmic disorder, and genito-pelvic pain/penetration disorder, among others.(187,188)

Clinicians, especially OBGYNs, should routinely screen for sexual dysfunction during well-woman visits, with special attention paid to menopausal women.(184) The initial evaluation for sexual concerns involves a comprehensive history, including medication review and physical examination.(187) Laboratory evaluation is reserved for patients with a suspected medical etiology.(187) Hormone concentration studies (i.e., FSH, estradiol, testosterone) are not recommended in menopausal patients, especially as serum levels do not reliably correlate with sexual function in menopausal women.(184)

Treating sexual dysfunction involves a multidisciplinary approach that may include lifestyle interventions, counseling, sex therapy, physical therapy, and/or medication. Nonpharmacologic options are often favored as first-line therapy. Psychological interventions, including sexual skills training, CBT, mindfulness-based interventions, and couples therapy, are a mainstay of treatment and can address symptoms related to interest, arousal, pain, and/or orgasm. For patients with myofascial pain or pelvic organ prolapse, pelvic floor physical therapy is also an effective option.

While these treatment modalities can be employed in women of all ages, it is critical for clinicians to understand specific considerations for the treatment of sexual dysfunction in menopausal women. Pain during intercourse (dyspareunia) is a frequent complaint, often related to hypoestrogenic changes like tissue thinning, loss of vaginal elasticity, reduced lubrication, and musculoskeletal issues.(186,187) Repeated associations between intercourse and painful stimuli can cause avoidance, situational anxiety, diminished arousal, and increased musculoskeletal tension.(185,189) Therefore, treating dyspareunia associated with genitourinary syndrome of menopause should be a priority, either as first-line or alongside other interventions.

The following recommendations (Recommendations 21 and 26-27) review pharmacologic interventions for the treatment of sexual dysfunction during menopause. The broader treatment of genitourinary syndrome of menopause is discussed in Recommendations 22-25 and 28-29.

Recommendation

21. We suggest local (non-systemic) vaginal and/or systemic estrogen therapy, for the management of sexual dysfunction in menopause, especially related to vaginal dryness and dyspareunia.
    (Weak for | Reviewed, New-added)

Discussion

The evidence review identified three SRs (115,190,191) that indicate that both local vaginal and systemic estrogen improve various measurements of sexual function for postmenopausal women. Evidence from 30 RCTs across these reviews confirms that estrogen provides a benefit over

placebo for painful intercourse for as long as 260 weeks. The reviews also show that estrogen improves global measures of sexual function, sexual satisfaction, and lubrication for up to 52 weeks.

In contrast, the impact of estrogen therapy on measures less directly related to the genital tract was mixed. For instance, studies on arousal and orgasm did not demonstrate improvement compared to placebo.(190,191) Similarly, evidence from 18 RCTs across all three reviews showed mixed findings for the effect of estrogen on sexual desire and interest.(115,190,191)

Systemic estrogen therapy carries several potential harms (See Sidebar 2), whereas local estrogen has minimal systemic absorption and thus offers a superior safety profile regarding cancer and cardiovascular risk. While all three reviews evaluated local (vaginal) and systemic (oral or transdermal) estrogen, only Meziou et al. 2023 (191) directly compared the two routes' effects on sexual function, finding no significant difference. The study authors acknowledge that this analysis was limited by study design and was not suited for a head-to-head comparison. It is worth noting that local vaginal estrogen can be prescribed alone or co-prescribed with systemic estrogen. For isolated genitourinary concerns, local vaginal estrogen is the preferred first-line therapy given its lower risk profile. In patients with both genitourinary concerns and systemic menopausal symptoms, local vaginal estrogen is a safe, effective addition to systemic estrogen MHT.

The reviewed studies exhibited significant heterogeneity, making it difficult to determine the precise mechanism by which estrogen improves sexual function. The RCTs included a diverse population of postmenopausal women, including those with and without baseline genitourinary concerns. (190,191) Furthermore, the SRs collectively evaluated treatment with estrogen that was administered in a local and systemic fashion. (190,191) This complicates efforts to determine whether the intervention benefits all women with sexual concerns or primarily those with genitourinary issues.

In addition to estrogen, Lara et al. 2023 (190) and Meziou et al. 2023 (191) also assessed SERMs for the treatment of sexual dysfunction in menopause. As a class, there was not sufficient data to support their use. Assessing these medications as a group is challenging due to their distinct mechanisms and tissue-specific binding patterns. For example, evidence from three RCTs suggests ospemifene, an estrogen agonist in vaginal tissue, improves painful intercourse in women with GSM. However, other SERMs like BZA, a tissue-selective estrogen complex dosed with CE, and raloxifene, an estrogen antagonist in the vaginal tissue, have not demonstrated a consistent positive vaginal effect.

In postmenopausal women, hypoestrogenic changes within the genital tract directly impact sexual function. While systemic changes in gonadotropins, estrogens, and androgens throughout the menopausal transition may also impact sexual interest, these relationships are less well understood. Estrogen is the standard of care for treating GSM and its related sexual symptoms, as it locally improves lubrication, sensation, and blood flow. Addressing sexual health concerns is an important part of holistic menopause care, a priority identified by focus group members.

Local vaginal estrogen can be initiated for menopausal women of any age and continued indefinitely, whereas systemic therapy requires consideration of a patient's age, comorbidities, and time since menopause onset (see Module B). Practical factors, such as a patient's mobility and dexterity, may pose limitations to using certain vaginal estrogen formulations like creams, tablets, or rings. Local estrogen may serve as monotherapy or be combined with systemic estrogen when genitourinary symptoms are not adequately improved. Patients often prefer systemic therapy when it addresses multiple concerns simultaneously, such as vasomotor and sexual symptoms. However, some patients may prefer to avoid hormonal therapies and focus instead on psychological interventions and physical therapy.

Service members and Veterans with sexual dysfunction and a history of sexual trauma, mood disorders, complex pelvic pain, and/or relationship discord may still derive benefit from hormonal treatment to target GSM-related sexual concerns. However, these patients will likely require multidisciplinary adjuncts to pharmacologic treatment incorporating behavioral health interventions, physical therapy, and/or gynecologic assessment.

The Work Group systematically reviewed evidence related to this recommendation.(115,190,191) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence included a large composite sample size; however, the evidence was downgraded for study quality (very serious limitations) and serious inconsistency (for sexual function composite score). The benefits of local estrogen therapy, including improved global sexual function, satisfaction, lubrication, and pain, outweigh the potential risk of local therapy, which is small. Conversely, the risks of systemic estrogen may not outweigh the benefit when compared to local treatment solely for this indication. Patient values and preferences varied somewhat because many patients may be prescribed systemic estrogen for various indications during the menopausal transition, while others may prefer to limit systemic hormone exposure and use local therapy, which may be safely used in menopause at any age. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

22. For genitourinary syndrome of menopause (GSM), we suggest treatment with local (non-systemic) vaginal estrogen.
    (Weak for | Reviewed, New-added)

Discussion

GSM is a group of symptoms that can include vaginal dryness, vaginal burning, dyspareunia, urinary frequency, urinary incontinence, and/or recurrent urinary tract infections (rUTIs).(192) These symptoms can affect the vagina, vulva, urethra, and/or bladder and can be with or without sexual dysfunction.(193) Evidence from one RCT and seven SRs composed of a total of 55 RCTs indicates that local vaginal estrogen treatment provides statistically significant improvement in all aspects of GSM, including vaginal dryness, dyspareunia, vulvovaginal pruritus, and rUTIs.(115,190-192,194-196) In addition, on physical exam, patients showed objective signs of clinical improvement.(192) Local vaginal estrogen has relatively low harms due to its localized effects and potential great benefit due to improvement in quality of life, sexual health, and

potentially reduced urgent care and emergency room visits due to rUTIs.(196) Lethaby et al. 2016 (192) showed that all forms of vaginal estrogen, compared with placebo, improved all components of GSM.

When selecting a local vaginal estrogen formulation, it is important to consider patient values and preferences. Several safe and effective options are available:

- Low-dose vaginal estrogen ring (2 mg of estradiol delivering 7.5 mcg of estradiol per day): Remains in place for three months, offering convenience and consistent relief.
- Estradiol tablets: Easy to use and well-tolerated.
- Estradiol creams and conjugates estrogen: Provides flexible dosing and application tailored to individual needs. Allows patients to place vaginally but also apply locally to vulvar, urethral, and/or clitoral areas.

All of these therapies are FDA-approved and have been shown to improve GSM symptoms significantly. The choice of therapy should be guided by the patient's lifestyle, preferences, and specific needs.

Local vaginal estrogen creams and tablets are generally more cost-effective. Patients with dexterity or mobility issues or a history of trauma might prefer a vaginal ring, as it requires less frequent insertions. Evidence supports the use of vaginal estrogen in patients with a history of breast cancer due to its localized effects (see Recommendation 23).(197)

The Work Group systematically reviewed evidence related to this recommendation.(115,190-192,194-197) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including serious inconsistency and imprecision across studies, varied inclusion/exclusion criteria, high heterogeneity of findings, and effect size was not always clearly stated. The benefits of local vaginal estrogen on GSM symptoms outweighed the potential harm of adverse events, which was small. Patient values and preferences were similar in favoring effective, lower-risk, localized treatment despite some minor variation in preference for rings or vaginal tablets over cream due to the messiness of application. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

23. For breast cancer survivors, we suggest local (non-systemic) vaginal estrogen therapy for the treatment of genitourinary syndrome of menopause (GSM).
(Weak for | Reviewed, New-added)

Discussion

Breast cancer is the most common cancer among American women, with approximately 300,000 women being diagnosed annually.(198) The five-year survival rate for early-stage breast cancer (Stages one and two) is an encouraging 99%, and there are currently 3.8 million breast cancer survivors in the United States. Notably, breast cancer survivors account for four in 10 female cancer survivors in the U.S.(198) While survival rates are improving, breast cancer treatment often leads to premature menopause or menopausal side effects, which can cause significant

sexual dysfunction, dyspareunia, vaginal dryness, and bladder concerns. These symptoms, collectively referred to as GSM, are further exacerbated by chemotherapy and adjuvant therapies such as AIs. These treatments significantly reduce estrogen levels, leading to profound GSM symptoms that can severely impact the quality of life for breast cancer survivors.

The Work Group reviewed the literature on the use of local vaginal estrogen to treat GSM symptoms in breast cancer survivors. Unfortunately, no RCTs were identified. The evidence team reviewed one SR of observational studies, which included six studies examining breast cancer recurrence and four studies assessing breast cancer mortality.(197)

The findings showed no difference in breast cancer recurrence or mortality among breast cancer survivors who used local vaginal estrogen, with follow-up periods of up to nine years. However, the strength of evidence was considered Very low due to several limitations. All studies were observational, potentially contributing to bias. The studies did not stratify results by receptor status, stage, or cancer treatment. There was likely a selection bias, as healthier women with lower-stage breast cancer were more likely to seek assistance for sexual activity and vaginal health.

Despite the limitations, there was no evidence of increased harm, and local vaginal estrogen was shown to improve GSM symptoms significantly (see Recommendations 23-26 and 29-30 on GSM treatment).

The Work Group noted that patient preference for local vaginal estrogen is likely variable, with some patients feeling comfortable using it while others are afraid of using any estrogen products despite their safety profile. Studies have shown that maintaining sexual activity is an important factor in quality of life for cancer survivors.(199) Provider and patient acceptability remains a challenge. Providers may lack understanding that vaginal estrogen has minimal systemic absorption, which may contribute to hesitancy in prescribing it. The removal of the FDA black box warning for local vaginal estrogen preparations in 2025 may improve provider confidence and acceptability.

The Work Group emphasizes the importance of shared decision-making when managing sexual dysfunction and GSM in breast cancer survivors. Recommendations should be tailored to the patient's unique situation. Local vaginal estrogen appears to be a safe and effective option for managing GSM symptoms, with minimal risk of harm. Educating providers on the safety of local vaginal estrogen and addressing patient preferences will be critical to improving care for this population. Any of the previously mentioned local vaginal estradiol treatment options in Recommendation 23 would be considered reasonable options in breast cancer survivors.

Effective management of GSM symptoms can restore comfort, enhance sexual health, and reduce bladder-related issues, empowering survivors to regain a sense of normalcy and well-being. By providing safe and individualized treatment options, healthcare providers can help breast cancer survivors navigate the challenges of GSM and improve their physical and emotional health. See Breast Cancer Risk for more.

The Work Group systematically reviewed evidence related to this recommendation.(197) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low for support for local vaginal estrogen. The body of evidence had several limitations, most notably the lack of RCTs. The observational studies that we did find included a heterogeneous population of breast cancer survivors that had varied stages, hormone status, and treatments. In addition, there was likely a healthy patient bias included in the studies. The benefits of managing GSM outweighed the potential harm of breast cancer recurrence and mortality, as no outcome differences were noted. Patient values and preferences varied only slightly as local vaginal estrogen is considered nonsystemic and no harm was seen. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

24. For dyspareunia, we suggest local (non-systemic) vaginal estrogen and/or vaginal dehydroepiandrosterone (DHEA).
    (Weak for | Reviewed, New-added)

Discussion

Perimenopausal and postmenopausal women are at an increased risk for female sexual dysfunction due to menopausal symptoms, including GSM and dyspareunia.(200) Dyspareunia can have multiple causes, often necessitating an interdisciplinary approach for proper evaluation.(200) The evidence review showed statistically significant improvement in hormonally mediated dyspareunia with the use of local vaginal estrogen or vaginal DHEA.(192,201) Since vaginal DHEA is more expensive and requires daily application, it is generally recommended to first try a course of vaginal estrogen. Additionally, for Service members stationed overseas, accessing vaginal DHEA may be more challenging at the time of publication. Both vaginal estrogen and vaginal DHEA present relatively low risks due to their localized effects and offer substantial benefits in enhancing sexual health. Local vaginal estrogen and vaginal DHEA are effective treatment options that are accessible to patients through the VA/DOD formulary.

The Work Group systematically reviewed evidence related to this recommendation.(192,194,196,200-202) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including serious inconsistency and imprecision across studies, and the effect size was not always clearly stated.(192,194,201,202) The benefits of local vaginal estrogen and DHEA on dyspareunia outweighed the potential harm of adverse events. Patient values and preferences for vaginal estrogen and DHEA were varied due to DHEA accessibility and desire for a low-maintenance treatment plan. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

25. For vaginal dryness, we suggest local (non-systemic) vaginal estrogen, vaginal DHEA, vaginal moisturizers, or ospemifene.
    (Weak for | Reviewed, New-added)

Discussion

Evidence from one SR composed of four RCTs favored vaginal moisturizers compared to placebo for improving vaginal dryness.(201) There were two trials in the SR that showed hyaluronic acid and lactic acid vaginal moisturizers improved vaginal dryness over placebo.(201) Another SR composed of six RCTs, with moderate strength of evidence, favored ospemifene compared to placebo for improvement in vaginal dryness.(203) One SR showed that four of seven RCTs favored vaginal estrogen over placebo for vaginal dryness; however, a second SR with a meta-analysis composed of four RCTs showed no difference between local vaginal estrogen and placebo.(194,201) One SR composed of four RCTs all showed statistical significance when using vaginal DHEA over placebo for vaginal dryness.(201) There were no comparative effectiveness studies for the treatment of vaginal dryness in the evidence review.

In the evidence reviewed, there were no direct comparative studies between vaginal estrogen, vaginal DHEA, vaginal moisturizers, or ospemifene. Clinical context and patient preferences are important to consider when identifying which of these treatment options to try. Lower-risk and lower-cost agents may be preferable, such as local vaginal estrogen, vaginal DHEA, and vaginal moisturizers, over ospemifene. Subsequently, if a patient does not have an adequate response and is bothered by the symptoms, a higher-cost and/or risk option may be trialed. For example, in patients who have a history of thromboembolism or who are at high-risk for thromboembolism, a trial of ospemifene may not be appropriate. In contrast, local vaginal estrogen, vaginal DHEA, and vaginal moisturizers all have a low risk of harm and, due to their localized effects, can be used in most patients.

The Work Group systematically reviewed evidence related to this recommendation.(194,201,203) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including high heterogeneity in the Ali et. al 2024 meta-analysis, inconsistent findings, and unclear effect size.(194,201,203) Specifically with local vaginal estrogen, variations between the studies included hormone types (estriol and estradiol), hormone formulations (rings, gels, creams, or tablets), dosages (0.005% ultra-low dose estriol versus conventional U.S. dosages of vaginal estradiol), and varied intervention length (follow-up ranged from 8 weeks to 4.1 years), which contributed to the Very low quality of evidence. The benefits of local vaginal estrogen, vaginal DHEA, vaginal moisturizers, or ospemifene slightly outweighed the potential harm. Patient values and preferences varied somewhat because some patients may prefer non-oral compared to oral medications. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

26. We suggest transdermal testosterone for the treatment of sexual dysfunction in menopause, especially related to interest, desire, and/or arousal.
    (Weak for | Reviewed, New-added)

Discussion

Few pharmacologic therapies are effective in treating female sexual dysfunction related to interest, desire, and arousal, yet patients avidly seek treatment for these concerns. Testosterone

is known to modulate sexual behavior and has shown efficacy in addressing these symptoms in select populations.

The evidence review identified two SRs (204,205) that addressed the impact of testosterone on sexual dysfunction in postmenopausal women. Most studies focused on postmenopausal women with Hypoactive Sexual Desire Disorder (HSDD, reclassified in the DSM-5 as FSIAD), though some of the RCTs in Islam et al. 2019 (204) also evaluated more diverse populations, including those without HSDD and premenopausal women. Both reviews assessed systemic testosterone doses that approximate physiological testosterone concentrations for premenopausal women with and without estrogen co-treatment. The findings should not be generalized to injectables, pellets, or other compounded preparations, as these formulations were not evaluated. A positive treatment effect was noted in postmenopausal women with sexual concerns both with and without a diagnosis of HSDD. Studies in premenopausal women were limited and demonstrated minimal significant treatment effect. No literature was identified specifically addressing treatment in perimenopausal women.

Among postmenopausal women with HSDD, transdermal testosterone was superior to placebo at 24 weeks for improving sexual desire, orgasm, the number of satisfying sexual episodes, and personal distress at 24 weeks.(205) Similarly, Islam et al. 2019 (204) found that testosterone provided benefits over placebo for most sexual function outcomes, including satisfying sexual events, sexual desire, arousal, orgasm, pleasure, sexual self-image, and sexual distress, for up to 52 weeks in postmenopausal women. It is noteworthy that the average increase in satisfying sexual experiences was less than one per month (Achilli: MD 0.92, 95% CI: 0.65, 1.19, P<.00001; Islam: MD 0.85, 95% CI: 0.52, 1.18, p=0.014).(204,205)

The primary harms identified were acne (Islam: Risk Ratio (RR): 1.46, 95% CI: 1.11 to 1.92; Achilli: RR 1.41, 95% CI: 1.05 to 1.88) and increased hair growth (Achilli: RR: 1.56, 95% CI: 1.17 to 2.09).(204,205) Importantly, no significant difference was found between testosterone and placebo regarding the risk of vocal changes, alopecia, clitoromegaly, breast cancer, deep vein thrombosis, stroke, or MI in studies lasting up to 52 months.(204,205)

Transdermal testosterone, in doses that approximate physiologic premenopausal levels, is recognized by the Menopause Society, ACOG, and other professional societies as an effective treatment for postmenopausal sexual interest and arousal disorders.(187,206,207) This consensus has improved its acceptability among providers. However, hesitancy in prescribing persists due to its modest benefit and the lack of long-term safety data. Regardless, testosterone is a highly publicized treatment that patients are eager to understand and obtain, whether from licensed healthcare professionals or alternative providers.

Prescribing testosterone to women also presents significant practical challenges. It is not FDA-approved for this indication, and female-dosed preparations are unavailable in the U.S. This necessitates the off-label use of male formulations in reduced dosage, which requires explicit patient counseling and consent. To ensure dosing remains within the physiological range, it is recommended to follow serum total testosterone concentrations at six-month intervals and discontinue treatment if a trial period shows no favorable response.(187,206) Furthermore, common side effects like acne and hair growth can be a deterrent for patients. See Appendix H for

testosterone dosing. Despite these barriers, testosterone is one of the few treatments that consistently improves sexual arousal/desire for menopausal women. Although the benefits are modest, it can be an appropriate treatment for a well-counseled patient. Pharmacotherapy for sexual dysfunction should always be considered alongside psychological interventions, such as sexual skills training, cognitive-behavioral therapy, mindfulness-based interventions, and couples therapy.

The Work Group systematically reviewed evidence related to this recommendation.(204,205) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations including population and intervention heterogeneity, and both reviews were downgraded for study quality (very serious limitations). The benefits of testosterone (including improved sexual desire, pleasure, orgasm, number of satisfying sexual episodes, and personal distress) slightly outweighed the potential harms to include acne, hair growth, and the unknown risks of long-term use. Patient values and preferences varied somewhat because of modest impact of treatment with unknown risk, however, there are few alternatives for a distressing condition. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

27. For the treatment of Hypoactive Sexual Desire Disorder (reclassified in the DSM-5 as Female Sexual Interest/Arousal Disorder) in perimenopause and menopause, we suggest flibanserin.
    (Weak for | Reviewed, New-added)

Discussion

The evidence review identified one SR of two RCTs (n=1585) evaluating flibanserin for the treatment of HSDD in postmenopausal women.(208) The DSM-IV diagnosis of HSDD has been replaced by FSIAD in the DSM-5; however, we use HSDD here to acknowledge the language of the original research.

Evidence from two RCTs indicated that flibanserin provided benefit over placebo for most outcomes at 24 weeks, including satisfying sexual events, desire, and distress.(208) However, similar to testosterone, the mean increase in satisfying sexual events per month was small (less than one) though statistically significant (Kamrul-Hasan: MD: 0.37; 95% CI: 0.14 to 0.61; p=0.002).(208)

Adverse events, including dizziness, fatigue, nausea, somnolence, and insomnia, were more common in premenopausal and postmenopausal patients treated with flibanserin compared to placebo. There was no statistically significant difference in serious adverse events between the treatment groups.

Flibanserin was approved by the FDA in December 2025 for the treatment of HSDD in postmenopausal women under age 65, making it the first approved therapy for this group. It had previously been available for premenopausal women since 2015. Provider acceptance for postmenopausal use will likely grow with awareness of this expanded indication. Nonetheless, the high cost of flibanserin presents a barrier to equitable access. This drug is not presently on the

formulary within the VA. While the drug is included on the formulary for the DOD, the prior authorization remains limited to pre-menopausal females. In addition, the Work Group did not review bremelanotide, as it is only FDA-approved for use to treat HSDD in premenopausal women, therefore outside of the scope of this CPG.

Although flibanserin is the only non-hormonal prescription therapy for postmenopausal HSDD, its efficacy in improving satisfying sexual experiences is less than half that observed in premenopausal patients. While this improvement is marginal, other sexual function indices favor flibanserin over placebo, and the value of even a small benefit varies by patient.

However, the drug's modest benefit becomes less pronounced when considering its adverse effects. Flibanserin has a black box warning for hypotension and syncope, with risks amplified by alcohol or CYP3A4 inhibitors. This is an important concern for older adults who are at a higher risk of falls and for those unwilling to abstain from alcohol within two hours of the nightly dose. Furthermore, the high cost presents a barrier to equitable access. Efficacy has only been established for women diagnosed with HSDD.

The Work Group systematically reviewed evidence related to this recommendation.(208) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including study quality (serious limitations). The benefits of flibanserin (e.g., improved satisfying sexual events, sexual function, and distress scores) were balanced with the potential harm of adverse events such as hypotension, dizziness, nausea, and sleep disturbance. Patient values and preferences would be expected to vary largely because of variation in the degree of distress induced from HSDD and willingness to risk treatment harms for marginal benefit. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

28. For dyspareunia, there is insufficient evidence to recommend for or against the use of vaginal moisturizers.
    (Neither for nor against | Reviewed, New-added)

Discussion

Evidence from one SR composed of four RCTs (n=338) did not show a statistically significant difference between vaginal moisturizers and placebo for improving dyspareunia at 12 weeks.(201) Vaginal moisturizers included in the evidence review included lactic acid, polycarbophil, and hyaluronic acid gels.(201) Notably, one RCT within the SR (n=98) found that lactic acid vaginal moisturizers applied 3 times weekly improved dyspareunia compared to placebo.(201)

Through shared decision-making and based on patient preference, patients may initially prefer nonpharmacological management of dyspareunia and may wish to try over-the-counter vaginal moisturizers. Given the low risk of harm associated with vaginal moisturizers, a trial based on patient preferences could be considered.

The Work Group systematically reviewed evidence related to this recommendation.(201) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality

of the evidence was Low. The body of evidence had some limitations, including serious imprecision due to no effect size and wide CIs.(201) The benefits of vaginal moisturizers were balanced with the potential harms. Patient values and preferences varied largely due to a lack of evidence for symptom improvement and fear of worsening other menopausal symptoms. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

29. For genitourinary syndrome of menopause (GSM), we suggest against the use of vaginal lasers.
    (Weak against | Reviewed, New-added)

Discussion

Evidence from two SRs (n=5,556) and two small RCTs (n=75) indicated no statistically significant difference between vaginal laser therapy and placebo for vaginal dryness, dyspareunia, vaginal burning, dysuria, pruritus, or urinary frequency.(209-212) The laser therapies included in the evidence synthesis were carbon dioxide (CO_2), mixed wavelength, and yttrium aluminum garnet (YAG) lasers.(209-212)

There was Moderate strength of evidence that showed no difference between CO_2 lasers and placebo for treating vaginal burning, pruritus, or dysuria.(209) In comparison, 1 small RCT showed improvement with mixed wavelength laser therapy over placebo for dyspareunia(212), and another small RCT showed improvement with YAG laser therapy over placebo for vaginal dryness.(211) Overall, the evidence showed no significant benefit with laser therapy compared to sham laser or placebo. While no serious adverse events were reported in the reviewed evidence (209), there are known risks to vaginal laser therapy, including pain, scarring, vaginal/vulva burns, erythema, edema, tissue damage, decreased vaginal sensation, and infection.(213)

Vaginal laser therapy is not widely available for patients within the VA/DOD, and it is not FDA-approved for GSM. Laser therapy can be a burden for patients due to the number of appointments required for treatment, costs, and treatment discomfort.

The Work Group systematically reviewed evidence related to this recommendation.(209-212) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including serious inconsistency and imprecision due to wide CIs, high heterogeneity, and small sample size.(209-212) The harms of vaginal laser therapy outweighed the potential benefit due to potential adverse events. Patient values and preferences varied somewhat because some patients may prefer nonpharmacological treatment options. Thus, the Work Group decided upon a *Weak against* recommendation.

f. Bone Health

Introduction to 2026 Menopause Recommendations for the Management of Bone Health

Osteoporosis is particularly prevalent in older postmenopausal women and significantly increases the risk of fractures, which are often associated with substantial morbidity and mortality. Postmenopausal bone loss, primarily driven by estrogen deficiency, is a key contributor to the

development of osteoporosis. Preventing the initial bone loss that occurs during the menopausal transition is critical to reducing long-term fracture risk.

The Work Group recognizes the profound impact osteoporosis can have on women's health and quality of life. It is accepted that in women without known osteoporosis, estrogen therapy (with or without a progestogen) effectively reduces bone loss and fracture, particularly for perimenopausal women with low bone density and additional risk factors. Therefore, no recent studies on this matter were captured in the literature search.

In this section, we review the available evidence on therapies that improve bone mineral density and decrease fracture risk, providing guidance on the most effective strategies for maintaining bone health in postmenopausal women.

Recommendation

30. In post-menopausal women with risk factors for osteoporosis, we suggest conjugated estrogen/bazedoxifene as an option to increase bone mineral density based on patient characteristics and preferences.
    (Weak for | Reviewed, New-added)

Discussion

CE/BZA is FDA-approved for women with a uterus for the treatment of moderate to severe VMS. While the medication also contains an FDA approval for prevention of osteoporosis in postmenopausal patients, it is noted that when prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered.

Gallagher et al. 2016 (214) was an SR containing two RCTs of 1,172 patients sponsored by the drug product's manufacturer. The patient population was women at increased risk of osteoporosis, based upon a BMD score between one and 2.5 at the lumbar spine and hip and at least one additional osteoporosis risk factor. Women received either CE 0.45 mg/BZA 20 (n=381), CE 0.625 mg/BZA 20 mg (n=394), or placebo (n=397). Comparisons favored CE/BZA over placebo, and while follow-up was limited to one year, improvement in BMD was noted in the lumbar spine, total hip, and femoral neck.

The specific treatment selected to address VMS in menopause must be individualized. CE/BZA appears to be an optimal selection for women with both VMS and increased risk of osteoporosis, given the favorable impact on BMD. However, there are no direct studies of comparative effectiveness between CE/BZA and other estrogen-containing menopause hormone therapies. For women with a uterus, there may be hesitancy to receive estrogen and progestogen hormone therapy because of the potential increased risk of breast cancer. In the case of CE/BZA, the use of BZA, a selective estrogen receptor modulator with antiestrogenic effects on uterine tissue, allows for CE to be administered without the need for progestogen. Thus, CE/BZA is an attractive treatment option for women desiring menopause hormone therapy but with concerns about increased cancer risks of breast cancer from estrogen and progestogen. There were no available studies reviewed that compared CE/BZA to other common treatments for the prevention of osteoporosis, such as calcium, Vitamin D, and weight-bearing exercises. These alternate non-

pharmacologic treatments are low risk and may provide additional benefits beyond just prevention of osteoporosis. Additionally, while women looking to avoid a progestogen may be optimal candidates for CE/BZA, there are some women who benefit from progestogens in the perimenopausal and menopausal period for bleeding management and sleep benefit. It is also worth noting that this medication is non-formulary for VA, thus creating the additional burden of a prior authorization for patient use. Given the pros and cons of CE/BZA use compared to other menopausal hormone therapies and other preventative strategies for osteoporosis, the overall patient characteristics and preferences are critical in making the decision to use CE/BZA for women at risk for osteoporosis.

The Work Group systematically reviewed evidence related to this recommendation.(214) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including potential bias given sponsorship from the drug manufacturer, small sample size, and inconsistency, with slightly different study designs in the two included RCTs. The benefits of improved BMD for those at increased risk for osteoporosis outweighed the potential harm related to the administration of oral estrogen. Patient values and preferences varied largely because some may not value improvement in BMD since this is not a direct clinical outcome and because women have variable beliefs, priorities, and concerns that impact their decisions on menopause hormone therapy. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

31. In post-menopausal patients, we suggest dietary calcium and/or calcium supplementation to increase bone mineral density.
    (Weak for | Reviewed, New-added)

Discussion

The use of calcium to support overall bone health in post-menopausal patients has been a long-standing recommendation from multiple leading medical societies and endorsed by the National Osteoporosis Foundation.(215) Calcium serves as both a structural component and a signaling molecule in bone formation. Wu et al. 2017 (216) performed an SR of 17 RCTs evaluating the impact of calcium doses ranging from 250 to 2000 mg/day alone or with Vitamin D3 on the change in BMD. An improvement in BMD (1.1% change) was seen in those receiving calcium as compared to the control group (total n=2537). However, it is important to note that a recent SR and meta-analysis did not demonstrate a reduction in fracture risk with the use of calcium supplementation, though this study was not included in the reviewed evidence base.(217)

Calcium supplementation is an easily accessible, low-risk intervention. While there is the potential for decreased gastrointestinal motility resulting in increased risk of colon polyps and constipation, increased risk of nephrolithiasis, increased risk of CVD events (218), or interactions with other medications, the Work Group believed this is an intervention likely to be recognized and acceptable to both patients and clinicians. To date, since observational data from calcium supplementation trials are mixed, in patients who are at high risk of hypercalcemia or are taking ≥1,000 mg/day calcium supplementation, we suggest monitoring calcium levels.

The Work Group systematically reviewed evidence related to this recommendation.(216) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had limitations, including serious imprecision.(216) The benefits of calcium for improved BMD outweigh the potential harms, which are usually minor and manageable. Patient values and preferences are felt to be similar because of familiarity with increasing fracture risk while aging and the potential of significant long-term harms if a fracture occurs. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

32. In post-menopausal patients without osteoporosis, there is insufficient evidence to recommend for or against Vitamin D3 for primary improvement of decreased bone mineral density or fracture.
    (Neither for nor against | Reviewed, New-added)

Discussion

Similar to calcium, the use of Vitamin D3 to support overall bone health in post-menopausal patients has been a long-standing recommendation from multiple leading medical societies and endorsed by the National Osteoporosis Foundation.(215) Unlike calcium, which has a direct role in bone mineralization and maintenance, Vitamin D in its active form increases intestinal calcium absorption and renal calcium reabsorption, thereby increasing calcium availability for bone remodeling. Kazemian et al. 2023 (219) performed an SR of twenty-three RCTs examining the impact of Vitamin D3 supplementation ranging from 300 to 10,000 IU/day on patients without known Vitamin D deficiency, osteopenia, or osteoporosis. The SR found no difference in BMD with Vitamin D supplementation as compared to placebo or no treatment.

The SR by Kahwati et al. 2018 (220) contained only a single RCT. The trial included only patients without a known history of Vitamin D deficiency, osteopenia, or osteoporosis and compared rates of hip and non-vertebral fractures in those receiving supplementation with calcium and Vitamin D3 to those receiving calcium supplementation alone. No difference in fracture rate was identified between the two groups.

Vitamin D3 is an overall low-risk intervention, with rare side effects including Vitamin D toxicity and complications from hypercalcemia such as nephrolithiasis or arrhythmias. Vitamin D3 is easily accessible with over-the-counter availability and is likely to be accepted by both clinicians and patients as a familiar and safe intervention. While there was no evidence to demonstrate Vitamin D3 as effective for the primary purpose of improving BMD in patients without Vitamin D deficiency, osteopenia, or osteoporosis, there were no SRs available for review in these higher-risk populations.

The Work Group systematically reviewed evidence related to this recommendation.(219,220) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including small sample size, with Kahwati et al 2018 (220) limited to a single RCT of only 232 patients. Kazemian et al. 2023 (219) was limited due to high risk of bias in at least one of the included studies, unclear risk of selection bias in half of the included studies, and heterogeneity in treatment with Vitamin D

dosing ranging from 300 to 10,000 IU/day across included studies. The benefits of Vitamin D3 related to BMD and fracture were balanced with the potential harms, which are rare and usually minor. Patient values and preferences were similar because patients often prefer interventions they are familiar with and perceive as low risk. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

33. For primary prevention of fracture in post-menopausal patients without documentation of osteoporosis or osteopenia, there is insufficient evidence to recommend for or against bisphosphonates.
    (Neither for nor against | Reviewed, New-added)

Discussion

Current medical practice does not include the use of bisphosphonates for primary prevention of fracture in a low-risk population, instead reserving this class of medications for those with osteoporosis, with an individualized approach for those with osteopenia and high risk for fracture.

The evidence reviewed for bisphosphonates included four SRs. The SRs excluded patients with osteopenia or osteoporosis, instead looking at potential fracture risk reduction only in a baseline population.

Wen et al. 2020 (221) included 57 RCTs with a total of 29,642 patients and studied vertebral and non-vertebral fractures with the use of ibandronate 150 mg/month. Mean follow-up was slightly over two years. There was no difference detected in vertebral fractures or non-vertebral fractures with ibandronate use.

Wells et al. 2022 (222) included four RCTs evaluating the impact of risedronate 5 mg/day on vertebral fractures or wrist fractures. No difference was detected over one to two years of follow-up.

Gazoni et al. 2023 (223) consisted of four RCTs examining the effectiveness of zoledronate mg infusion for primary prevention of fracture compared to placebo (n=2,717). Zoledronate was more effective (RR 0.39) than placebo at reducing morphometric vertebral fractures, vertebral fractures, and all clinical fractures after 36 to 72 months of use in postmenopausal women. However, there was no difference in the risk of hip fracture between zoledronate and placebo.

Wells et al. 2025 (224) evaluated thirty-four RCTs containing over 15,000 patients who received alendronate 10 mg/day over one to five years of follow-up. While there was a reduction in vertebral and non-vertebral fractures, there was no reduction in fractures of the wrist or hip.

Overall, the data was mixed for bisphosphonates as a medication class impacting fracture risk. Ardebili et al. 2023 (225) consisted of an SR evaluating bisphosphonates (risedronate, alendronate, ibandronate, or zoledronate) as a class to placebo and found improved BMD with bisphosphonate use. However, the more meaningful clinical outcome of fracture risk reduction was only seen in studies evaluating zoledronate and alendronate. Additionally, the benefit was only observed in relation to fractures at specific sites. Zoledronate reduces lumbar spine, femoral neck, monomorphic vertebral, and non-vertebral fractures but has mixed evidence for hip

fractures. Alendronate reduces vertebral and non-vertebral fractures but has no reduction in hip and wrist fractures.

Risks of bisphosphonate use include difficulty swallowing, inflammation of the esophagus, and gastric ulceration. There have been reports of osteonecrosis of the jaw with bisphosphonate use. This risk is extremely small when use is limited to less than five years, but less certain with extended use. Administration of the medication can be somewhat burdensome. Alendronate and risedronate must be taken on an empty stomach, first thing in the morning, before eating or drinking, and must remain upright for at least 30 minutes after administration. When taken orally, ibandronate must be taken on the same day each month, on an empty stomach, with nothing to eat or drink for 60 minutes after. When administered intravenously, ibandronate is administered once every three months, and serum creatinine must be monitored. Zoledronate is an annual infusion. An acute phase reaction including arthralgia, headache, myalgia, and fever may occur following infusion.

The Work Group systematically reviewed evidence related to this recommendation.(221-224) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including serious indirectness, with some patients included in the study being more than 10 years from menopause and serious imprecision.(221-224) The benefits of bisphosphonate use for primary prevention of fracture were balanced with the potential harms of adverse events and the burden of bisphosphonate administration. Patient values and preferences varied largely. Some patients may have a significant interest in any intervention that could reduce rates of fracture. Other patients may not be accepting of the risks and inconveniences of bisphosphonate usage for prevention while not belonging to a population at increased risk. Some patients may also prefer non-pharmacologic strategies for prevention with which they are more likely to be familiar (i.e., weight bearing exercise, calcium, vitamin D). Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

34. In post-menopausal patients with osteopenia, there is insufficient evidence to recommend for or against raloxifene to reduce fracture risk and improve bone mineral density. **(Neither for nor against | Reviewed, New-added)**

Discussion

The evidence base consisted of two SRs. Naylor et al. 2016 (226) is an older study with very serious limitations and very serious imprecision (single study <50 patients). Patients who were postmenopausal, and patients with low BMD were included. While it did favor raloxifene over placebo in improvement of bone mineral density, the authors noted that improvement was seen in only three women out of 63 in the raloxifene group, and the change was minimally clinically significant.

Wen et al. 2020 (221) examined rates of fracture with raloxifene compared to placebo. In a patient population with known BMD between one and 2.5, there was a reduction in vertebral fractures with raloxifene but not in non-vertebral fractures.

Raloxifene is a selective estrogen receptor modulator with progestogenic effects on the bone and antiestrogenic effects on the breast. Raloxifene does not treat VMS of menopause but rather can cause hot flashes and increases risk of venous thromboembolism. Raloxifene is an oral daily medication. It is likely a medication less well known to prescribers compared to other interventions for osteoporosis prevention. Furthermore, the medication has to be stored away from excessive heat and light, making it a medication not easily accessible in a deployed environment.

The Work Group systematically reviewed evidence related to this recommendation.(221,226) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations including small sample size (226) and serious indirectness (221,226) with patients in studies >10 years post menopause. The benefits of improved BMD and reduction in fracture risk are balanced with the potential harms of VMS and the potential increase in risk of venous thromboembolism. Patient values and preferences are similar, as many patients may prefer this oral medication over other medications which are injectable and many patients prioritize the clinical outcome of fracture risk reduction. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

g. Overweight and Obesity Management

Introduction to 2026 Menopause Recommendations for Overweight and Obesity Management

The menopausal transition is associated with significant changes in body composition and fat distribution. Declining estrogen levels, combined with decreased energy expenditure, contribute to a redistribution of fat to the abdominal and visceral regions, which many women notice as an increase in waist circumference. These changes may also increase the risk of metabolic and cardiovascular conditions.

This section reviews the current evidence on weight management strategies during menopause, including diets and lifestyle interventions for women with overweight or obesity. At the time of this publication, there were no RCTs specifically evaluating the use of Glucagon-like peptide-1 (GLP-1) receptor agonists in menopausal women. However, since the evidence review, emerging studies have demonstrated the potential benefits of GLP-1 receptor agonists when used in conjunction with MHT[1].(227,228) Future research may further explore the role of these medications in weight management during the menopausal transition.

Recommendation

35. In post-menopausal women with overweight or obesity, we suggest a calorie-restricted diet for weight management, depending on patient characteristics and preferences (see the VA/DOD CPG for the Management of Overweight and Obesity in Adults[1]).
(Weak for | Reviewed, New-added)

[1] See the VA/DOD Clinical Practice Guideline for the Management of Adult Overweight and Obesity. Available at: https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/cd/obesity/index.asp

Discussion

Current evidence suggests that a calorie-restricted diet is effective for supporting weight loss in post-menopausal women with overweight or obesity. The findings from two RCTs reported in four publications indicated that the calorie-restricted groups had greater weight loss than usual diet controls. This was demonstrated over the course of a 12-week low-caloric diet and an additional four-week low-caloric diet sustainment period. However, the evidence also indicated that exercise and diet combined led to greater weight loss than diet alone. These studies held a low certainty of evidence for an effect on weight change, and the poor overall quality of included studies, based on small sample sizes and inclusion criteria, led to a Weak recommendation suggesting a calorie-restricted diet for weight loss in post-menopausal women with overweight or obesity. Based on the evidence, greater weight loss was achieved with a calorie-restricted diet, especially combined with exercise, and, while not critical outcomes, cognitive symptoms and cardiovascular disease risk were found to be decreased as a result of the interventions (i.e., calorie restriction and calorie restriction combined with exercise). These findings support the short-term efficacy of calorie-restricted diets in menopausal populations with overweight or obesity; however, the absence of extended follow-up data precludes the assessment of long-term weight maintenance or metabolic impact. The 2014 CPG supports the use of calorie restriction for weight loss, recommending a daily caloric deficit of 500-750 kilocalories (kcal) for effective weight management. The 2020 evidence further contributed to the field, while recent comparative effectiveness studies from 2025 continue to explore the different impacts of negative energy balance through various dietary and lifestyle interventions. Further studies are needed to determine whether initial weight loss can be maintained or whether compensatory mechanisms, such as calorie restriction combined with increased physical activity, attenuate these effects over time.

Some variation exists in patient values and preferences due to the varying levels of willingness to adhere to a calorie reduction for an indeterminate length of time. In addition, with the Low strength of the evidence reviewed, the intervention of calorie restriction may result in low efficacy on weight change. Additionally, according to the VA/DOD Clinical Practice Guideline for the Management of Overweight and Obesity in Adults[1], it is desirable to have the guidance of a registered dietitian to effectively implement a calorie-restricted diet. This may pose challenges across the VA and DOD based on dietitian availability and scheduling, as well as patient willingness to attend regular appointments with a registered dietitian nutritionist for ongoing medical nutrition therapy and monitoring of anthropometric data. One specific subgroup population that requires regular monitoring by a registered dietitian nutritionist is patients with a history of or who are at risk for eating disorders due to lifestyle habits and dietary intake restrictions when implementing a calorie-restricted diet to manage weight in menopause. A thorough review by a registered dietitian of a patient's eating behaviors, including meal frequency, physical activity, supplement regimen, and prior experience with weight management interventions, should be considered. For menopausal women who display disordered eating or eating disorder symptoms, interdisciplinary care is vital, and a referral to a mental health provider should be considered regardless of weight status. Finally, equitable access to care and resources is an implication that must be considered to outweigh the potential harm versus benefits of a calorie-restricted diet to ensure patients have safe and consistent access to nutritious foods.

The Work Group systematically reviewed evidence related to this recommendation.(229-232) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Low. The body of evidence had some limitations, including small sample sizes and low certainty of evidence for an effect on body weight across the body of evidence synthesized. Additionally, the studies applied a calorie deficit, also associated with exercise, compared to the usual diet to achieve significantly greater weight loss outcomes than with diet changes alone. The benefits of a calorie-restricted diet may provide weight loss in post-menopausal women with overweight or obesity, with significantly greater results when combined with exercise. This outweighed the potential harms and/or burdens of a calorie-restricted diet, which includes potential for an imbalance of macronutrients when calories are restricted and varying effects depending on the length of time that calories are restricted. Patient values and preferences varied somewhat because some patients may be less willing to adopt a calorie-restricted diet, which is associated with the burden of documenting food intake. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

36. We suggest exercise for peri-menopausal or post-menopausal women for reduction of weight and/or waist circumference (e.g., aerobic activity, resistance training, or combination).
    (Weak for | Reviewed, New-added)

Discussion

The Work Group suggests exercise (specifically walking for physical activity) for body weight reduction based on Very low strength of evidence from one SR/MA comprised of eight RCTs with a total sample of 853 women in peri- or post-menopause.(233) The overall findings of the Gao et al. 2016 (233) SR/MA showed evidence for the benefits of walking to decrease body weight. Two other single RCTs were reviewed of Low and Very low strength of evidence (234,235) but did not show a difference in body weight between the exercise and control group.

The Work Group also suggests exercise for waist circumference reduction based on Very low strength of evidence from two SRs (236,237) one Moderate (237) and one Very low (236) in respective strength of evidence. Both indicated that various types of exercise reduce waist circumference in women less than 65 and women over 65 years. These positive findings using a variety of exercise regimens allow results to be interpreted as potentially applicable to a variety of exercise program options. The Khalafi et al. 2023 SR (237) included 101 RCTs consisting of 5697 participants and multiple forms of exercise training: aerobic, resistance, combined, and other (water-based, yoga/pilates/tai chi, dance, etc.). Beneficial effects were seen with medium- and long-term interventions and also in both middle-aged and older post-menopausal women (>65 years). The Huynh et al. 2024 SR (236) reviewed 12 RCTs consisting of 1254 participants using predominantly aerobic exercise activities (treadmill or cycle, aquatic aerobic training, walking, or bench stepping) and also had a significant reduction in waist circumference despite having a high risk of bias due to failure to report attrition data, having missing outcome data, and lack of intention-to-treat analyses.

The benefits of exercise outweigh harms by reducing body weight and reducing waist circumference and reducing depression symptoms (See Recommendation 17) directly in addition to improving cardiovascular risk reduction through improved cardiometabolic risks, musculoskeletal function, cognition, mood (reduction in depression), and sleep allowing for overall healthy improvements through health behavior change (or lifestyle changes) and allowing for improved military readiness among active duty and reduction of health risks among Veterans. Moreover, for Veterans, exercise programs have the potential to increase social connections among mid-life adults. The major burden is the potential for injury or soreness at initiation of activity and specific consideration of adaptations for those with limited mobility, in addition to time and consistency required for exercise to become a disciplined activity and outcomes to be seen.

The body of evidence had some limitations including small sample size in the individual RCTs as well as some of the SRs/MAs, confounders in the analysis, lack of any patients with common co-morbidities (i.e., overweight/obesity, diabetes, pre-diabetes), numerical information on drop-outs in each arm and reason for study attrition, and specifics on age or menopause transition status for mid-life women.

For weight change assessment, using the Gao et al. 2016 (233) SR/MA's eight RCTs and 14 RCT study groups assessing body weight, and the pooled data indicated an overall reduction of body weight of 1.14 kilogram (kg) (95% CI -1.86 to -0.42kg) in those participating in the walking intervention.

For waist circumference, the Khalafi et al. 2023 (237) SR/MA demonstrated that in 26 intervention arms (from the reviewed 101 RCTs) exercise training decreased waist circumference (weighted mean difference [WMD] -1.45 centimeter [cm]; 95% CI -2.05 to -0.83; p=0.001) in the overall participant comparison as well as with women <65 years (WMD -1.42cm, -2.25 to -0.59cm; p=0.001) and women >65 years (WMD -1.50, 95% CI -2.94 to -.0;06; p=0.004). The Huynh et al. 2024 (236) SR/MA also showed a decrease in mean difference in waist circumference (MD -2.03cm; 95% CI -2.65 to -1.41cm; p<0.01).

While these weighted mean changes in weight and waist circumference of the SR/MAs are small, approximately 2.5 pounds and 0.5 inches respectively, they remain significant outcomes showing reductions which are important despite various exercise modalities and durations. In an overview of 12 systematic reviews and 149 studies examining the impact of exercise training on weight loss and body composition changes in overweight and obese adults, the authors found that mean weight loss ranged from -1.5 to -3.5kg.(238) That review covered overweight and obese adults of both sexes as well as across the life spectrum including menopausal and aging adults. Thus, the SR for this guideline recommendation is slightly lower (mean body weight 1.14kg, 95% CI -1.86 to -0.42kg) yet remains statistically significant. Additionally, multiple key body composition changes occur in midlife women and overlap with the menopause transition. All create challenges for losing or maintaining weight. Women in midlife have a net loss of lean muscle mass, net gain of adipose tissue with a trend toward central adiposity (i.e., increased waist circumference), and a likely shift down in metabolic rate.(239) Current theory suggests the hormonal changes during menopause transition may be the driving factor for altered body composition. Thus, lifestyle changes that implement any new or intensified, regular physical activity and healthy diet changes are imperative for women in midlife to optimize their health during and after the menopause transition.

The Work Group systematically reviewed evidence related to this recommendation.(233-237) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. Benefits outweighed harms for participating in exercise for both the weight and waist circumference components. The potential for adverse events was small (separate from potential injury) or not reported. However, hidden barriers or adverse events may occur from social determinants of health. Thus, women may need to discuss environmental hazards, costs, and safety risks associated with initiating exercise in their community in addition to patient preferences to set pragmatic goals. Patient values include the desire to reduce weight and/or waist circumference during the peri- and post-menopausal periods of life as per findings from the focus group, and many women (across the age spectrum) struggle with both body image as well as composition changes, difficulties with initiation, motivation or adherence to physical activity regimens, and preferences to have non-pharmacologic interventions. These current findings provide evidence to advocate for lifestyle change through initiating physical activity with regular exercise programs during the peri- and post-menopause period. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

37. In post-menopausal women, there is insufficient evidence to recommend for or against any of the following dietary approaches for weight management:
    - High protein
    - Intermittent fasting
    - Low fat
    - Mediterranean
    - Paleolithic
    - Vegan (with soy supplementation)

    (Neither for nor against | Reviewed, New-added)

Discussion

Overall, the evidence comparing various diets to achieve weight loss in postmenopausal women is insufficient. The results are mixed, and the strength of evidence is mostly Low or Very low; the included studies evaluated weight change only in postmenopausal women.

The RCTs investigating high protein and paleolithic diets indicated either no difference in weight or an unclear relationship between the diet and weight change outcomes. Both studies had very Low strength of evidence, and the sample sizes were small.

Keawtep et al. 2024 (240) compared intermittent fasting, both combined with and without physical and cognitive exercise, to exercise alone and usual diet and activity as the control. Intermittent fasting in this study was portrayed as a gradual reduced caloric intake, which promoted metabolic adaptation to fasting, represented as a 25-75% reduction in estimated energy requirements throughout the 12-week study. This study found that participants in the intermittent fasting group both with and without physical and cognitive exercise experienced significantly greater weight loss than those in the control group. It is of note that weight loss results were not significantly different in comparison across the arms of the study (i.e., intermittent fasting with physical and cognitive

exercise versus intermittent fasting without physical and cognitive exercise); however, it is uncertain whether weight loss was achieved due to diet, exercise, both, or a calorie deficit overall.

The evidence reviewed to investigate the effect of a low-fat diet on weight change showed significant weight loss at one year, but long-term weight loss is not reported. There was no difference in the outcomes indicated between the intervention and major cardiac events at a median 13-year follow-up. It is also noted that weight loss was not an intervention goal or primary outcome intended of this study.

An RCT by Tan et al. 2025 (241) investigated the Mediterranean diet with interval training, performed at a high-intensity training level, in comparison to exercise alone and usual diet with usual activity on the effect on weight change. The diet and exercise group experienced significant weight loss at eight weeks, while the control group had significant weight gain. However, the sample size was very small, with 10 participants per arm for an eight-week intervention. Therefore, there is insufficient evidence to suggest adopting a Mediterranean diet to achieve weight loss in postmenopausal women.

Finally, Brennan et al. 2024 (242) and Barnard et al. 2023 (243) discussed the intervention of a vegan diet supplemented with soybeans compared to usual diet control. Although the sample size was small (n=71) and the study duration was short (12 weeks), greater weight loss was reported among participants assigned to the vegan diet supplemented with soybeans. The evidence is insufficient to support the recommendation of a vegan diet with soy supplementation due to the overall intervention of the diet demonstrating a caloric restriction, so it is indeterminate to acknowledge whether a vegan diet, soy supplementation, exercise, or caloric restriction achieves weight loss in postmenopausal women.

Ultimately, each of the diets investigated in the evidence reviewed reported that calories were also restricted, and a physical activity component was typically included in the intervention. Therefore, it cannot be inferred that any specific dietary pattern alone can reveal weight loss results for postmenopausal women.

While the evidence reviewed regarding high protein diet, intermittent fasting, low fat diet, Mediterranean diet, paleolithic diet, or vegan diet with soy supplementation is insufficient to recommend for or against these diets to achieve weight loss in postmenopausal women, evidence reviewed in the VA/DOD CPG for the Management of Overweight and Obesity in Adults[1] supports the evidence also included in these guidelines for suggesting a calorie-restricted diet for weight loss in postmenopausal women with overweight or obesity. Since the variety of diets reviewed demonstrated a calorie restriction in conjunction with the specific dietary pattern, the evidence is insufficient to recommend one specific dietary pattern rather than a calorie restriction. Some variation exists in patient values and preferences because each dietary pattern reviewed requires a foundation of nutrition education. However, it cannot be assumed across diverse populations that all individuals possess a foundational understanding of nutritional education or have access

[1] See the VA/DOD Clinical Practice Guideline for the Management of Adult Overweight and Obesity. Available at: https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/cd/obesity/index.asp

to resources to obtain this education from a registered dietitian nutritionist. In addition, the low efficacy of weight change results in postmenopausal women may outweigh a patient's willingness to adopt a restricted diet and for an indeterminate length of time.

Subgroup populations that should be considered when observing these dietary patterns include chronic kidney disease in the setting of a high protein diet, patients with a history of or who are at risk of eating disorders, and those with pre-existing iron or vitamin B12 deficiencies or anemia. The equity and resource use must be considered when evaluating these reviewed dietary patterns to obtain high-quality and/or safe food sources, including the cost of diet components, specifically in rural areas, that VA patients potentially receive fixed income, and/or military members may have a basic allowance for subsistence parameters, and the prevalence of food insecurity in these populations.

The Work Group systematically reviewed evidence related to this recommendation.(240-243) Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence had some limitations, including a very small sample size and a short study duration of approximately 12 weeks. The benefits of a high-protein diet, intermittent fasting, low-fat diet, Mediterranean diet, paleolithic diet, or vegan diet with soy supplementation were balanced with the potential harms of potential effects on renal function, unintentional calorie restriction, micronutrient deficiencies, and unbalanced macronutrient distribution. Patient values and preferences varied somewhat because some patients may be unwilling or hesitant to adopt a specific diet for an indeterminate length of time, especially without the guidance of a registered dietitian nutritionist, and the burden of macronutrient tracking without a history of nutrition education. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

C. Safety

Introduction to 2026 Menopause Recommendations For Safety

We recognize that significant fear and hesitation surrounding MHT persist among both patients and prescribers, largely stemming from the results of the Women's Health Initiative (WHI) study, a RCT addressing the efficacy of oral hormonal therapy in the primary prevention of coronary heart disease.(244) To address these concerns, we conducted a thorough review of the available data on the safety of MHT. As reflected in our recommendations, many have been carefully adjusted to balance the risks and benefits based on the most current evidence.

The WHI study provided critical insights into the safety of MHT. The WHI study analyzed MHT using conjugated equine estrogens and medroxyprogesterone acetate. The WHI findings may not be generalizable to other estrogen and progestogen formulations such as estradiol and micronized progesterone that are currently used in healthy postmenopausal women. Notably, the estrogen-alone arm of the WHI study did not show an increased risk of breast cancer, suggesting that the increased breast cancer risk observed in the combined therapy arm is likely attributable to the progestogen component. Additionally, the WHI demonstrated that initiation of MHT after age 60 or more than 10 years after menopause was associated with worse cardiovascular outcomes, emphasizing the importance of timing when considering MHT initiation.

Our review focused on key safety considerations, including the risks of CVD, breast cancer, uterine cancer, and stroke. We evaluated these risks both in the context of MHT use and in patients with preexisting conditions. This section provides evidence-based guidance to help clinicians make informed, individualized decisions about the use of MHT, ensuring patient safety remains a top priority.

a. Cardiovascular Disease Risk

Recommendation

38. For the primary prevention of post-menopausal cerebrovascular events, we recommend against oral estrogen or estrogen and progestogen.
(Strong against | Reviewed, New-added)

Discussion

In one RCT from an SR (97), there was Moderate evidence that showed oral conjugated estrogen alone (as MHT) led to an increased risk of stroke compared to placebo over a 7.2-year intervention period (HR 1.35 [95% CI 1.07 to 1.70]). Interestingly, in the cumulative long-term follow-up of 19.4 years, conjugated estrogen alone (as MHT) showed no difference in stroke risk (HR 1.06 [95% CI 0.92 to 1.22]). However, adding progestogen to the conjugated estrogen in the same SR (97), two RCTs had Moderate evidence to suggest a similar elevated risk of stroke compared to placebo over a cumulative follow-up of 19.4 years.

While focus group members did not specifically discuss CVD prevention, they noted that discussing individualized risk factors and treatment options is desired. Subgroup considerations include different baseline cardiovascular disease risk based upon co-occurring conditions and age. Most patients would not want to experience cardiovascular outcomes, though they may be interested in an intervention that could prevent cerebrovascular disease. While the Work Group did not include venous thromboembolism (VTE) as a critical outcome, the findings also suggested that oral estrogen alone is associated with an elevated risk of VTE during an intervention period of 7.2 years, which may not be an acceptable risk to patients.*(97)* The evidence also suggests that a similar risk of VTE is present in patients taking oral estrogen plus progestogen, and that this risk may persist at a follow-up period of 19.4 years, even if the intervention is stopped.*(97)* There are potential variations in risk based upon the timing of MHT initiation and duration, as well as potential differences in route of administration and risk due to the avoidance of hepatic first-pass metabolism with non-oral routes, which were not included in this study. Other implications include equity, as healthcare disparities continue to exist in the VA/DOD systems, with military servicewomen having less prevalence of MHT use than their VA counterparts, even with adequate access.

The Work Group systematically reviewed evidence related to this recommendation.*(97)* Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, such as the fact that the studies did not include nonsystemic estrogen formulations (i.e., rings, creams, gels, contraceptives, and other hormonal preparations), and the mean age of the participants was 53-75.*(97)* Overall, as oral MHT did not show a benefit of primary prevention of cerebrovascular

events, and in fact did show an elevated risk of stroke with use, the Work Group decided upon *Strong against* recommendation.

Recommendation

39. For primary prevention of post-menopausal cardiovascular disease (CVD), we suggest against oral menopausal hormone therapy, whether it is estrogen alone or with progestogen, and whether it is low-dose or conventional dose.
(Weak against | Reviewed, New-added)

Discussion

Two studies *(*97*,*245*)* showed no differences between oral CEE only compared to placebo in the outcomes of major adverse cardiovascular events (MACE) and SAEs. Included participants were healthy women with ages varying from an average of 42 to 58 who were within three years of menopause. The literature did not include outcomes for acute myocardial infarction (AMI) with estrogen alone. There were no differences between oral estrogen plus progestogen compared to placebo in AMI, MACE, or SAEs. The strength of evidence for this recommendation is Very low and did not evaluate other formulations and delivery of estrogen (i.e., transdermal estradiol), and the Work Group was unable to determine the benefits and harms based on the available evidence.

Evidence from one SR (246) and one RCT (247) identified during this review was insufficient to inform on a preference for low-dose or conventional-dose MHT for primary prevention of CVD. Neither the SR nor the RCT reported on critical outcomes predefined by the Work Group. The Casanova et al. 2015 SR (246) evaluated the effects of low-dose MHT versus conventional-dose MHT and placebo on various cardiovascular risk markers in postmenopausal women without evidence of cardiovascular disease. Conventional dose MHT was defined as at least 0.625 mg of CEE or equipotent doses of other products, and low dose MHT was defined as formulations using doses less than those considered conventional (e.g., ≤0.3 mg of CEE). Several MHT formulations (oral, transdermal patch, transdermal gel, intranasal) were studied in conjunction with several formulations of progestogens (micronized progesterone, medroxyprogesterone acetate, drospirenone, norethindrone acetate).

The SR included 13 relevant RCTs and 2,649 postmenopausal patients with mean ages ranging from 50 to 57 years and a follow-up ranging from 2 to 26 months. Conventional dose MHT was associated with small, statistically significant improvements in total cholesterol and low-density lipoprotein (LDL) vs. low dose MHT; however, the five milligram/deciliter (mg/dL) and 4.5 mg/dL reductions, respectively, were not considered clinically important. No significant differences were identified for the markers of weight, body mass index (BMI), systolic and diastolic blood pressure, triglycerides, or C-reactive protein between conventional and low-dose MHT groups. The second reference identified for this review was a small RCT by Raz et al. 2016 (247) that included a subgroup of 49 menopausal patients from the larger Kronos Early Estrogen Prevention Study (KEEPS)-Cog study, with a mean age of 52 years, and who were followed for 48 months. Raz et al. 2016 (247) evaluated two formulations of MHT: a lower-than-conventional dose of oral CEE 0.45 mg per day plus 200 mg oral progesterone (12 days per month) vs. transdermal estradiol 50 mcg per day plus 200 mg oral progesterone (12 days per month). Low-dose oral

CEE/progesterone was associated with a statistically significant increase in triglycerides compared to conventional-dose transdermal estradiol/progesterone. There were no differences observed in other cardiovascular risk factors, including BMI, waist circumference, systolic and diastolic blood pressure, LDL, high density lipoprotein (HDL), fasting blood glucose, or carotid intima-medial thickness. Of note, these results were reported as descriptive clinical characteristics rather than specified outcomes.

While focus group members did not specifically discuss CVD prevention, they noted that discussing individualized risk factors and treatment options is desirable when determining whether or not to use MHT. Patients have different baseline risks depending upon co-occurring conditions and age, and the benefits and harms of MHT may be dependent on these individual risk factors. Additionally, there are potential variations in risk based upon timing of MHT initiation and duration. There is some variation in patient values and preferences anticipated. While certain patients may prioritize using the lowest dose with minimal adverse effects, others may prefer a higher dose if associated with a positive impact on cardiovascular markers. There is a wide variety of MHT options available in VA and DOD, including a full range of doses and products with different modes of delivery; however, there are some regional and operational factors that influence availability. There are equity considerations, as healthcare disparities exist in the VA/DOD healthcare systems, as evidenced by the higher prevalence of MHT in the VA beneficiaries compared with active duty Service members of the same age.

The Work Group systematically reviewed evidence related to this recommendation.*(*97,245-247*)* Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Very low. The body of evidence for CVD had some limitations, including short follow-up time and unclear formulation of MHT (i.e., systemic, transdermal, vaginal, oral, etc.), making it difficult to determine which mode of delivery was being assessed.*(*97,245*)* Additionally, the body of evidence evaluating conventional versus low-dose MHT lacked evaluation of critical outcomes of interest to patients. Aside from the dose of MHT, comparisons of different formulations of oral vs. non-oral systemic formulations of MHT could have influenced cardiovascular markers and confounded results. Insufficient evidence is available to inform for or against the use of MHT, whether it is estrogen alone or with progestogen, and whether it is low-dose or conventional dose for the primary prevention of CVD. The VMS benefits of MHT and the potential harms of major adverse cardiovascular events, total coronary heart disease mortality, all-cause mortality, and AMI appear to be balanced, though the evidence did not show any benefit of prevention of CVD. Patient values and preferences are similar because most patients value cardiovascular disease prevention. Thus, the Work Group decided upon a *Weak against* recommendation.

Recommendation

40. For women less than 60 years old and less than 10 years from the onset of menopause with established cardiovascular disease (CVD) and significant VMS, we suggest consideration of systemic estrogen-containing therapies based on the lack of evidence for increased cerebrovascular and cardiovascular morbidity and mortality.
    (Weak for | Reviewed, New-added)

Discussion

CVD refers to conditions that affect the heart and blood vessels and generally includes coronary heart disease (invasive and noninvasive angiographic obstructive and nonobstructive coronary atherosclerosis, angina, MI, and coronary revascularization), cerebrovascular disease (stroke and transient ischemic attack), and venous thromboembolic disease (deep vein thrombosis and pulmonary embolus). In one SR of six RCTs, treatment with low and moderate oral estrogen alone and combined sequential and continuous CEE and medroxyprogesterone in perimenopausal and postmenopausal women with a mean age of 66.5 years with established CVD did not result in increased cardiovascular death or nonfatal MI during a mean follow-up of 2.7 years (range 1 to 4.1 years).(248) A second SR of 4 RCTs also found no difference between placebo and moderate dose of oral estrogen alone (estradiol valerate 2 mg, RR 1.00, 95% CI: 0.72 to 1.39, p=0.99; CEE 0.625 mg, RR 1.13, 95% CI: 0.54 to 2.40, p=0.74) or combined (CEE 0.625 mg plus MPA 2.5 mg, RR 1.07, 95% CI: 0.86 to 1.33, p=0.56) and sequential oral estrogen and progestogen (estradiol one mg plus MPA five mg for 12 days a year, RR 0.97, 95% CI: 0.57 to 1.65, p=0.91) in coronary heart death or MI in perimenopausal and post-menopausal women with a mean age of 67 years during follow-up of 1-6.8 years.(249)

Bontempo et al. 2024 (248) (five RCTs) found no excessive risk of stroke when peri- and post-menopausal women were treated with oral estrogen alone or with combined sequential and continuous CEE and medroxyprogesterone during a 2-4.2 year follow-up period. Similarly, Marjoribanks et al. 2017 (249) (five RCTs) also did not find increased first or recurrent stroke, transient ischemic attack, or stroke death risk in women who received oral hormonal therapy when compared to placebo. The follow-up period in this SR, however, was shorter at 2.8 years.

In peri- and post-menopausal women who were treated with a moderate dose of oral estrogen alone (CEE or estradiol valerate), a SR of three RCTs did not demonstrate increased risk of developing first or recurrent deep venous thrombosis or pulmonary embolus.(249) However, data are mixed when women were prescribed combined continuous oral hormonal therapy. Those who were treated with oral estradiol and norethisterone acetate did not experience adverse venous thromboembolic events compared to placebo. In contradistinction, women who received CEE and medroxyprogesterone had a three-fold increase (95% CI 1.5 to 6.04) in developing first or recurrent deep venous thrombosis or pulmonary embolus during three years of follow-up (three RCTs). Interestingly, one RCT with a similar number of participants did not demonstrate an increased risk of deep vein thrombosis or pulmonary embolus, but this study was unblinded, and follow-up duration was longer, ranging between four and seven years.(249) In addition to the ambiguous clinical outcomes data, the paucity of high-quality data in the Evidence Base precludes the inclusion of venous thromboembolic disease in the Work Group's recommendation.

High-quality data on the impact of non-oral estrogen preparations on cardiovascular, cerebrovascular, and venous thromboembolic disease are not available. Similarly, RCTs examining the safety of estrogen-containing therapies in peri- and post-menopausal women with established microvascular disease, spontaneous coronary artery dissection, and adverse pregnancy outcomes (gestational, preeclampsia, eclampsia, hemolysis, elevated liver enzymes, low platelets [HELPP] syndrome, gestational diabetes, preterm birth, intrauterine growth restriction [birthweight ≤10th percent for gestational age], small-for-gestational age delivery [birthweight <5th

percentile for gestational age], placental abruption, stillbirth, and pregnancy loss) have not been conducted.

Although not included in the current CPG evidence base because the publication date was not within the evidence review time frame, in the Multi-Ethnic Study of Atherosclerosis (MESA) prospective observational cohort of 2,427 women with mean age 63.3 years who were treated with hormonal therapy (estrogen only and estrogen and progesterone; formulations of oral or patch was not specified) within 5 years of menopausal onset, there was a 28% reduction in MACE (death from cardiac cause, resuscitated cardiac arrest, MI, stroke, new heart failure diagnosis, or any coronary revascularization) and a 38% reduction in all-cause; mortality during a median follow-up period of 14 years.(250) These risk reductions were not observed in women who received hormonal therapies five years after menopause onset. Compared to women who did not receive hormonal therapy, disaggregated data with respect to racial subgroups revealed that MACE was reduced only in the Black and Hispanic subgroups, was similar in the White subgroup, and was increased in the Chinese subgroup. A reduction in all-cause mortality was observed only in the White and Black subgroups. This study highlights the importance of examining the effects of hormonal therapy in underrepresented population groups.

In another study not included in our CPG evidence review because the publication date also fell outside of the evidence review time frame, Xu et al. 2025 reported that in a large cohort of 9,295 women Veterans without pre-existing CVD and with median age of 51.5 years, who were treated with any oral or transdermal estrogen containing product or any oral or transdermal combined estrogen and progestin product experienced a higher risk of developing CVD, stroke, and venous thromboembolic disease and a higher risk of dying from any cause over a 15-year follow-up period. (251) Even though this retrospective longitudinal study focused on women Veterans, it was rated Low quality based on its non-randomized study design and thus was not included in the evidence review.

Data from the Heart and Estrogen/progestin Replacement Study (HERS) trial, a secondary CVD prevention trial, and its sub-studies were reviewed in the evidence base within Bontempo et al. 2024 SR and meta-analysis because the primary publications fell outside of the review inclusive dates. Since the results have influenced clinical practice for the past 28 years, it is important to review its major safety endpoints even though the data may not be generalizable to present-day menopausal women because contemporary treatment of CVD risk factors, particularly hyperlipidemia, diabetes, and obesity, has advanced dramatically. Menopausal hormonal therapy has not been prescribed for perimenopausal or post-menopausal women with established CVD because in addition to the adverse effects experienced by healthy women reported in the WHI trial, the HERS trial reported a higher risk of nonfatal MI, coronary heart death, and venous thromboembolic event in the oral hormonal therapy arm after one year of treatment despite neutral overall coronary heart disease risk at 4.1 years (252), and at 6.8 years follow-up.(253) However, it should be emphasized that this early observation of adverse outcome is only applicable to older women (mean age 66.7 years) who initiated oral hormonal therapy (CEE 0.625 mg daily +/- MPA 2.5 mg daily) >10 years after menopause onset (mean 18 years). In addition, the HERS trial did not examine alternative formulations such as transdermal estradiol and lower-dose regimens. Furthermore, although the WHI trial enrolled healthy women without clinical

evidence of CVD, its ancillary study, WHI- Coronary Artery Calcium Study (CACS) examined the effect of oral estrogen monotherapy (CEE 6.25 mg daily) on subclinical atherosclerosis as measured by the surrogate marker coronary artery calcium score and found that in women age 50 to 59 years, the calcified plaque burden was significantly lower compared to the placebo group (mean CAC score 83.1 vs 123.1, p=0.02).(254)

The HERS and HERS II studies found that women randomized to CEE + MPA did not experience an increased risk of nonfatal or fatal stroke.(252,253) On the contrary, women who were treated with oral CEE + MPA were more likely to experience a venous thromboembolic event throughout the 6.8 years follow-up period, unlike like coronary heart disease risk, which dissipated over time.(255)

After reviewing the evidence base and historical data in totality, the Work Group determined that treatment of severe VMS in postmenopausal women younger than age 60 years, with menopausal onset less than 10 years, and without high CVD risk (history of high burden of atherosclerotic cardiovascular disease (ASCVD)/peripheral artery disease (PAD), deep vein thrombosis (DVT), pulmonary embolus, breast cancer, congenital heart disease, or high Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) or VA women CV risk score-derived 10-year ASCVD risk) after shared-decision discussion does not increase the stroke and CHD risk. Thus, women who meet both the age and menopause onset specifications and have only had remote cardiovascular events with low CVD risk, can be candidates for systemic estrogen-containing therapies, with the caveat that the optimal duration of MHT treatment is unknown. RCTs comparing the cardiovascular effects of systemic and nonsystemic estrogen products in postmenopausal women with known CVD are not available. Despite the removal of the Black Box warning from estrogen products used for menopausal treatment by the FDA in November 2025, the Work Group acknowledges that providers may be reluctant to change clinical practice because of variable knowledge or uncertainty with paradigm shift.

The VA/DOD Menopause Patient Focus Group participants strongly favor a shared-decision approach when weighing the risks and benefits of menopausal hormonal therapies in the setting of pre-existing CVD. They desire evidence-based counseling from providers on the effect of hormonal treatment on subsequent cardiovascular outcomes based on their CVD risk profile. Therefore, our evidence base determined that systemic MHT should not be withheld for women with pre-existing CVD without individualized consideration of the age of menopausal onset, the duration of menopause status, the severity of menopausal symptoms, and the magnitude of CVD risk profile.

The Work Group systematically reviewed evidence in two SRs composed of seven RCTs (248) and six RCTs (249) related to this recommendation. Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including variable odds ratios, imprecision in effect estimates, and a wide range of follow-up durations. Some of the subgroup analyses were underpowered (249) (coronary heart death/moderate estrogen only; first or recurrent stroke/CEE; first or recurrent stroke/combined continuous hormonal therapy; and first or recurrent venous thromboembolic event/combined continuous hormonal therapy). Furthermore, some investigations

were conducted >20 years ago and potentially could have underestimated the magnitude of adverse risk from diabetes and obesity, which are now more prevalent. Finally, the five RCTs that examined the risk of venous thromboembolic events had a large variance in both the results and the CI.(249) The benefits of mitigating significant VMS considering oral systemic hormonal therapy in peri- and post-menopausal women with established cardiovascular disease, provided they meet age and menopause duration restrictions, slightly outweigh the harms of withholding hormonal treatment. Patient values and preferences varied somewhat because their hormonal therapy treatment preference is dependent on balancing the undesirable effects of menopause with their unique cardiovascular and cerebrovascular risk profile. They prefer a shared decision approach with integration of all of their co-occurring medical conditions. Thus, the Work Group decided upon a *Weak for* recommendation.

b. Breast Cancer Risk

Recommendation

41. For hormone-positive breast cancer survivors, we suggest against the use of systemic hormone therapy.
(Weak against | Reviewed, New-added)

Discussion

The Work Group reviewed evidence from five RCTs included in two SRs (256,257) comparing systemic MHT, both with and without progestogen, to placebo. The findings suggest that systemic MHT is associated with higher rates of breast cancer recurrence, with a Moderate strength of evidence.

A subgroup analysis based on HR status (one SR of four RCTs (256)) indicates that HR-positive breast cancer survivors are at increased risk of recurrence when using systemic MHT, with Moderate strength of evidence. Conversely, the subgroup analysis for HR-negative disease did not show higher rates of recurrence. However, the Work Group determined that the evidence was insufficient to make a separate recommendation for HR-negative breast cancer survivors due to limited data supporting safety for or against systemic MHT use in this population.

Interestingly, evidence from four RCTs in one SR (257) suggests no difference in breast cancer mortality between systemic MHT and controls, again with Moderate strength of evidence. However, the studies lacked stratification for stage, receptor status, and treatment, making it challenging to interpret the results for all breast cancer survivors.

The Work Group carefully balanced the increased risk of recurrence with the lack of increased mortality risk and ultimately settled on a *Weak against* recommendation for the use of systemic MHT in HR-positive breast cancer survivors. This decision reflects the potential harm of recurrence. The Work Group also acknowledged the likely variation in patient values and preferences, which may be influenced by the severity of menopausal symptoms experienced by the patient. Additionally, there is significant variation in provider comfort levels when discussing systemic MHT in this patient population.

The Work Group emphasizes the importance of shared decision-making when managing menopausal symptoms in breast cancer survivors. Recommendations should be tailored to the patient's unique clinical context, including symptom severity, cancer stage, receptor status, and treatment history.

Breast cancer is the most common cancer among American women with high survival rates.

Breast cancer treatment often leads to premature menopause or menopausal side effects, presenting significant challenges for survivors. Breast cancer is one of the most common contraindications to MHT, making the management of menopausal symptoms particularly complex in this population.

Managing menopausal symptoms in breast cancer survivors requires a nuanced approach due to the heterogeneity of the disease. Breast cancer includes HR-positive and HR-negative subtypes, as well as a spectrum of stages ranging from DCIS (stage 0) to metastatic disease. Treatment modalities vary widely, from bilateral mastectomy with no remaining breast tissue to lumpectomy with preserved breast tissue. These factors must be carefully considered when providing care and engaging in shared decision-making with breast cancer survivors. A "one-size-fits-all" approach is not appropriate.

Given the current evidence, shared decision-making is essential in managing menopausal symptoms in breast cancer survivors. Each patient's unique clinical context, including cancer stage, HR status, treatment history, and the presence of remaining breast tissue, should guide individualized care.

The Work Group systematically reviewed evidence related to this recommendation, Poggio et al. 2022 (256) and Mudhune et al. 2019 (257). Therefore, it is categorized as Reviewed, New-added. The Work Group's confidence in the quality of the evidence was Moderate. The body of evidence had some limitations, including a heterogeneous population of breast cancer survivors, varied formulations of MHT, and not accounting for the stage or treatment course of patients. The benefits of managing menopausal symptoms did not outweigh the adverse event of breast cancer recurrence in hormone positive breast cancer survivors. Patient values and preferences varied largely because the risks of breast cancer recurrence are serious and the severity of menopausal symptoms varies from patient to patient. Thus, the Work Group decided upon a *Weak against* recommendation for the use of systemic MHT for the management of menopausal symptoms in HR-positive breast cancer survivors.

Recommendation

42. For women with an intact uterus taking systemic estrogen, there is insufficient evidence to recommend for or against any one of the following progestogen formulations over another to modify breast cancer risk:
    - Oral Drospirenone
    - Transdermal or 52 mg levonorgestrel intrauterine device (LNG IUD)
    - Oral micronized progesterone
    - Oral medroxyprogesterone acetate (MPA)
    - Oral or transdermal Norethindrone acetate

(Neither for nor against | Reviewed, New-added)

Discussion

As a result of the findings noted in the WHI, the risk of breast cancer and its possible association with medroxyprogesterone have been raised. By further extension, the safety and efficacy of other progestogens with and without estrogen for menopause hormone therapy have been questioned in reference to breast cancer risk.

Multiple studies have been conducted and reviewed for the safety and efficacy of various progestogens for use in menopause hormone therapy for endometrial protection, but none specifically for breast cancer risk. As noted in this recommendation, there is insufficient evidence to recommend one progestogen over another to modify breast cancer risk. Based on an SR with Low strength evidence (258), review of all available progestogens showed that none had clinical superiority for modifying breast cancer risk.

Multiple studies compared Medroxyprogesterone, Norethindrone acetate, and micronized progesterone both in cyclical vs continuous administration at various dosages, and the 52 mg LNG IUD for their use in prevention of endometrial intraepithelial neoplasm (EIN).(258) Studies were lacking for the same progestogens and their ability to modify breast cancer risk. When reviewing the available data specifically for the association of the use of progestogens and the development of breast cancer or breast cancer risk, the data is lacking. Most of the available literature referencing progestogen use and breast cancer risk comes from studies reviewing progestogen use in reference to EIN prevention. Only one study in the SR, Lobo et al. 2018(93) specifically noted breast cancer risk as part of its summary data. It showed no increased risk of breast cancer after one year of micronized progesterone use for EIN prevention, but the study was limited by the time interval and small numbers of participants in the study. See Recommendation 5 for more on progestogen risk.

Only one study addressed the question of breast cancer risk and progestogen use. It was not included in the review as it was an observational study and considered poor quality.(259) To date, there have been no head-to-head studies comparing the various progestogens for breast cancer safety.

The use of SERMs and vaginal progesterone were not addressed in this recommendation.

When making the recommendation, the Work Group considered patient values and preferences as well as mode of delivery (transdermal and LNG IUD) options. The addition of the LNG IUD for women who still need contraception and/or control of irregular bleeding during the perimenopause transition gives the patient additional options beyond traditional oral contraceptives and other modalities. Given the LNG IUD's mode of action being localized to the endometrium of the uterus with minimal systemic absorption, it is empirically thought to have minimal effect on the breast tissue, so off-label use has been supported. Given our patient population and the national pharmaceutical formulary in the VHA and DOD, these options are available and allow for shared decision-making with the patient.

The Work Group systematically reviewed the relevant studies in the current CPG evidence base.(93,258) Therefore, it is categorized as Reviewed, New-added. The Work Groups

confidence in the quality of the evidence was Low. The body of evidence had insufficient evidence evaluating the use of progestogens and their effect on breast cancer risk modification, benefits outweigh the risk of use in safety and efficacy. Patient values and preferences varied due to preferred modes of delivery. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

43. When selecting a progestogen in women with an intact uterus taking systemic estrogen, there is insufficient evidence to recommend any one of the following progestogen formulations over another for protection against endometrial cancer:
    - Oral Drospirenone
    - Transdermal or 52 mg levonorgestrel intrauterine device (LNG IUD) Oral micronized progesterone
    - Oral medroxyprogesterone acetate (MPA)
    - Oral or transdermal Norethindrone acetate

    (Neither for nor against | Reviewed, New-added)

Discussion

The safety and efficacy of the use of a progestogen with systemic estrogen use for the prevention of endometrial hyperplasia/ EIN has been established in multiple studies. As noted in this recommendation, there is insufficient evidence to recommend one progestogen over another for this treatment. Based on an SR of the Low strength evidence (70 RCTs, Stute et al. 2024 (258)), review of all available progestogens showed that none had clinical superiority for the prevention of EIN.

Multiple studies compared Medroxyprogesterone, Norethindrone acetate, micronized progesterone, both in cyclical vs continuous administration at various dosages, and the 52 mg LNG IUD. All studies failed to show superior effectiveness over another in EIN prevention.(258) It is important to note that the recent recommendation by the National Comprehensive Cancer Network has recommended the use of the 52 mg LNG IUD as first-line therapy for endometrial cancer limited to the uterus and not suitable for surgery or in patients who desire future fertility. Even with this recommendation, there is a lack of data to recommend one progestogen over another at this time.(260)

From the review of the evidence, all progestogens performed equally well with limited to no incidence of EIN. All of the studies reviewed showed an incidence of EIN to be less than 1% by histology confirmation.(258) This evidence led the Work Group to conclude that any of the above-noted progestogens can be used to prevent EIN.

The Work Group noted that there are considerable differences in the mode of action of natural micronized progesterone and synthetic progestogens. Although micronized progesterone appears theoretically to be a more favorable progestogen to use long term in MHT due to effects at the receptor site and its possible decreased breast cancer and cardiovascular risks, the data does not exist to favor that formulation over another at this time.

The risk/benefit of each progestogen was reviewed in the analysis. The conclusion after review of the data was also mixed, with a slightly increased risk of breast cancer noted with the use of medroxyprogesterone, as suggested in the WHI and others. In contrast, Lobo et al. 2018 (93) showed no increased risk of breast cancer after one year of micronized progesterone use for EIN prevention, but the study was limited by the time interval and small numbers of participants in the study.

Vaginal progesterone was reviewed in the SR but was recommended against given the increased incidence of EIN and poor study quality (Early Versus Late Intervention Trial with Estradiol [ELITE Study]).(261) The use of SERMs, although included in some of the studies, was not addressed in this recommendation.

When making the recommendation, the Work Group considered patient values and preferences, including mode of delivery (transdermal or LNG IUD), when recommending treatment options. These modalities were found to be effective, with low adverse risk noted. Given our patient population and the national formularies available in the VA and DOD, these options are available and allow for shared decision-making with the patient.

The addition of the LNG IUD for women who still need contraception and/or control of irregular bleeding during the perimenopause transition gives women additional options beyond traditional oral contraceptives and other modalities. Although the use of the levonorgestrel 52 mg intrauterine device has been extended up to eight years for contraception by recent data, its length of use for endometrial protection for EIN remains unclear. At present, its off-label use for EIN protection is limited to 5 years. Beyond that time, shared-decision making in low-risk patients with close monitoring, i.e., possible transvaginal ultrasound for endometrial lining checks, can be considered.(262)

Prevention of EIN supports better overall health of menopausal women by preventing EIN while being treated with estrogen for other symptomatic menopausal issues. Having multiple options for prevention helps to ensure patient compliance and overall decreased risk of EIN.

The Work Group systematically reviewed the relevant studies in the current CPG evidence base, Stute et al. 2024 (258). It is categorized as Reviewed, New-added. The confidence in the quality of the evidence was Low based on the unblinding of participants/personnel, underpowering (due to small numbers) increasing risk of bias in the studies. The benefits of treatment clearly outweigh the risk of use in terms of safety and efficacy for the prevention of EIN. Patient values and preferences were taken into account primarily by prevention of EIN, safety noted in all treatment modalities, and patient preference in mode of delivery. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

X. Research Priorities

The development of the VA/DOD Menopause Clinical Practice Guideline highlights meaningful advances in menopausal care while also revealing significant evidence gaps that warrant further investigation and stronger evidence. Continued research in the following categories is essential to strengthen the quality, safety, and applicability of clinical recommendations, particularly for Veterans and active duty Service members.

A. Menopause Diagnosis, Biomarkers, and Clinical Benchmarks

Research is needed to further refine diagnostic strategies and biologic predictors of the menopausal transition. Although current evidence does not support the routine use of laboratory testing for the diagnosis of menopause, emerging biomarkers, particularly AMH, may have clinical utility as assay precision improves. Future investigations should prioritize enhancing the reliability and predictive validity of these biomarkers, particularly across diverse populations and clinical contexts.

Additional research is needed to clarify whether biomarker-based approaches can meaningfully inform individualized treatment timing and therapeutic decision-making, especially during perimenopause, when hormonal variability and symptom burden are most pronounced. Establishing the appropriate clinical role of laboratory markers will be essential to ensure diagnostic accuracy while avoiding unnecessary testing.

Research on menopause faces major methodological challenges, including inconsistent measures of symptom severity (e.g., for VMS) and a lack of established clinically meaningful difference benchmarks, which limit comparability across studies. Future research would benefit from standardized terminology and outcome measures to enable clearer evaluation and synthesis of results across the menopause literature.

B. Hormone Therapy: Formulations, Safety, Timing, and Special Populations

A substantial portion of the recommendations developed pertain to MHT, with emphasis on comparative effectiveness, long-term safety, and subgroup-specific outcomes. Research is needed for adequately powered, head-to-head RCTs comparing estrogen-only therapy with combined estrogen-progestogen regimens, as well as direct comparisons among commonly used formulations. These include CEE plus MPA versus estradiol-based regimens combined with progesterone or alternative progestins. Critical variables requiring systematic evaluation include dosage, route of administration (oral, transdermal, vaginal, and systemic), duration of therapy, and long-term risks such as breast cancer, CVD, stroke, venous thromboembolism, and dementia. Research into key symptoms such as VMS that are inherently subjective would benefit from standardized clinically meaningful patient-reported outcome measures.

Further research should also examine the influence of the timing of initiation, particularly during perimenopause vs. early or late post menopause, on outcomes including cognition, mood, sleep, osteoporosis prevention/treatment, musculoskeletal symptoms, and dementia prevention. Contemporary studies are needed in subpopulations with established cardiovascular or cerebrovascular disease, microvascular disease, spontaneous coronary artery dissection,

adverse pregnancy outcomes (gestational, preeclampsia, eclampsia, HELPP syndrome [hemolysis, elevated liver enzymes, low platelets], gestational diabetes, preterm birth, intrauterine growth restriction [birthweight ≤10th percent for gestational age], small-for-gestational age delivery [birthweight <5th percentile for gestational age], placental abruption, stillbirth, and pregnancy loss), and coexisting psychiatric conditions. This population was not adequately addressed by WHI. Focused investigations in breast cancer survivors, individuals with contraindications to systemic estrogen, and those at elevated baseline cancer or cardiovascular risk are similarly critical. Additional research into specific progestogens, SERMs, and bazedoxifene-containing regimens is necessary to outline optimal strategies for endometrial protection and breast safety while facilitating individualized therapeutic selection.

Research is also needed to identify and address knowledge and training gaps among healthcare providers regarding the evaluation and management of menopause and female sexual dysfunction, including the appropriate use of hormone therapies such as testosterone for FSIAD, to improve access to evidence-based care for women.

C. Non-Hormonal Pharmacologic Therapies for Menopausal Symptoms

A key research priority for this CPG is further research on non-hormonal therapies for VMS. Rigorous comparative effectiveness studies are needed to evaluate SSRIs, SNRIs, gabapentin, and NK1 and NK3 receptor antagonists, both relative to one another and in comparison with standardized hormone therapy regimens. Additionally, data on sertraline and fluoxetine is limited and warrants further investigation. Such trials should incorporate standardized dosing protocols, adequate duration of follow-up, and systematic assessment of adverse effects and treatment discontinuation rates.

Long-term safety data are particularly necessary for newer agents, including NK1 and NK3 receptor antagonists, especially among patients with common mental health and medical comorbidities. Greater representation of individuals with pre-existing mood disorders will enhance generalizability. Well-designed head-to-head trials assessing durability of symptom control, adverse event profiles, and patient-reported outcomes are essential to inform shared decision-making, including in Veteran and active duty populations.

Additionally, further research on non-hormonal therapies for menopausal symptoms beyond VMS is warranted. Evidence supporting effective interventions for symptoms such as menopause-related sleep disturbances and musculoskeletal symptoms remains limited. Addressing these gaps could improve symptom management and overall quality of life.

D. Behavioral, Complementary, and Integrative Health Interventions

Behavioral interventions, including CBT and mindfulness-based interventions demonstrate potential benefit for psychological and menopausal symptoms; however, further investigation is required to clarify their role. Future studies should evaluate targeted CBT approaches for specific symptom domains, such as sexual health to determine relative effectiveness and scalability. Comparative trials between CBT and MBSR, as well as subgroup analyses based on menopausal stage and psychiatric comorbidity, would further refine clinical guidance.

CIH interventions (such as acupuncture, chiropractic interventions, clinical hypnosis, meditation, protocolized mindfulness, and Tai Chi) and dietary supplements require more methodologically rigorous evaluation. Larger RCTs utilizing standardized and pharmacologically consistent dosing of commonly used supplements, including black cohosh, ginseng, and red clover, are necessary to generate higher-quality evidence for clinical counseling. Comparative effectiveness research and intentional inclusion of diverse patient cohorts will be essential to determine which individuals may derive meaningful benefit from these interventions.

E. Genitourinary Syndrome of Menopause (GSM) and Sexual Dysfunction

Research priorities in GSM and sexual dysfunction emphasize comparative effectiveness, safety, and population-specific outcomes. Direct comparisons of local versus systemic estrogen therapy for sexual function are needed, including evaluation of route-specific effects and the impact of concomitant progesterone in individuals with an intact uterus. Subgroup analyses across perimenopause, early menopause, and late menopause, as well as among individuals with and without genitourinary symptoms, will enhance individualized treatment recommendations.

Further investigation is warranted for vaginal therapies, including moisturizers, DHEA, and estrogen preparations, with larger sample sizes and direct comparative trials. Long-term safety data beyond 52 weeks are required for testosterone therapy, particularly in perimenopausal populations where new-onset sexual dysfunction is prevalent. FDA-approved options of testosterone for women are desperately needed. Additional subgroup analyses of flibanserin efficacy in perimenopausal individuals and trials evaluating bremelanotide in postmenopausal populations represent important unmet research needs. High-quality RCTs assessing the safety of local vaginal estrogen in breast cancer survivors are strongly recommended and needed to build on/bolster existing observational studies.

F. Bone Health, Weight Management, Cardiometabolic Risk, and Lifestyle Interventions

Future research should refine preventive and therapeutic strategies for osteoporosis, fracture risk, and cardiometabolic outcomes. Studies are needed to determine optimal dosing, duration, and patient selection criteria for calcium supplementation, vitamin D3, bisphosphonates, raloxifene, and conjugated estrogen/bazedoxifene combinations. Extended follow-up periods are critical to evaluate long-term safety, particularly for bisphosphonates and hormone-based therapies. Comparative effectiveness trials across pharmacologic agents will support risk-based, individualized fracture prevention strategies. Another key research priority is to investigate the effect of menopause on musculoskeletal pain and to evaluate the efficacy of MHT as a treatment option for managing these symptoms.

Lifestyle interventions, including calorie restriction, dietary modification, and structured exercise, require more rigorous and standardized investigation. Future trials should evaluate varying degrees of caloric restriction, macronutrient composition, vegetarian versus vegan dietary patterns, and long-term sustainability and harms. Exercise studies should standardize clinically relevant outcome measures (e.g., weight, body mass index, waist circumference, and body composition), compare structured versus self-directed programs, and assess combined aerobic

and resistance approaches. Adequate sample sizes, longer follow-up durations, and stratification by menopausal stage and baseline comorbidity will enhance clinical applicability and external validity. Future research studies should also focus on musculoskeletal pain and sleep disturbance associated with menopause. More studies are needed on the benefits of GLPs in perimenopause and menopause.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence, review, the Work Group drafted 20 KQs on clinical topics of the highest priority for the VA and DOD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ) (see **Table A-1**).

Table A-1. PICOTS (263)

P	Patients, Population, or Problem	Patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic/screening test used with the patient or population.
C	Comparison	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
O	Outcome	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
(T)	Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
(S)	Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs were not able to be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of highest priority, and those were included in the review. **Table A-2** contains the final set of KQs used to guide the systematic evidence review for this CPG.

a. Population(s)

- The clinical population considered in this SR is individuals with naturally occurring or surgically/iatrogenically induced perimenopause or menopause (within 10 years). Note that individuals under 40 with natural menopause should be evaluated by specialists.
- The population of interest differs for the following KQs:
    - KQ11 – peri- and menopausal breast cancer survivors. Subgroups of interest for KQ11 include those on adjuvant therapy (Tamoxifen vs AI vs completed), Estrogen Receptor/Progesterone Receptor (ER/PR) negative breast cancer survivors, and DCIS and Human Epidermal Growth Factor Receptor 2 (HER2)
    - KQ12 – peri- and post-menopausal women with depression

- KQ13 – women already on estrogen – either peri-menopausal women with an intact uterus or menopausal women with an intact uterus
- KQ17 – menopausal women on MHT within 10 years of menopause
- KQ18 – patients with a history of nonobstructive coronary artery disease, myocardial infarction, spontaneous coronary artery dissection, microvascular disease, or a history of VTE.

- For the remaining 15 KQs, the overall clinical population applies, although some KQs additionally focus on specified subgroups:
  - KQ1 – MHT for vasomotor: age, time since menopause onset, intact uterus, hysterectomy, demographic groups (i.e., smoking status, race/ethnicity), baseline severity of vasomotor symptoms
  - KQ2 – non-hormonal for vasomotor: age, time since menopause onset, demographic groups (i.e., smoking status, race/ethnicity), baseline severity of vasomotor symptoms
  - KQ5 – patients with GSM
  - KQ6 – MHT for CVD: Age <60 years, Within 10 years of menopause onset, Age ≥ 60 to 69 years, Age ≥ 70 to 79
  - KQ7 – MHT for sleep: With and without vasomotor symptoms
  - KQ8 – MHT on cognition/dementia: Patients with and without cognitive impairment
  - KQ10 – MHT/other pharmacotherapy for osteoporosis: after stopping hormone replacement therapy (HRT) and Iatrogenic menopause
  - KQ19 – pharmacotherapy for genitourinary: patients with a history of hormone-sensitive cancer

b. Interventions and Comparators

KQ	Intervention(s)	Comparator(s)
1	▪ Combination estrogen and progesterone ▪ Conjugated estrogens/bazedoxifene (CE/BZA) ▪ Low dose estrogen (0.3 mg oral/day or <0.05 mg/day transdermal) ▪ Micronized progesterone ▪ Selective estrogen receptor agonist/antagonist (ospemifene) ▪ Synthetic hormones, including estradiol, conjugated equine estrogens, estradiol valerate, bioidentical estrogen ▪ Synthetic progestogens **Note: Evidence team will table duration of therapy if provided**	▪ No pharmacotherapy ▪ Placebo
2	▪ Antidepressants (See Antidepressants Table) ▪ Clonidine	▪ No pharmacotherapy ▪ Placebo

KQ	Intervention(s)	Comparator(s)
	▪ Gabapentin or pregabalin ▪ Kisspeptins neurokinin B antagonist class (Fezolinetant) ▪ Oxybutynin	
3	▪ Acupuncture ▪ Aromatherapy ▪ Biofeedback ▪ Chiropractic interventions ▪ Hypnosis (self-managed) ▪ Low-frequency sound-wave therapy ▪ Meditation ▪ Mindfulness (not therapist delivered) ▪ Paced breathing ▪ Relaxation techniques and breath-based techniques, relaxation response training ▪ Yoga and Tai Chi	▪ No treatment ▪ Placebo ▪ Sham treatment ▪ Treatment as usual **Note: monotherapy and adjunctive are both of interest**
4	▪ Behavioral Therapy (e.g., using cooling techniques to help manage hot flashes or avoid eating habits that tend to increase symptoms) ▪ CBT/CBT-Meno ▪ Clinical Hypnosis (therapist/provider delivered) ▪ Cognitive Therapy ▪ Mindfulness-based therapies (MBCT, MBSR) **Note: WG interested in the following forms of delivery: Individual (in person), individual (virtual), group (in person), group (virtual), group (virtual), Apps**	▪ Education only (e.g., psychoeducation, menopause education ▪ Placebo ▪ Treatment as usual ▪ Wait list
5	▪ Bazedoifene ▪ Bremelanotide ▪ Bupropion ▪ Buspirone ▪ Estrogen (systemic or vaginal) ▪ Flibanserin ▪ Ospemifene ▪ Raloxifene ▪ Sildenafil ▪ Testosterone and derivatives ▪ Vaginal dehydroepiandrosterone (DHEA) ▪ Vaginal lubricants and moisturizers ▪ Vaginal oxytocin	▪ No medication ▪ Placebo
6	▪ Combination estrogen and progesterone ▪ Estradiol gels, sprays, creams ▪ Estradiol patches ▪ Estrogens, oral ▪ Estrogens, transdermal ▪ Low-dose hormonal therapies ▪ Natural and synthetic estrogens, conjugated equine estrogens	▪ No treatment ▪ Placebo

KQ	Intervention(s)	Comparator(s)
	▪ Progestins ▪ Synthetic estrogens, including estradiol, estradiol valerate ▪ Synthetic progestogens ▪ Synthetic, selective estrogen receptor modulator (SERM), raloxifene, etc. ▪ Tibolone, which exhibits estrogenic, progestogenic, and androgenic effects	
7	Systemic hormone replacement therapy including estrogen only, progesterone only, and combined menopause hormone therapy (estrogen plus progesterone)	▪ No MHT (could include CBT, SSRI/SNRI, or Neurokinin B receptor antagonists delivered to both intervention and comparator groups) ▪ Placebo
8	▪ Progesterone only ▪ Systemic combined estrogen and progesterone (oral, transdermal) ▪ Systemic estrogen only (oral, transdermal, vaginal) ▪ Testosterone	▪ No MHT ▪ Placebo **Note: Utilization prior to or after age 65 and duration of therapy will be tabled if provided**
9	▪ Ammonium succinate ▪ Black cohosh ▪ Cannabinoids such as marijuana, ▪ Chasteberry, ▪ Dong quai, ▪ Evening primrose, ▪ Ginseng ▪ Lactobacillus acidophilus ▪ Maca (Andean plant of mustard family) ▪ Magnesium ▪ Milk thistle ▪ Omega-3 fatty acid ▪ Pollen extract ▪ Red clover (t.pratense isoflavones) ▪ Rhubarb ▪ Soy extracts, and soy metabolite equol (S-equol) ▪ Vitamin E ▪ Wild yam (dioscorea)	▪ No treatment ▪ Placebo
10	▪ Anabolic agents (teriparatide, raloxifene, etc.) ▪ Bisphosphonates (oral or IV, denosumab) ▪ Calcium ▪ Conjugated estrogen/bazedoxifene combination ▪ D3 ▪ MHT	▪ No treatment ▪ Placebo
11	▪ Ospemifene ▪ Systemic MHT (oral, transdermal, vaginal) ▪ Topical estrogen for GSM (creams, rings, tablets) ▪ Vaginal DHEA (prasterone)	▪ No treatment ▪ Placebo ▪ Usual Care
12	▪ Estrogen therapy ▪ Estrogen + progesterone	▪ Antidepressants alone (See Antidepressants Table)

KQ	Intervention(s)	Comparator(s)
	▪ Testosterone with or without Antidepressants	▪ Placebo
13	▪ Hormonal IUD at different doses ▪ Oral micronized progesterone ▪ SERMs (Bazedoxifene) ▪ Synthetic progesterone (Medroxyprogesterone acetate, norethindrone) ▪ Vaginal micronized progesterone	▪ One intervention compared to itself but by 1) another delivery method, 2) a different duration, or 3) at a different dosage ▪ One type or generation of progesterone compared to another
14	▪ Anti-inflammatory diet ▪ Low-carb diet ▪ Mediterranean diet ▪ Negative energy balance diet ▪ Phytoestrogens/Soy diet ▪ Plant-based diet ▪ Vegan Diet ▪ Whole food	▪ No specified diet ▪ Standard American diet
15	▪ Hormonal therapies: ▪ Synthetic hormones including estradiol, conjugated equine estrogens, estradiol valerate, bioidentical estrogen ▪ Synthetic progestogens ▪ Combination estrogen and progesterone ▪ Conjugated estrogens/bazedoxifene (CE/BZA) ▪ Selective estrogen receptor agonist/antagonist (ospemifene)	▪ Non-hormonal therapies: ▪ Antidepressants (See Antidepressant Table) ▪ Clonidine ▪ Gabapentin or pregabalin ▪ Kisspeptins neurokinin B antagonist class (Fezolinetant) ▪ Oxybutynin
16	▪ Anti-Muellerian hormone ▪ FSH ▪ STRAW staging system – including FSH and Anti-Muellerian hormone ▪ Validated questionnaires	Standard clinical evaluation (e.g., history and physical)
17	Low dose estrogen (0.3 mg oral/day or <0.05 mg/day transdermal)	Standard dose estrogen (0.625 mg/day oral or 0.05 mg/day transdermal)
18	▪ Combined estrogens and progestins, oral and transdermal ▪ Estrogens only oral or transdermal ▪ Local MHT ▪ Systemic MHT ▪ Vaginal estrogens only	▪ No MHT ▪ Placebo **Note: we will capture if patients are on Guideline-Directed medical therapy for CVD, if reported**
19	▪ Systemic MHT ▪ Vaginal creams (estradiol, conjugated estrogen, estrone) ▪ Vaginal inserts (estradiol, DHEAS) ▪ Vaginal moisturizers ▪ Vaginal ring (estradiol) ▪ Selective estrogen receptor agonist/antagonist (ospemifene) ▪ Vaginal laser ▪ Oxybutynin	▪ No MHT ▪ Placebo

KQ	Intervention(s)	Comparator(s)
20	▪ Aerobic exercises ▪ Combination exercise program ▪ High Intensity Interval Training (HIIT) ▪ Resistance exercises ▪ Strength training	No exercise

c. Antidepressant Medications

Drug Class	Agents
SSRIS	▪ Citalopram ▪ Escitalopram ▪ Fluoxetine ▪ Fluoxetine weekly ▪ Paroxetine ▪ Paroxetine CR ▪ Sertraline ▪ Vilazodone ▪ Vortioxetine
SNRIS	▪ Desvenlafaxine ▪ Duloxetine ▪ Levomilnacipran ▪ Venlafaxine IR ▪ Venlafaxine XR
NDRIs	▪ Bupropion IR ▪ Bupropion SR ▪ Bupropion XR
5-HT2 receptor antagonist	▪ Trazadone ▪ Nefazodone
Noradrenergic antagonist	▪ Mirtazapine
TCAs	▪ Amitriptyline ▪ Amoxapine ▪ Clomipramine ▪ Desipramine ▪ Doxepin ▪ Imipramine ▪ Nortriptyline ▪ Protriptyline ▪ Trimipramine
MAOIs	▪ Isocarboxazid ▪ Phenelzine ▪ Selegiline patch ▪ Tranylcypromine
NMDA Antagonists	▪ Esketamine ▪ Ketamine

d. Outcomes

KQ	Critical Outcome(s)	Important Outcome(s)
1	▪ Breast CA/uterine cancer/estrogen-related cancers ▪ Cerebrovascular accidents ▪ Common menopausal vasomotor symptoms ▪ MACE (e.g., AMI, stroke, other CV outcomes)	▪ SAEs ▪ Venous thrombosis ▪ Weight change **Note: duration of therapy, when benefit started, dose/route of administration will be abstracted if reported**
2	Common menopausal VMS- frequency and severity	▪ Adverse effects ▪ Common menopausal sleep symptoms **Note: dose/route of administration will be abstracted if reported**
3	Common menopausal vasomotor symptoms, frequency and severity	▪ Common menopausal behavioral health symptoms (i.e., anxiety and depression) ▪ Common menopausal cognitive symptoms ▪ Common menopausal sleep symptoms ▪ Common menopausal sexual function symptoms ▪ Weight change
4	Common menopausal behavioral health symptoms (i.e., anxiety and depression)	▪ Common menopausal musculoskeletal pain/symptoms ▪ Common menopausal sexual function symptoms ▪ Common menopausal vasomotor symptoms ▪ Menopause-specific behaviors (coping) ▪ Menopause-specific negative beliefs/ Dysfunctional attitudes ▪ Weight change
5	Common menopausal sexual function symptoms	▪ AEs (all) ▪ Common menopausal vaginal symptoms ▪ SAEs
6	▪ AMI ▪ Cardiovascular mortality ▪ Coronary artery dissection ▪ MACE (e.g., AMI, stroke, other CV outcomes) ▪ SAEs ▪ Stroke	Thromboembolic disease/VTE
7	Common menopausal sleep symptoms	▪ Daytime sleepiness ▪ Fatigue ▪ Nighttime awakenings ▪ Sleep duration ▪ Sleep latency ▪ Sleep quality

KQ	Critical Outcome(s)	Important Outcome(s)
8	▪ Development of a Dementia diagnosis (including specifically Alzheimer's diagnosis) ▪ Memory (verbal and global memory) ▪ Mild cognitive impairment	▪ Executive function tests ▪ Mini mental status test/MoCA/SLUMS ▪ Neuropsych battery testing results
9	Common menopausal vasomotor symptoms	▪ Common menopausal sleep symptoms ▪ SAEs
10	▪ DEXA scan (BMD) ▪ DEXA scan (New diagnosis of osteoporosis) ▪ Fracture	N/A
11	▪ AEs (VTE risk, stroke, serotonin syndrome) ▪ Breast cancer mortality ▪ Breast cancer recurrence ▪ SAEs	N/A
12	▪ Reduction in depression scores on standardized scales ▪ Remission of depression	▪ Functional status ▪ QOL
13	▪ Endometrial Intraepithelial Neoplasia (EIN)/Hyperplasia with biopsy/histology results ▪ Prevalence or incidence of breast cancer ▪ Prevalence or incidence of endometrial cancers	▪ MACE (e.g., AMI, stroke, other CV outcomes) ▪ SAEs ▪ Ultrasound ECE ▪ Venous thromboembolism (VTE)
14	Weight change	▪ Body composition ▪ Common menopausal cognitive symptoms ▪ Common menopausal musculoskeletal symptoms ▪ Common menopause vasomotor symptoms ▪ MACE (e.g., AMI, stroke, other CV outcomes) ▪ QOL
15	▪ Breast CA/Uterine cancer/Estrogen-related cancers ▪ Cerebrovascular accidents ▪ Common menopausal vasomotor symptoms	▪ MACE (e.g., AMI, stroke, other CV outcomes) ▪ SAEs ▪ Venous thrombosis
16	▪ Sensitivity/Specificity/PPV/NPV in relation to identifying menopausal status ▪ Sensitivity/Specificity/PPV/NPV in relation to identifying perimenopausal status	Sensitivity/Specificity/PPV/NPV in relation to change of >7 days in the intermenstrual interval
17	▪ Cerebrovascular accident (stroke)/Transient ischemic attack (TIA) ▪ MACE (e.g., AMI, stroke, other CV outcomes)	▪ Coronary artery disease/Angina ▪ Heart failure ▪ Markers of CVD (hsCRP, elevated CAC score) ▪ Venous thromboembolism (VTE)

KQ	Critical Outcome(s)	Important Outcome(s)
	▪ Myocardial infarction	
18	▪ Cardiovascular mortality ▪ Coronary artery dissection ▪ MACE (e.g., AMI, stroke, other CV outcomes) ▪ NSTEMI	▪ Angina ▪ Stroke ▪ Thromboembolic disease
19	▪ Common menopausal vaginal symptoms (includes vaginal dryness for all KQs) ▪ Common menopausal urinary symptoms ▪ Dyspareunia	▪ Breast CA ▪ Female Sexual Function Index (FSFI) and other validated measures of sexual function ▪ SAEs (to capture venous thrombosis) ▪ Tissue atrophy
20	▪ Weight change ▪ Waist circumference/central adiposity	▪ Attitudes about weight ▪ Body composition ▪ Depression

e. Timing

Key Question	Timing
KQs 1, 5, 8-10, 14, 16-17, 19-20	No minimum follow-up
KQ 2-4, 12	≥6-8 weeks after the start of treatment
KQ 6, 18	≥1 year with short-term defined as 1-2 years or <5 years and long-term defined as >5 years
KQ 7	≥3 months after the start of treatment
KQ 11, 13, 15	≥6 months after treatment

f. Setting(s)

The standard setting for the KQs is Ambulatory or outpatient care. Settings of particular interest were identified for KQ1 (MHT for vasomotor) including home-based management, Primary vs Specialty (OB/GYN or Endocrinology), rural vs urban.

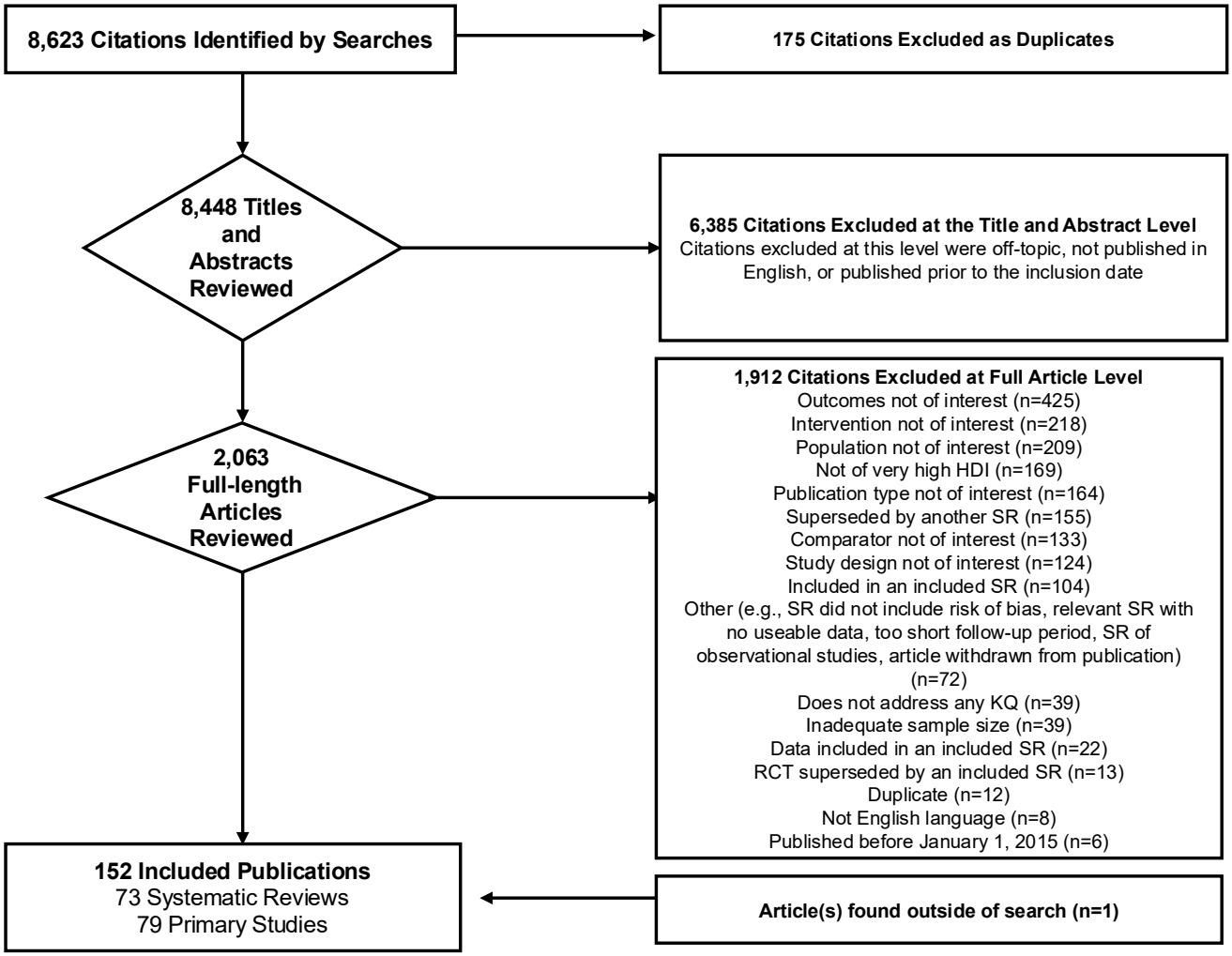
B. Conducting the Systematic Review

Literature searches identified 8,623 citations potentially addressing the KQs of interest for this evidence review. After 175 duplicates were removed, there were 8,448 citations. Of these, 6,385 were excluded upon title and abstract review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to the study inclusion publication date, or not a full-length article). A total of 2,063 full-length articles were reviewed. Of these, 1,912 were excluded for the following reasons: outcomes not of interest (425), intervention not of interest (218), population not of interest (209), not a country of very high Human Development Index (HDI) (169), publication type not of interest (164), superseded by another SR (155), comparator not of interest (133), study design not of interest (124), study included in an included SR (104), other (e.g., SR did not include risk of bias, relevant SR with no useable data, too short

follow-up period [72]), does not address any KQ (39), inadequate sample size (39), data included in included SR (22), RCT superseded by an included SR (13), duplicate (12), not English language (8) or published before January 1, 2015 (6). One additional primary study was found outside of the literature searches and was included. Detailed information on inclusions and exclusions throughout the review process are provided in **Figure A-1** below.

Overall, 152 publications addressed one or more of the KQs and were considered as evidence in this review, including 73 SRs and 79 primary studies. **Table A-2** indicates the number of studies that addressed each of the questions, with some publications being used for more than one KQ.

Figure A-1. Study Flow Diagram



Abbreviations: HDI: Human Development Index; KQ: key question; RCT: randomized controlled trial; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with eight labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step, and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the number of excluded citations).

1. Box 1: 8,623 citations identified by searches.
    a. Right to Box 2: 175 citations excluded as duplicates
    b. Down to box 3.
2. Box 3: 8,448 titles and abstracts reviewed.
    a. Right to Box 4: 6,385 citations excluded at the title and abstract level. Citations excluded were off-topic, not published in English, or published prior to inclusion date.
    b. Down to Box 5.
3. Box 5: 2,063 full-length articles reviewed.
    a. Right to Box 6: 1,912 citations excluded at full-article level.
        i. 425 outcomes not of interest
        ii. 218 intervention not of interest
        iii. 209 population not of interest
        iv. 169 not of very high HDI
        v. 164 publication type not of interest
        vi. 155 superseded by another SR
        vii. 133 comparators not of interest
        viii. 124 study design not of interest
        ix. 104 included in an included SR
        x. 72 other (e.g., SR did not include risk of bias, relevant SR with no useable data, too short follow-up period, SR of observational studies, article withdrawn from publication
        xi. 39 does not address any KQ
        xii. 39 inadequate sample size
        xiii. 22 data included in an included SR
        xiv. 13 RCT superseded by an included SR
        xv. 12 duplicates
        xvi. 8 not English language
        xvii. 6 published before January 1, 2015

   b. Down to Box 7.
4. Box 7: 152 included publications.
   a. 73 SRs.
   b. 79 primary studies.

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	Are Menopause Hormonal Therapies (MHT) safe and effective in treating menopausal vasomotor symptoms?	6 SRs, 8 RCTs, and 1 post hoc pooled analysis of 2 RCTs
2	Is non-hormonal pharmacotherapy effective for management of vasomotor menopausal symptoms?	5 SRs and 1 RCT
3	Are complementary and integrative health interventions effective for menopausal symptoms?	3 SRs and 7 RCTs
4	Are behavioral health interventions effective for the management of menopausal symptoms?	1 SR and 10 RCTs
5	Is pharmacotherapy effective in the management of sexual function symptoms of menopause?	8 SRs and 1 secondary data analysis of 5 RCTs
6	Are Menopause Hormonal Therapies (MHT) safe and effective for primary prevention of post-menopausal cardiovascular disease?	3 SRs
7	Are Menopause Hormonal Therapies (MHT) effective in improving sleep symptoms due to menopause?	2 SRs
8	Are Menopause Hormonal Therapies (MHT) effective in treating changes in cognition or preventing dementia during menopause?	3 SRs and 1 continuation study of an RCT
9	Are herbals and nutraceuticals effective for menopausal vasomotor symptoms?	7 SRs and 16 RCTs
10	Are Menopause Hormonal Therapies (MHT) and other pharmacotherapies effective in delaying or preventing the development of post-menopausal osteoporosis?	9 SRs, 4 RCTs, and 2 secondary pooled analyses of RCTs
11	What hormonal pharmacotherapies are safe in managing menopause in breast cancer survivors?	3 SRs
12	What is the effectiveness of Menopause Hormonal Therapies (MHT) for the treatment of perimenopausal and/or menopausal-related depression?	3 SRs and 1 RCT
13	In perimenopausal and menopausal women on estrogen therapy with an intact uterus, what is the comparative effectiveness and safety of progesterone therapies for endometrial protection?	1 SR
14	Which diets are effective in managing weight in the perimenopausal period and managing menopausal symptoms?	9 RCTs
15	What is the comparative effectiveness of nonhormonal vs. hormonal treatments for VMS?	1 NMA and 3 RCTs
16	What tests or assessments are effective in diagnosing menopause or perimenopause?	1 SR
17	What is the comparative effectiveness of low dose versus conventional dose hormonal therapies on cardiovascular outcomes?	1 SR and 1 RCT
18	What are the risks and benefits of various estrogen preparations (type and dose) in patients with nonobstructive coronary artery disease, myocardial infarction, spontaneous coronary artery dissection, microvascular disease, or a history of VTE?	2 SRs
19	Which pharmacotherapy interventions are effective in treating genitourinary syndrome of menopause?	9 SRs and 4 RCTs

KQ Number	KQ	Number and Study Type
20	Which exercise is effective in weight management during menopause?	4 SRs, 1 NMA, 1 RCT, and 1 secondary analysis of an RCT
Total Evidence Base		**152*** (71 SRs, 65 RCTs, 1 secondary analysis of 5 RCTs, 1 continuation study of an RCT, 1 post hoc pooled analysis of 2 RCTs, 2 secondary pooled analyses, 2 NMA)

*Some papers address more than one KQ, and some studies are reported in more than one paper, therefore the total number for the evidence base is greater than the number of includes in the study flow diagram and description.

Abbreviations: KQ: key question; MHT: menopausal hormonal therapies; NMA: network meta-analysis; RCT: randomized controlled trial; SR: systematic review; VMS: vasomotor symptoms; VTE: venous thromboembolism

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SR of RCTs published on or after January 1, 2015, through June 30, 2025.
- Studies had to be published in English.
- Publications had to be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, research protocols, and other publications that were not full-length clinical studies were not accepted as evidence.
- SRs must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) or something compatible (e.g., the tool used by the AHRQ Evidence-based Practice Centers [AHRQ-EPCs]). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review. If multiple SRs address a KQ, we selected the most recent and/or comprehensive review. In many cases, we used multiple SRs to address a single KQ, as each SR will deal with a different intervention or intervention-comparator combination.
- RCTs must have had an independent control group. Randomized crossover trials were only included if data from the first period (prior to treatment crossover) were reported separately and an adequate washout period was used.
- For KQ16, diagnostic accuracy studies were included. Similarly, SRs with these study designs were included. For all other KQs, only SRs of RCTs and individual RCTs were considered.
- Studies must have enrolled at least 20 patients (10 per study group for RCTs and 20 for observational studies) unless otherwise noted.
- Studies must have enrolled at least 85% of patients who meet the study population criteria. If the patient population fell below this threshold but the relevant population of patients is reported separately, then that study was included.
- To ensure applicability to the VA/DOD healthcare systems, and ensure consistency across the CPG program, inclusion of individual studies was limited to very high Human Development Index (HDI), countries with an index ≥0.8 where standards of healthcare are comparable (e.g., United States, Canada, United Kingdom, Western Europe, Israel, Japan, Hong Kong, Australia, and New Zealand). Inclusion of SRs was limited to those including more than half of the studies from eligible regions.
- These regions of interest are listed in Table 1 of the Statistical Annex of the 2023/24 Human Development Report produced by the United Nations Development Program.
- Study must have reported on at least one outcome of interest.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in **Table A-3** below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix E.

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform/ Provider
Bibliographic Database	Embase	January 1, 2015, to June 30, 2025	Elsevier
	PsycINFO	January 1, 2015, to June 30, 2025	EBSCO
	PubMed	January 1, 2015, to June 30, 2025	National Library of Medicine
Grey Literature Resources	AHRG Evidence-based Practice Center (EPC) Reports	January 1, 2015, to June 30, 2025	AHRQ
	Cochrane Database of Systematic Reviews	January 1, 2015, to June 30, 2025	Cochrane Library
	VA Evidence Synthesis Program (ESP) Reports	January 1, 2015, to June 30, 2025	VA ESP

c. Rating the Quality of Individual Studies and the Body of Evidence

Sigma Health Consulting assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the USPSTF method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(264)

Next, the Sigma team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low*.

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, Defense Health Agency, and the Sigma Team convened a 3.5-day in-person recommendation development meeting from January 13-16, 2026, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Sigma Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting (see Determining Recommendation Strength and Direction).

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Determining Recommendation Strength and Direction

Per GRADE methodology, to assess the quality of the evidence base and assign a grade for the strength of each recommendation, the GRADE system uses the following four domains to assess the strength of each recommendation (74):

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease their strength. The evidence review used for the development of recommendations for menopause, conducted by the Sigma Team, assessed the confidence in the quality of the evidence base and assigned a rate of "High," "Moderate," "Low," or "Very Low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

2. Balance of Desirable and Undesirable Outcomes

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid events, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse events, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that most providers will offer patients therapeutic or preventive measures if the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the provider about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience

of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having “similar values,” “some variation,” or “large variation” in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient’s values and preferences?
- Are the assumed or identified relative values similar across the target population?

4. Other Implications

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below (Table A-4) was used by the Work Group to guide discussions on each domain.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgement
Balance of desirable and undesirable outcomes	▪ What is the magnitude of the anticipated desirable outcomes? ▪ What is the magnitude of the anticipated undesirable outcomes? ▪ Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	▪ Benefits outweigh harms/burdens ▪ Benefits slightly outweigh harms/burdens ▪ Benefits and harms/burden are balanced ▪ Harms/burden slightly outweigh benefits ▪ Harms/burden outweigh benefits
Confidence in the quality of evidence	▪ Among the designated critical outcomes, what is the lowest quality of relevant evidence? ▪ How unlikely is further research to change the confidence in the estimate of effect?	▪ High ▪ Moderate ▪ Low ▪ Very low
Patient values and preferences	▪ Are you confident about the typical values and preferences and are they similar across the target population? ▪ What are the patient's values and preferences? ▪ Are the assumed or identified relative values similar across the target population?	▪ Similar values ▪ Some variation ▪ Large variation
Other implications (e.g. resource use, equity, acceptability, feasibility, subgroup considerations)	▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there lots of variability in resource requirements across settings?	Various considerations

D. Recommendation Categorization

Recommendation Categories and Definitions

For use in the 2026 Menopause CPG, a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Clinical Excellence (NICE).(79,80). A summary of the recommendation categories and definitions is available in Table 4. For this new CPG, all recommendations were categorized as Reviewed, New-added (See Recommendations). *Reviewed, New-added* recommendations are original, and new recommendations based entirely on evidence included in the systematic evidence review.

E. Drafting and Finalizing the Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations. The Work Group also created tables, appendices, and other sections for inclusion in the 2026 VA/DOD Menopause CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the CPG, an iterative review process was used to solicit feedback on and revise the CPG. Once they were developed, the first two drafts of the CPG were posted on the Menopause Wiki Website for a period of 10-20 business days for internal review and comment by the Work Group. Draft 3 was made available for a 14-day peer review and comment period (see External Peer Review). All feedback submitted during each review period was reviewed and discussed by the Work Group, and appropriate revisions were made to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DOD EBPWG for approval, and the final CPG was approved in September 2026. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, quick reference guide, and patient summary.

Appendix B: Evidence Table

Table B-1. 2026 Menopause Evidence Table [1, 2, 3]

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
1.	We suggest against using laboratory testing (e.g., anti-müllerian hormone and/or follicle-stimulating hormone) for the diagnosis of menopause and perimenopause.	(89) **Additional References** (12,87,88)	Weak against	Reviewed, New-added
2.	In women with a uterus, we recommend systemic estradiol and progesterone for the treatment of vasomotor symptoms.	(93,94) **Additional References** (95-97,265)	Strong for	Reviewed, New-added
3.	In women with a uterus, we suggest the use of conjugated estrogen with bazedoxifene for the treatment of vasomotor symptoms.	(98,99)	Weak for	Reviewed, New-added
4.	In women without a uterus, we suggest the use of systemic estradiol monotherapy for the treatment of vasomotor symptoms.	(100) **Additional References** (101)	Weak for	Reviewed, New-added
5.	For the treatment of vasomotor symptoms of menopause, we suggest against the use of progestogen monotherapy.	(102,103)	Weak against	Reviewed, New-added
6.	We recommend cognitive behavioral therapy (CBT) to manage vasomotor symptoms related to menopause.	(104,105)	Strong for	Reviewed, New-added

[1] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[2] 2026 Strength of Recommendation column: The 2026 VA/DOD Menopause CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Grading Recommendations section for more information.

[3] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
7.	We suggest elinzanetant or fezolinetant for vasomotor symptoms in menopausal women.	(106,107) **Additional References** (108-110)	Weak for	Reviewed, New-added
8.	There is insufficient evidence to favor fezolinetant or elinzanetant versus hormone therapy for vasomotor symptoms.	(111) **Additional References** (90,112-114)	Neither for nor against	Reviewed, New-added
9.	We suggest selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin as non-hormonal options for menopausal vasomotor symptoms based on patient characteristics and preferences.	(115,117)	Weak for	Reviewed, New-added
10.	For menopausal vasomotor symptoms, in patients without a contraindication to hormone therapy, we suggest hormone therapy over either venlafaxine or gabapentin.	(116,117) **Additional References** (90,112-114)	Weak for	Reviewed, New-added
11.	There is insufficient evidence to recommend for or against the following complementary and integrative health (CIH) interventions for menopausal vasomotor symptoms: • Acupressure • Acupuncture • Tai Chi/Qigong • Yoga	(118-124)	Neither for nor against	Reviewed, New-added
12.	There is insufficient evidence to recommend for or against the following supplements and nutraceuticals for menopausal vasomotor symptoms: • Amino Acids • Black Cohosh • Danggwijagyaksan • Fenugreek • Giant Fennel • Ginseng • Kamishoyosan	(125-127,131-133,135,136,138,139,141,142,144-154) **Additional References** (128-130,134,137,140,143,155,156)	Neither for nor against	Reviewed, New-added

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
	• Maca • Magnesium • Melatonin • Probiotics • Red Clover • Resveratrol + Equol • Salvia • Soy Supplements • Succinate			
13.	There is insufficient evidence to recommend for or against menopausal hormone therapy used solely for sleep symptoms.	(157,159) **Additional References** (158)	Neither for nor against	Reviewed, New-added
14.	We recommend cognitive behavioral therapy (CBT) to treat depressive and/or anxiety symptoms during perimenopause and menopause.	(104,105)	Strong for	Reviewed, New-added
15.	We recommend mindfulness-based stress reduction (MBSR) for menopause-related depressive and/or anxiety symptoms (See VA/DOD CPG for Major Depressive Disorder [MDD]).	(104,168,169) **Additional References** (170)	Strong for	Reviewed, New-added
16.	In perimenopausal women, we suggest menopausal hormone therapy to treat depressive symptoms, depending on patient characteristics and preferences (For patients with Major Depressive Disorder [MDD], see VA/DOD CPG for MDD).	(171) **Additional References** (160,161,172,173)	Weak for	Reviewed, New-added
17.	For depressive symptoms during perimenopause or menopause, we suggest exercise (e.g., mind-body exercise, aerobic activity, or combination).	(174)	Weak for	Reviewed, New-added
18.	For depressive symptoms during perimenopause or menopause, there is insufficient evidence to recommend for or against the use of phytoestrogens (e.g., soy supplements).	(175) **Additional References** (176)	Neither for nor against	Reviewed, New-added

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
19.	There is insufficient evidence to recommend for or against menopausal hormonal therapy (MHT) used solely for the prevention of dementia.	(97)	Neither for nor against	Reviewed, New-added
20.	We suggest against the use of menopausal hormonal therapy (MHT) solely for treatment of cognitive symptoms in perimenopausal and menopausal women.	(97,180-182)	Weak against	Reviewed, New-added
21.	We suggest local (non-systemic) vaginal and/or systemic estrogen therapy, for the management of sexual dysfunction in menopause, especially related to vaginal dryness and dyspareunia.	(115,190,191)	Weak for	Reviewed, New-added
22.	For genitourinary syndrome of menopause (GSM), we suggest treatment with local (non-systemic) vaginal estrogen.	(115,190-192,194-197) **Additional References** (193)	Weak for	Reviewed, New-added
23.	For breast cancer survivors, we suggest local (non-systemic) vaginal estrogen therapy for the treatment of genitourinary syndrome of menopause (GSM).	(197) **Additional References** (198,199)	Weak for	Reviewed, New-added
24.	For dyspareunia, we suggest local (non-systemic) vaginal estrogen and/or vaginal dehydroepiandrosterone (DHEA)	(192,194,196,200-202)	Weak for	Reviewed, New-added
25.	For vaginal dryness, we suggest local (non-systemic) vaginal estrogen, vaginal DHEA, vaginal moisturizers, or ospemifene.	(194,201,203)	Weak for	Reviewed, New-added
26.	We suggest transdermal testosterone for the treatment of sexual dysfunction in menopause, especially related to interest, desire, and/or arousal.	(204,205) **Additional References** (187,206,207)	Weak for	Reviewed, New-added
27.	For the treatment of Hypoactive Sexual Desire Disorder (reclassified in the DSM-5 as Female Sexual Interest/Arousal Disorder) in perimenopause and menopause, we suggest flibanserin.	(208)	Weak for	Reviewed, New-added

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
28.	For dyspareunia, there is insufficient evidence to recommend for or against the use of vaginal moisturizers.	(201)	Neither for nor against	Reviewed, New-added
29.	For genitourinary syndrome of menopause (GSM), we suggest against the use of vaginal lasers.	(209-212) **Additional References** (213)	Weak against	Reviewed, New-added
30.	In post-menopausal women with risk factors for osteoporosis, we suggest conjugated estrogen/bazedoxifene as an option to increase bone mineral density based on patient characteristics and preferences.	(214)	Weak for	Reviewed, New-added
31.	In post-menopausal patients, we suggest dietary calcium and/or calcium supplementation to increase bone mineral density.	(216) **Additional References** (215,217,218)	Weak for	Reviewed, New-added
32.	In post-menopausal patients without osteoporosis, there is insufficient evidence to recommend for or against Vitamin D3 for primary improvement of decreased bone mineral density or fracture.	(219,220) **Additional References** (215)	Neither for nor against	Reviewed, New-added
33.	For primary prevention of fracture in post-menopausal patients without documentation of osteoporosis or osteopenia, there is insufficient evidence to recommend for or against bisphosphonates.	(221-224) **Additional References** (225)	Neither for nor against	Reviewed, New-added
34.	In post-menopausal patients with osteopenia, there is insufficient evidence to recommend for or against raloxifene to reduce fracture risk and improve bone mineral density.	(221,226)	Neither for nor against	Reviewed, New-added
35.	In post-menopausal women with overweight or obesity, we suggest a calorie-restricted diet for weight management, depending on patient characteristics and preferences (see the VA/DOD CPG for the Management of Overweight and Obesity in Adults).	(229-232)	Weak for	Reviewed, New-added

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
36.	We suggest exercise for peri-menopausal or post-menopausal women for reduction of weight and/or waist circumference (e.g., aerobic activity, resistance training, or combination).	(233-237) **Additional References** (238,239)	Weak for	Reviewed, New-added
37.	In post-menopausal women, there is insufficient evidence to recommend for or against any of the following dietary approaches for weight management: • High protein • Intermittent fasting • Low fat • Mediterranean • Paleolithic • Vegan (with soy supplementation)	(240-243)	Neither for nor against	Reviewed, New-added
38.	For the primary prevention of post-menopausal cerebrovascular events, we recommend against oral estrogen or estrogen and progestogen.	(97)	Strong against	Reviewed, New-added
39.	For primary prevention of post-menopausal cardiovascular disease (CVD), we suggest against oral menopausal hormone therapy, whether it is estrogen alone or with progestogen, and whether it is low-dose or conventional dose.	(97,245-247)	Weak against	Reviewed, New-added
40.	For women less than 60 years old and less than 10 years from the onset of menopause with established cardiovascular disease (CVD) and significant vasomotor symptoms, we suggest consideration of systemic estrogen-containing therapies based on the lack of evidence for increased cerebrovascular and cardiovascular morbidity and mortality.	(248,249) **Additional References** (250-255)	Weak for	Reviewed, New-added
41.	For hormone-positive breast cancer survivors, we suggest against the use of systemic hormone therapy.	(256,257) **Additional References** (198)	Weak against	Reviewed, New-added

#	Recommendation	Evidence[1]	2026 Strength of Recommendation[2]	2026 Recommendation Category[3]
42.	For women with an intact uterus taking systemic estrogen, there is insufficient evidence to recommend for or against any one of the following progestogen formulations over another to modify breast cancer risk: • Oral Drospirenone • Transdermal or 52 mg levonorgestrel intrauterine device (LNG IUD) • Oral micronized progesterone • Oral medroxyprogesterone acetate (MPA) • Oral or transdermal Norethindrone acetate	(93,258) **Additional References** (259)	Neither for nor against	Reviewed, New-added
43.	When selecting a progestogen in women with an intact uterus taking systemic estrogen, there is insufficient evidence to recommend any one of the following progestogen formulations over another for protection against endometrial cancer: • Oral Drospirenone • Transdermal or 52 mg levonorgestrel intrauterine device (LNG IUD) • Oral micronized progesterone • Oral medroxyprogesterone acetate (MPA) • Oral or transdermal Norethindrone acetate	(258) **Additional References** (93,260-262)	Neither for nor against	Reviewed, New-added

Appendix C: Participant List

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Appendix D: Patient Focus Group Methods and Findings

A. Methods

VA and DOD Leadership recruited a large number of participants for the focus group, with support from the Champions and other Work Group members as needed. The VA and DOD leadership overrecruited when seeking participants for the Patient Focus Group, with the expectation that some participants may not be able to attend. A convenience sample was utilized in the selection of participants, and therefore, the sample of patients used is not generalized for the entirety of VA and DOD patients who have experience with perimenopause or menopause. The goal of recruitment for this Patient Focus Group was to have a group of engaging, diverse patients receiving VA or DOD healthcare services, who could cogently explain their experience with menopause. Participants were not incentivized for their participation or reimbursed for travel expenses.

The Work Group, with support from the Sigma Team, identified topics on which patient input was important to consider in developing the CPG. The Sigma Team developed, and the Work Group approved, a patient focus group guide covering these topics. The focus group facilitator led the discussion and used the guide to elicit the patients' perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

Thirteen women participated in the Patient Focus Group on menopause. Participants were receiving care from the VA and DOD. The participants were primarily younger, ranging from the age of 42-57 years old. Many of the participants were currently active duty military personnel, and others were Veterans, military personnel, or dependents. Some participants shared other co-occurring conditions they have with their menopause, including DCIS, fibromyalgia, and Hashimoto's thyroiditis. The participants shared remarks on their experiences of having their menopause diagnosed, the symptoms they have experienced, and the treatments they use to manage those symptoms.

B. Patient Focus Group Findings

a. Participants emphasized the need for provider and patient education in identifying and treating menopause and its symptoms.

- Participants value a well-informed and empathetic provider.
- Participants utilized non-medical information sources and highlighted the need for reliable patient education and resources.
- Identifying menopausal symptoms remains a challenge for patients and providers.

b. Participants discussed the importance of a holistic approach to the treatment of menopause symptoms.

- Participants value an integrated, "whole person" approach for menopause diagnosis and treatment.

- Participants' medical history and comorbidities impacted menopause treatment.

c. *Participants highlighted the challenges of managing their weight during menopause.*

- Participants expressed the need for change in the way providers assess and treat menopausal weight gain.
- Participants shared the challenges that their menopausal weight gain has had on their daily lives.

d. *Participants discussed the impact that their menopause symptoms and treatment have had on their mental health and career aspirations, emphasizing the need for effective symptom management to maintain career standards and personal well-being.*

- Participants elaborated on the mental challenges weight gain has on their military career, from questioning their ability to perform the physical requirements to fearing the perception from others that they have “let themselves go”.
- Participants shared that military standards need to be updated to consider women of menopausal age.

e. *In patients of menopausal age and/or those experiencing perimenopausal symptoms, participants emphasized the need for early and regular screening.*

- Participants emphasized the importance of providers listening to the patients when discussing their symptoms and being up to date on the latest menopause research.
- Participants shared that they experienced symptoms early during transition but were unaware that they were menopause symptoms.
- Participants shared that menopause symptoms need to be a part of PHA screenings and want to be alerted to talk to a provider as soon as their symptoms start.

f. *Participants highlighted the benefits and challenges of non-pharmacological therapies, lifestyle interventions, and social support when managing menopausal symptoms.*

- Participants used a wide variety of complementary and integrative health and lifestyle interventions for the management of menopausal symptoms.
- Participants relied on peer and social support throughout their menopausal transition.

Appendix E: Literature Review Search Terms and Strategy

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table E-1. Embase Search Strategy

Search Number	Query
#1	'menopause and climacterium'/de OR 'climacterium'/exp OR 'menopause'/exp OR 'postmenopause'/exp OR climacteri*:ab,ti OR menopaus*:ab,ti OR perimenopaus*:ab,ti OR postmenopaus*:ab,ti
#2	'hormonal therapy'/exp OR ((hormone* NEAR/3 (bioidentical OR derivative OR replace* OR substitut* OR synthetic OR therap* OR treatment*)):ab,ti) OR androgen:ab,ti OR azedoxifene:ab,ti OR bazedoxifene:ab,ti OR biestrogen:ab,ti OR bremelanotide:ab,ti OR dehydroepiandrosterone:ab,ti OR dhea:ab,ti OR dihydroepiandrosterone:ab,ti OR drospirenone:ab,ti OR dydrogesterone*:ab,ti OR estradiol:ab,ti OR estriol*:ab,ti OR estrogen:ab,ti OR estron*:ab,ti OR estropipate:ab,ti OR ethinylestradiol:ab,ti OR flibanserin:ab,ti OR gestagen:ab,ti OR hemihydrate*:ab,ti OR levonorgestrel:ab,ti OR medroxyprogesterone:ab,ti OR norethindrone:ab,ti OR 'norethisterone norgestimate':ab,ti OR oestradiol:ab,ti OR oestrogen*:ab,ti OR oestron*:ab,ti OR ospemifene:ab,ti OR oxybutynin:ab,ti OR oxytocin:ab,ti OR prasterone:ab,ti OR progesterone*:ab,ti OR progestin*:ab,ti OR progestogen*:ab,ti OR 'selective estrogen receptor*':ab,ti OR testosterone:ab,ti OR tibolone:ab,ti OR triestogen:ab,ti OR valerate:ab,ti OR vazadoxifene:ab,ti
#3	('depression'/exp OR depression:ab,ti) AND ('drug therapy'/exp OR 'psychopharmacotherapy'/de OR pharmacotherapy:ab,ti OR medicine*:ab,ti OR medicat*:ab,ti OR drug*:ab,ti) OR 'antidepressant agent'/exp OR 'anti depressant*':ab,ti OR antidepressant*:ab,ti OR amitriptyline:ab,ti OR amoxapine:ab,ti OR anafranil:ab,ti OR aplenzin:ab,ti OR bisphosphonate*:ab,ti OR bupropion:ab,ti OR buspirone:ab,ti OR calcium:ab,ti OR chlorimipramine:ab,ti OR cholecalciferol:ab,ti OR clonidine:ab,ti OR clomipramine:ab,ti OR citalopram:ab,ti OR d3:ab,ti OR denosumab:ab,ti OR desipramine:ab,ti OR desvenlafaxine:ab,ti OR doxepin:ab,ti OR duloxetine:ab,ti OR escitalopram:ab,ti OR elinzanetant:ab,ti OR esketamine:ab,ti OR fetzima:ab,ti OR fezolinetant:ab,ti OR fluoxetine:ab,ti OR fluvoxamine:ab,ti OR forfivo:ab,ti OR gabapentin:ab,ti OR imipramine:ab,ti OR isocarboxazid:ab,ti OR ketamine:ab,ti OR khedezla:ab,ti OR 'kisspeptins neurokinin b antagonist':ab,ti OR levomilnacipran:ab,ti OR maprotiline:ab,ti OR mesylate:ab,ti OR milnacipran:ab,ti OR mirtazapine:ab,ti OR mitriptyline:ab,ti OR nefazodone:ab,ti OR 'neurokinin-receptor antagonist*':ab,ti OR 'noradrenalin serotonin reuptake inhibitor*':ab,ti OR 'noradrenalin serotonin uptake inhibitor*':ab,ti OR nonestrogen:ab,ti OR nonhormonal:ab,ti OR 'norepinephrine serotonin reuptake inhibitor*':ab,ti OR 'norepinephrine serotonin uptake inhibitor*':ab,ti OR norpramin:ab,ti OR nortriptyline:ab,ti OR oleptro:ab,ti OR oxybutynin:ab,ti OR pamelor:ab,ti OR paroxetine:ab,ti OR pexeva*:ab,ti OR phytoestrogen*:ab,ti OR phenelzine:ab,ti OR pregabalin:ab,ti OR protriptyline:ab,ti OR prudoxin:ab,ti OR raloxifene:ab,ti OR remeron:ab,ti OR 'selegiline patch':ab,ti OR sertraline:ab,ti OR 'serotonin and noradrenaline reuptake inhibitor*':ab,ti OR 'serotonin and noradrenaline uptake inhibitor*':ab,ti OR 'serotonin noradrenalin uptake inhibitor*':ab,ti OR 'serotonin and norepinephrine reuptake inhibitor*':ab,ti OR 'serotonin norepinephrine reuptake inhibitor*':ab,ti OR 'serotonin reuptake inhibitor*':ab,ti OR sildenafil:ab,ti OR silenor*:ab,ti OR surmontil*:ab,ti OR teriparatide:ab,ti OR tofranil*:ab,ti OR trazadone:ab,ti OR trimipramine*:ab,ti OR tranylcypromine:ab,ti OR trazodone:ab,ti OR trintellix*:ab,ti OR venlafaxine:ab,ti OR vilazodone:ab,ti OR vivactil*:ab,ti OR vortioxetine:ab,ti OR wellbutrin:ab,ti OR zimeldine:ab,ti OR zyban:ab,ti OR zonalon*:ab,ti

Search Number	Query
#4	'acupuncture'/exp OR 'alternative medicine'/exp OR 'biofeedback'/exp OR 'breathing'/exp OR 'hypnotherapy'/exp OR 'integrative medicine'/exp OR 'leisure'/exp OR 'manipulative medicine'/exp OR 'meditation'/exp OR 'mindfulness'/exp OR 'relaxation training'/exp OR 'tai chi'/exp OR 'yoga'/exp OR acupuncture:ab,ti OR aromatherap*:ab,ti OR 'bio feedback':ab,ti OR biofeedback:ab,ti OR breath*:ab,ti OR chiropract*:ab,ti OR hypnosis:ab,ti OR hypnotherap*:ab,ti OR 'manual therap*':ab,ti OR massag*:ab,ti OR meditat*:ab,ti OR 'mind body':ab,ti OR mindful*:ab,ti OR relax*:ab,ti OR 'sound wave*':ab,ti OR 'spinal manipulation':ab,ti OR 'tai chi':ab,ti OR 'tai ji':ti,ab OR yoga:ab,ti OR yogic:ab,ti OR (((alternative OR complementary OR integrat*) NEAR/5 (health* OR medicine OR therap* OR treatment*)):ab,ti) OR ((leisure NEAR/5 (activit* OR time)):ab,ti) OR ((manipulation NEAR/5 (therap* OR treatment*)):ab,ti) OR ((manipulative NEAR/5 (medicine OR therap* OR treatment*)):ab,ti)
#5	'behavioral training'/exp OR 'bladder training'/exp OR 'counseling'/exp OR 'hypnotherapy'/exp OR 'mindfulness'/exp OR 'psychoeducation'/exp OR 'anger management':ab,ti OR cbt:ab,ti OR counseling:ab,ti OR dbt:ab,ti OR hypnosis:ab,ti OR hypnotherap*:ab,ti OR 'mind body':ab,ti OR mindful*:ab,ti OR psychoeducat*:ab,ti OR ((behavio* NEAR/5 (chang* OR condition* OR counsel* OR intervention* OR modific* OR support* OR technique* OR therap* OR train* OR treatment*)):ab,ti) OR ((bladder NEAR/5 (drill OR 're train*' OR retrain* OR train*)):ab,ti) OR ((cognitive NEAR/5 (behavio* OR remediation OR therap*)):ab,ti)
#6	(intravaginal*:ab,ti OR 'vagina'/exp OR vagina*:ab,ti) AND ('agents used intravaginally'/exp OR 'emollient agent'/exp OR 'lubricating agent'/exp OR emollient*:ab,ti OR lubricat*:ab,ti OR moisturiz*:ab,ti)
#7	'herbaceous agent'/exp OR 'nutraceutical'/exp OR 'actaea racemosa'/exp OR 'alpha tocopherol'/exp OR 'angelica sinensis extract'/exp OR 'cannabinoid'/exp OR 'dioscorea extract'/exp OR 'ginseng'/exp OR 'lactobacillus acidophilus'/exp OR 'lepidium meyenii'/exp OR 'oenothera'/exp OR 'omega 3 fatty acid'/exp OR 'pollen extract'/exp OR 'primrose oil'/exp OR 'red clover'/exp OR 'red clover extract'/exp OR 'rhubarb'/exp OR 'rhubarb extract'/exp OR 'silybum marianum'/exp OR 'vitamin d'/exp OR 'yam'/exp OR 'actaea racemosa':ab,ti OR 'alpha tocopherol':ab,ti OR 'ammoniumum succinate':ab,ti OR 'angelica sinensis':ab,ti OR 'black cohosh':ab,ti OR cannabi*:ab,ti OR chasteberry:ab,ti OR cimicifuga:ab,ti OR dioscorea:ab,ti OR 'dong quai':ab,ti OR 'evening primrose':ab,ti OR flaxseed:ab,ti OR ginseng:ab,ti OR herbal*:ab,ti OR isoflavone*:ab,ti OR 'lactobacillus acidophilus':ab,ti OR 'lepidium meyenii':ab,ti OR maca:ab,ti OR magnesium:ab,ti OR marijuana:ab,ti OR melatonin:ab,ti OR 'milk thistle':ab,ti OR nutraceutical*:ab,ti OR oenothera:ab,ti OR 'omega 3':ab,ti OR 'pollen extract*':ab,ti OR primrose:ab,ti OR 'red clover':ab,ti OR rhubarb:ab,ti OR 'silybum marianum':ab,ti OR 'st. johns wort':ab,ti OR soy:ab,ti OR 's-equol':ab,ti OR 'trifolium pratense':ab,ti OR yam:ab,ti OR 'vitamin d':ab,ti OR 'vitamin e':ab,ti
#8	'anti inflammatory diet'/exp OR 'diet therapy'/exp OR 'low carbohydrate diet'/exp OR 'mediterranean diet'/exp OR 'phytoestrogen'/exp OR 'plant-based diet'/exp OR 'vegan diet'/exp OR 'whole food'/exp OR (((diet* OR nutrition*) NEAR/5 ('anti inflammatory' OR antiinflammatory OR fasting OR 'low calori*' OR 'low carb*' OR mediterranean OR 'negative energy balance' OR 'plant based' OR 'standard american' OR therap* OR vegan OR vegetarian OR 'whole food*')):ab,ti) OR phytoestrogen*:ab,ti
#9	('diagnostic test'/exp/mj OR 'predictive value'/exp/mj OR 'questionnaire'/exp/mj) AND ('follitropin'/exp/mj OR 'muellerian inhibiting factor'/exp/mj) OR (('anti mullerian':ti OR antimullerian:ti OR 'bio marker*':ti OR biomarker*:ti OR 'follicle stimulating':ti OR follitropin:ti OR fsh:ti OR 'muellerian inhibit*':ti OR questionnaire*:ti OR test*:ti) AND ('bio marker*':ti OR biomarker*:ti OR defin*:ti OR diagnos*:ti OR estimat*:ti OR level*:ti OR measur*:ti OR model*:ti OR predict*:ti OR relationship*:ti OR test*:ti) AND ('menopause and climacterium'/mj OR 'climacterium'/exp/mj OR 'menopause'/exp/mj OR 'postmenopause'/exp/mj OR climacteri*:ti OR menopaus*:ti OR perimenopaus*:ti OR 'peri menopaus*':ti OR postmenopaus*:ti OR 'post-menopaus*':ti)) OR 'stages of reproductive aging workshop':ab,ti

Search Number	Query
#10	('vagina'/exp OR intravagin*:ab,ti OR vagin*:ab,ti) AND ('laser'/exp OR cream*:ab,ti OR insert*:ab,ti OR laser*:ab,ti OR ring*:ab,ti)
#11	'aerobic exercise'/exp OR 'resistance training'/exp OR 'resistive exercise'/exp OR ((aerobic NEAR/5 (exercise* OR train*)):ab,ti) OR aerobics:ab,ti OR exercis*:ab,ti OR 'high intensity interval training':ab,ti OR 'physical* activit*':ab,ti OR 'pelvic floor':ab,ti OR 'strength train*':ab,ti OR (((resistance OR resistive) NEAR/5 (exercis* OR train*)):ab,ti) OR ((weight NEAR/5 (lift* OR train*)):ab,ti)
#12	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13	#1 AND #9 AND ('cohort analysis'/exp OR 'comparative study'/exp OR 'controlled study'/exp OR 'diagnostic accuracy'/exp OR 'evaluation study'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'sensitivity and specificity'/exp OR 'treatment outcome'/de OR 'between groups':ti,ab OR 'case control*':ti,ab OR 'clinical utility':ti,ab OR cohort*:ti,ab OR comparison:ti,ab OR comparative:ti,ab OR 'control group*':ti,ab OR 'controlled study':ti,ab OR 'controlled trial':ti,ab OR 'cross over':ti,ab OR crossover:ti,ab OR 'diagnostic accuracy':ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR longitudinal:ti,ab OR 'matched controls':ti,ab OR ((observational NEXT/3 study):ti,ab) OR prospective:ti,ab OR sensitivity:ti,ab OR sham:ti,ab OR specificity:ab,ti OR versus:ti OR vs:ti)
#14	#12 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR 'phase 3':ti,ab OR 'phase iii':ti,ab OR random*:ti,ab OR rct:ti,ab)
#15	#12 AND ('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR cochrane*:ti,ab OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR (search*:ti,ab AND (cinahl*:ti,ab OR databases:ti,ab OR ebsco*:ti,ab OR embase*:ti,ab OR psychinfo*:ti,ab OR psycinfo*:ti,ab OR 'science direct*':ti,ab OR sciencedirect*:ti,ab OR scopus*:ti,ab OR systematic*:ti,ab OR 'web of knowledge*':ti,ab OR 'web of science':ti,ab)) OR ((systematic* NEAR/3 review*):ti,ab))
#16	#13 OR #14 OR #15
#17	#16 AND [01-01-2015]/sd NOT [01-07-2025]/sd AND [2015-2025]/py
#18	#17 NOT (abstract:nc OR annual:nc OR 'book'/de OR book:it OR book:pt OR 'case report'/de OR 'case report':ti OR 'chapter'/it OR comment:ti OR conference:nc OR [conference abstract]/lim OR 'conference paper'/exp OR [conference paper]/lim OR 'conference proceeding':ti OR 'conference proceeding':pt OR [conference review]/lim OR 'conferences and congresses'/exp OR congress:nc OR [editorial]/lim OR editorial:ti OR 'letter'/de OR letter:it OR [letter]/lim OR letter:ti OR meeting:nc OR proceedings:nc OR sessions:nc OR 'symposium'/exp OR symposium:nc)
#19	#18 NOT ([animals]/lim NOT [humans]/lim OR ((animal:ti OR animals:ti OR canine*:ti OR dog:ti OR dogs:ti OR feline:ti OR hamster*:ti OR lamb:ti OR lambs:ti OR mice:ti OR monkey:ti OR monkeys:ti OR mouse:ti OR murine:ti OR pig:ti OR piglet*:ti OR pigs:ti OR porcine:ti OR primate*:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep*:ti OR swine:ti OR veterinar*:ti OR (vitro:ti NOT vivo:ti)) NOT (human*:ti,ab OR patient*:ti,ab)))
#20	#19 NOT ((adolescen*:ti OR babies:ti OR baby:ti OR boys:ti OR child*:ti OR girls:ti OR infancy:ti OR infant*:ti OR juvenile*:ti OR neonat*:ti OR newborn*:ti OR nurser*:ti OR paediatric*:ti OR pediatric*:ti OR preschool*:ti OR 'school age*':ti OR schoolchildren*:ti OR teen*:ti OR toddler*:ti OR youth*:ti) NOT (adult*:ti OR men:ti OR women:ti))
#21	#20 AND [english]/lim

Table E-2. Embase.com Syntax Key

Embase.com Syntax	
*	Truncation character (wildcard)
NEAR/n	Search terms within a specified number (n) of words from each other in any order
/exp	"Explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
/mj	Denotes a term that has been searched as a major subject heading
/de	Non-exploded subject heading
/lim	Limit
/sd	Entry date (date that the record is added to the database)
:ti	Limit to title
:ab,ti	Limit to abstract and title fields

Table E-3. Concept Tables for Embase

Concept	Embase Controlled Terms (EMTREE)	Key Words
Menopause	'menopause and climacterium'/de 'climacterium'/exp 'menopause'/exp 'postmenopause'/exp	climacteri* menopaus* perimenopaus* postmenopaus* *word variations have been searched
Menopause Hormonal Therapies	'hormonal therapy'/exp	androgen azedoxifene bazedoxifene biestrogen bioidentical hormon* bremelanotide dehydroepiandrosterone dhea dihydroepiandrosterone drospirenone dydrogesterone* estradiol estriol* estrogen estron* estropipate ethinylestradiol flibanserin gestagen hemihydrate* hormon* derivative hormon* replace* hormon* substitut* hormon* therap* hormon* treatment* levonorgestrel medroxyprogesterone norethindrone norethisterone norgestimate

Concept	Embase Controlled Terms (EMTREE)	Key Words
		oestradiol oestrogen* oestron* ospemifene oxybutynin oxytocin prasterone progesterone* progestin* progestogen* selective estrogen receptor* synthetic hormone* testosterone tibolone triestogen valerate vazadoxifene *word variations have been searched
Non-Hormonal Pharmacotherapies	'antidepressant agent'/exp 'drug therapy'/exp 'psychopharmacotherapy'/de	anti depressant* antidepressant* amitriptyline amoxapine anafranil aplenzin bisphosphonate* bupropion buspirone calcium chlorimipramine cholecalciferol clonidine clomipramine citalopram d3 denosumab desipramine desvenlafaxine doxepin duloxetine escitalopram elinzanetant esketamine fetzima fezolinetant fluoxetine fluvoxamine forfivo gabapentin imipramine isocarboxazid ketamine khedezla

Concept	Embase Controlled Terms (EMTREE)	Key Words
		kisspeptins neurokinin b antagonist levomilnacipran maprotiline mesylate milnacipran mirtazapine mitriptyline nefazodone neurokinin-receptor antagonist* noradrenalin serotonin reuptake inhibitor* noradrenalin serotonin uptake inhibitor* nonestrogen nonhormonal norepinephrine serotonin reuptake inhibitor* norepinephrine serotonin uptake inhibitor* norpramin nortriptyline oleptro oxybutynin pamelor paroxetine pexeva* phenelzine pregabalin protriptyline prudoxin raloxifene remeron selegiline patch sertraline serotonin and noradrenaline reuptake inhibitor* serotonin and noradrenaline uptake inhibitor* serotonin noradrenalin uptake inhibitor* serotonin and norepinephrine reuptake inhibitor* serotonin norepinephrine reuptake inhibitor* serotonin reuptake inhibitor* sildenafil silenor* surmontil* teriparatide tofranil* trazadone trimipramine* tranylcypromine trazodone

Concept	Embase Controlled Terms (EMTREE)	Key Words
		trintellix* venlafaxine vilazodone vivactil* vortioxetine wellbutrin zimeldine zyban zonalon* *word variations have been searched
Complementary & Integrative Health Interventions	'acupuncture'/exp 'alternative medicine'/exp 'biofeedback'/exp 'breathing'/exp 'hypnotherapy'/exp 'integrative medicine'/exp 'leisure'/exp 'manipulative medicine'/exp 'meditation'/exp 'mindfulness'/exp 'relaxation training'/exp 'tai chi'/exp 'yoga'/exp	acupuncture alternative health* alternative medicine alternative therap* alternative treatment* aromatherap* bio feedback biofeedback breath* chiropract* complementary health* complementary medicine complementary therap* complementary treatment* hypnosis hypnotherap* integrat* health* integrat* medicine integrat* therap* integrat* treatment* leisure activit* leisure time manipulation therap* manipulation treatment* manipulative medicine manipulative therap* manipulative treatment* manual therap* massag* meditat* mind body mindful* relax* sound wave* spinal manipulation tai chi tai ji yoga yogic *word variations have been searched

Concept	Embase Controlled Terms (EMTREE)	Key Words
Behavioral Health Interventions	'behavioral training'/exp 'bladder training'/exp 'counseling'/exp 'hypnotherapy'/exp 'mindfulness'/exp 'psychoeducation'/exp	anger management behavio* chang* behavio* condition* behavio* counsel* behavio* intervention* behavio* modific* behavio* support* behavio* technique* behavio* therap* behavio* train* behavio* treatment* bladder drill bladder 're train*' bladder retrain* bladder train* cbt cognitive behavio* cognitive remediation cognitive therap* counseling dbt hypnosis hypnotherap* mind body mindful* psychoeducat* *word variations have been searched
Lubricants & Moisturizers	'agents used intravaginally'/exp 'emollient agent'/exp 'lubricating agent'/exp 'vagina'/exp	emollient* intravaginal* lubricat* moisturiz* vagina* *word variations have been searched
Herbals & Nutraceuticals	'actaea racemosa'/exp 'alpha tocopherol'/exp 'angelica sinensis extract'/exp 'cannabinoid'/exp 'dioscorea extract'/exp 'ginseng'/exp 'herbaceous agent'/exp 'lactobacillus acidophilus'/exp 'lepidium meyenii'/exp 'nutraceutical'/exp 'oenothera'/exp 'omega 3 fatty acid'/exp 'pollen extract'/exp 'primrose oil'/exp 'red clover'/exp 'red clover extract'/exp 'rhubarb'/exp 'rhubarb extract'/exp	actaea racemosa alpha tocopherol ammoniumum succinate angelica sinensis black cohosh cannabi* chasteberry cimicifuga dioscorea dong quai evening primrose flaxseed ginseng herbal* isoflavone* lactobacillus acidophilus lepidium meyenii maca

Concept	Embase Controlled Terms (EMTREE)	Key Words
	'silybum marianum'/exp 'vitamin d'/exp 'yam'/exp	magnesium marijuana melatonin milk thistle nutraceutical* oenothera omega 3 pollen extract* primrose red clover rhubarb silybum marianum st. johns wort soy s-equol trifolium pratense yam vitamin d vitamin e *word variations have been searched
Dietary Interventions	'anti inflammatory diet'/exp 'diet therapy'/exp 'low carbohydrate diet'/exp 'mediterranean diet'/exp 'phytoestrogen'/exp 'plant-based diet'/exp 'vegan diet'/exp 'whole food'/exp	anti inflammatory diet* anti inflammatory nutrition antiinflammatory diet* antiinflammatory nutrition fasting diet* fasting nutrition low calori* diet* low calori* nutrition low carb* diet* low carb* nutrition mediterranean diet* mediterranean nutrition negative energy balance diet* negative energy balance nutrition phytoestrogen* plant based diet* plant based nutrition standard American diet* diet* therap* vegan diet* vegan nutrition vegetarian diet* vegetarian nutrition whole food* diet* whole food* nutrition *word variations have been searched

Concept	Embase Controlled Terms (EMTREE)	Key Words
Diagnostic Tests	'diagnostic test'/exp/mj 'follitropin'/exp/mj 'muellerian inhibiting factor'/exp/mj 'predictive value'/exp/mj 'questionnaire'/exp/mj	anti mullerian antimullerian bio marker* biomarker* defin* diagnos* estimat* follicle stimulating follitropin fsh level* measur* muellerian inhibit* model* predict* questionnaire* relationship* stages of reproductive aging workshop test* *word variations have been searched
Vaginal Inserts & Lasers	'laser'/exp 'vagina'/exp	cream* insert* intravagin* laser* ring* vagin* *word variations have been searched
Exercise	'aerobic exercise'/exp 'resistance training'/exp 'resistive exercise'/exp	aerobic exercise* aerobic train* aerobics exercis* high intensity interval training physical* activit* pelvic floor resistance exercis* resistance train* resistive exercis* resistive train* strength train* weight lift* weight train* *word variations have been searched

Appendix F: Alternative Text Descriptions of Algorithm

The following outlines narratively describe Module A, Module B, Module C, and Module D. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

Module A: Perimenopause and Menopause Diagnosis

1. Module A begins with Box 1, in the shape of a rounded rectangle: "Adult female with the following symptoms (See **Sidebar 1**)"
2. Box 1 connects to Box 2, in the shape of a rectangle: "Do a thorough history and physical **without** checking hormone levels"
3. Box 2 connects to Box 3, in the shape of a rectangle: "Consider alternative etiologies"
4. Box 3 connects to Box 4, in the shape of a hexagon, and asks the question: "Is the patient older than 40 y/o?"
    a. If the answer is "No" to Box 4, then Box 5, in the shape of a rectangle: "Refer to OBGYN or reproductive endocrinologist for primary ovarian insufficiency (POI) workup"
    b. If the answer is "Yes" to Box 4, then Box 6.
5. Box 6, in the shape of a hexagon, asks the question: "Was the patient's last menstrual period greater than a year ago, or have they had a hysterectomy?"
    a. If the answer is "Yes" to Box 6, then Box 8, in the shape of an oval: "See **Menopause Management Module B**"
    b. If the answer is "No" to Box 6, then Box 7, in the shape of an oval: "See **Perimenopause Management Module C**"

Module B: Menopause Management

1. Module B begins with Box 9, in the shape of a rounded rectangle: "Patient who desires treatment of symptomatic menopause (See **Sidebar 1**)"
2. Box 9 connects to Box 10, in the shape of a rectangle: "Discuss options for treatment using shared decision-making, including the benefits and risks of MHT"
3. Box 10 connects to Box 11 in the shape of a hexagon, asks the question: "Was the patient's last menstrual period greater than a year ago, or have they had a hysterectomy?"
    a. If the answer is "No" to Box 11, then Box 12, in the shape of an oval: "See **Perimenopause Management Module C**"
    b. If the answer is "Yes" to Box 11, then Box 13.
4. Box 13 in the shape of a hexagon, asks the question: "Is the patient >60 y/o and/or more than 10 years from menopause?"
    a. If the answer is "Yes" to Box 13, then Box 14, in the shape of a rectangle: "Offer non-hormonal therapy options (See **Sidebar 3**)."
        i. Box 14 connects to Box 15, in the shape of an oval: "Monitor and continue therapy until shared decision-making to discontinue"
    b. If the answer is "No" to Box 13, then Box 16.
5. Box 16, in the shape of a hexagon, asks the question: "Contraindications or patient risk outweighs benefit? (See **Sidebar 2**)"

   a. If the answer is “Yes” to Box 16, then Box 14, in the shape of a rectangle: “Offer non-hormonal therapy options (See **Sidebar 3**)”
      i. Box 14 connects to Box 15, in the shape of an oval: “Monitor and continue therapy until shared decision-making to discontinue”
   b. If the answer is “No” to Box 16, then Box 17.
6. Box 17, in the shape of a hexagon, asks the question: “Uterus present?”
   a. If the answer is “Yes” to Box 17, then Box 18, in the shape of a rectangle: “Estrogen+Progestogen, Favor non-oral estrogen with micronized progesterone”
      i. Box 18 connects to Box 20.
   b. If the answer is “No” to Box 17, then Box 19, in the shape of a rectangle: “Estrogen only, Favor non-oral estrogen”
      i. Box 19 connects to Box 20.
7. Box 20, in the shape of a hexagon, asks the question: “After 4-12-week trial, does the patient have either: 1. bothersome side effects[a] or 2. persistent symptoms?”
   a. If the answer is “No” to Box 20, then Box 15, in the shape of an oval: “Monitor and continue therapy until shared decision-making to discontinue”
   b. If the answer is “Yes”, to Box 20 then Box 21, in the shape of a rectangle: “1. For side effects:
      - reduce estrogen dosage,
      - change formulation, or
      - consider alternative therapy

      2. If bothersome menopausal symptoms persist: increase the estrogen dosage”
8. Box 21 connects to Box 22, in the shape of a hexagon, and asks the question: “After 4-12-week trial of adjusted therapy, have the patient’s symptoms improved?”
   a. If the answer is “Yes” to Box 22, then Box 15, in the shape of an oval: “Monitor and continue therapy until shared decision-making to discontinue”
   b. If the answer is “No” to Box 22, then Box 23, in the shape of an oval: “Consider a referral to a menopause specialist if symptoms are not relieved by dose adjustments”

[a] For example: Breast tenderness, headaches, irregular vaginal bleeding

Module C: Perimenopause Management

1. Module C begins with Box 24, in the shape of a rounded rectangle: “Adult perimenopausal woman with menopausal symptoms”
2. Box 24 connects to Box 25, in the shape of a hexagon, asks the question: “Does the patient desire pregnancy?”
   a. If the answer is “Yes” to Box 25, then Box 26, in the shape of a rectangle: “Refer to Reproductive Endocrinology and Infertility”
   b. If the answer is “No” to Box 25, then Box 27.
3. Box 27, in the shape of a hexagon, asks the question: “Is the patient at risk of an unintended pregnancy and <51 y/o?”

   a. If the answer is "Yes" to Box 27, then Box 28, in the shape of a rectangle: "Offer hormonal options for menopausal symptoms which also provide contraceptive benefit tailored to patient characteristics and preference."
   b. If the answer is "No" to Box 27, then Box 29, in the shape of a rectangle: "Counsel on benefits and contraindications of MHT (See **Sidebar 2**)"
4. Box 29 connects Box 30, in the shape of a hexagon, asks the question: "Does the patient wish to initiate MHT?"
   a. If the answer is "No" to Box 30, then Box 31, in the shape of a rectangle: "Offer non-hormonal therapy (see **Sidebar 3**)"
   b. If the answer is "Yes", to Box 30 then Box 32, in the shape of a rectangle "Estrogen+Progestogen, Favor non-oral estrogen with micronized progesterone"
5. Box 32 connects to Box 33 in the shape of a hexagon, asks the question: "After 4-12-week trial, does the patient have either: 1. bothersome side effects[a] or 2. persistent symptoms?"
   a. If the answer is "No" to Box 33, then Box 36 in the shape of an oval: "Monitor and continue therapy until shared decision making to discontinue"
   b. If the answer is "Yes", to Box 33 then Box 34, in the shape of a rectangle:
   "1. For side effects:
      - reduce estrogen dosage,
      - change formulation, or
      - consider alternative therapy

   2. If bothersome menopausal symptoms persist: increase the estrogen dosage"
6. Box 34 connects to Box 35, in the shape of a hexagon, asks the question: "After 4-12-week trial of adjusted therapy, have the patient's symptoms improved?"
   a. If the answer is "No" to Box 35, then Box 37, in the shape of an oval: "Consider a referral to a menopause specialist if symptoms are not relieved by dose adjustments"
   b. If the answer is "Yes" to Box 35, then Box 36, in the shape of an oval: "Monitor and continue therapy until shared decision making to discontinue"

[a] For example: Breast tenderness, headaches, irregular vaginal bleeding

Module D: Genitourinary Syndrome of Menopause (GSM) and/or Sexual Dysfunction Symptoms Treatment

1. Module D begins with Box 38, in the shape of a rounded rectangle: "Patient with GSM and/or Sexual Dysfunction Symptoms"
2. Box 38 connects to Box 39 in the shape of a rectangle: "Obtain history and relevant physical exam[a]"
3. Box 39 connects to Box 40 in the shape of a rectangle: "Vaginal Dryness"; Box 46 in the shape of a rectangle: "Dyspareunia"; Box 52 in the shape of a rectangle: "Problems with sexual desire, arousal, and/or orgasm"; and Box 54 in the shape of a rectangle: "Bladder-related symptoms[d] (recurrent UTI, nocturia, urgency, overactive bladder)"
4. Box 40 connects to Box 41, in the shape of a hexagon, asks the question: "Does the history suggest an etiology besides GSM? (Perform pelvic exam as clinically indicated)"

a. If the answer is “No” to Box 41, then Box 42, in the shape of a rectangle: “Discuss the following options using shared decision making:
    - Vaginal moisturizers
    - Local vaginal estrogen
    - Vaginal DHEA
    - Oral ospemifene”
b. If the answer is “Yes” to Box 41, then Box 48, in the shape of a rectangle: “Treat as appropriate or refer to OBGYN”

5. Box 42 connects to Box 43, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    a. If the answer is “No” to Box 43, then Box 44, in the shape of a rectangle: “Adjust treatment and try different option(s) (See **Sidebar 1**)”
        i. Box 44 connects to Box 43, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    b. If the answer is “Yes” to Box 43, then Box 45, in the shape of an oval: “Monitor and continue therapy as indicated”
6. Box 46, in the shape of a rectangle: “Dyspareunia” stems from Box 39.
7. Box 46 connects to Box 47, in the shape of a hexagon, asks the question: “Does the history suggest an etiology besides GSM? (Perform pelvic exam as clinically indicated)”
    a. If the answer is “Yes”, to Box 47 then Box 48, in the shape of a rectangle: “Treat as appropriate or refer to OBGYN”
    b. If the answer is “No” to Box 47, then Box 49, in the shape of a rectangle: “Trial of local vaginal estrogen[b] or DHEA”
8. Box 49 connects to Box 50, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    a. If the answer is “No” to Box 50, then Box 51, in the shape of a rectangle: “Re-evaluate, consider referral to specialty care, and explore options for further evaluation and treatment (See **Sidebar 1**)”
        i. Box 51 connects to Box 50, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    b. If the answer is “Yes” to Box 50, then Box 45, in the shape of an oval: “Monitor and continue therapy as indicated”
9. Box 52, in the shape of a rectangle: “Problems with sexual desire, arousal, and/or orgasm” stems from Box 39.
10. Box 52 connects to Box 53, in the shape of a rectangle: “Trial of appropriate first-line behavioral therapy[c] (See **Sidebar 4**).”
11. Box 53 connects to Box 50, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    a. If the answer is “No” to Box 50, then Box 51, in the shape of a rectangle: “Re-evaluate, consider referral to specialty care, and explore options for further evaluation and treatment (See **Sidebar 1**)”
        i. Box 51 connects to Box 50, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    b. If the answer is “Yes” to Box 50, then Box 45, in the shape of an oval: “Monitor and continue therapy as indicated”

12. Box 54, in the shape of a rectangle: “Bladder-related symptoms[d] (recurrent UTI, nocturia, urgency, overactive bladder)” stems from Box 39.
13. Box 54 connects to Box 55, in the shape of a rectangle: “Treat with local vaginal estrogen”
14. Box 55 connects to Box 50, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    a. If the answer is “No” to Box 50, then Box 51, in the shape of a rectangle: “Re-evaluate, consider referral to specialty care, and explore options for further evaluation and treatment (See **Sidebar 1**)”
        i. Box 51 connects to Box 50, in the shape of a hexagon, asks the question: “Did patient improve after 3 months?”
    b. If the answer is “Yes” to Box 50, then Box 45, in the shape of an oval: “Monitor and continue therapy as indicated”

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[a] Do not delay treatment if patient declines pelvic exam

[b] See Pharmacotherapy Appendix

[c] Consider MHT if other concomitant symptoms

[d] Evaluate UTI and treat with antibiotics as appropriate

Appendix G: Routine Care

Topic	Peri-Menopause: Age 40-50+ (starts with changes in the length of menstrual bleeding or time between periods and lasts up to 12 months after the last period)	Post-Menopause: Average Age: 51 (starting after one year without a period)
General Health Care Maintenance and Prevention	• Cancer risk assessment and screening as appropriate, including sex-specific cancers (e.g., breast and cervical) and non-sex-specific (e.g., colorectal) • Cardiovascular risk assessment and risk reduction, including reviewing sex-specific risk-enhancing factors (e.g., history of gestational diabetes, hypertensive disorders of pregnancy, autoimmune conditions) and promoting health behaviors (e.g., physical activity, control of blood pressure) • Screen for depression, anxiety, sleep disorders, and other mental health conditions • Other preventive care as indicated outside of sex-specific recommendations (e.g., vaccinations, diabetes, cognitive function) **Menopause occurring before the age of 40 is premature ovarian insufficiency and requires evaluation*	• Assess bone health (e.g., DEXA scan when age-appropriate and based on risk factors, calcium/vitamin D intake) • Continued management/screening for cancer and cardiovascular risk assessment and reduction as needed • Other preventive care as indicated outside of sex-specific recommendations (e.g., vaccinations, diabetes, cognitive function)

Menopausal Symptoms	• Ask about menopausal symptoms, including vasomotor symptoms, brain fog, vaginal dryness, sexual function concerns, urinary complaints, mood changes, sleep disturbances, and musculoskeletal complaints. (Many women begin having menopausal symptoms despite having monthly cycles)
	• Manage bothersome menopausal symptoms with treatment including hormone therapy (systemic and vaginal) and non-hormonal options
	  ▪ Considerations:
	  ▪ Do they have a uterus?
	  ▪ Are there contraindications to MHT?
	  ▪ Non-oral routes preferred
	
	Note: Can use MHT even if still having menstrual cycles.
		• Assessment and management of menopausal symptoms, including hormone therapy (systemic and vaginal) and non-hormonal options
		• Assessment and management of urinary incontinence
		• Assessment of sleep disturbances
		• Assessment of sexual function

Topic	Peri-Menopause: Age 40-50+ (starts with changes in the length of menstrual bleeding or time between periods and lasts up to 12 months after the last period)	Post-Menopause: Average Age: 51 (starting after one year without a period)
Contraception	Assess need for contraception (Contraception should be considered until amenorrhea for 1 year after previously regular menses or at least until age 50-55) **Menopausal hormone therapy does not prevent pregnancy*	N/A
Menses	Assessment and management of abnormal uterine bleeding ▪ Pelvic US ▪ Labs: HCG, CBC, TSH ▪ Gynecology consultation for consideration of endometrial sampling	• Evaluate all PMB with pelvic US (+/- endometrial sampling) • Endometrial biopsy may be omitted from the initial evaluation of a patient with postmenopausal bleeding when all of the following are present: ▪ A single episode of postmenopausal bleeding, ▪ A sonographically fully visualized endometrium with a thickness of 4mm or less, ▪ No risk factors strongly associated with malignancy* and, ▪ Access to prompt gynecologic care and follow-up **Factors strongly associated with increased risk of endometrial cancer:* ▪ *Exogenous estrogen use (e.g., supplements and hormone therapy with or without progestin)* ▪ *SERM use (e.g., tamoxifen)* ▪ *BMI >30* ▪ *Nulliparity* ▪ *Genetic predisposition to endometrial cancer (e.g., known or suspected Lynch or Cowden syndromes or family history of endometrial cancer)* ▪ *Black race (independent association with high-grade endometrial cancers)* ▪ *Diabetes mellitus* ▪ *Patients experiencing unscheduled bleeding more than 6 months after initiation of hormone therapy should undergo further evaluation*

Abbreviations: ACOG: American College of Obstetricians and Gynecologists; BMI: body mass index; CBC: complete blood count; DEXA: Dual-energy X-ray absorptiometry; HCG: Human chorionic gonadotropin; MHT: menopausal hormone therapy; mm; millimeter; PMB: postmenopausal bleeding; SERM: selective estrogen receptor modulator; TSH: Thyroid stimulating hormone; US: ultrasound

Appendix H: Pharmacotherapy

A. Systemic Menopausal Hormone Therapy*

Brand Name[a]	Progesterone	Estrogen	Testosterone[b]	Available Dosages	Notes
Oral Estrogen					
Estrace	N/A	Estradiol	N/A	0.5 mg, 1 mg, 2 mg	
Menest	N/A	Esterified estrogen	N/A	0.3 mg, 0.625 mg, 1.25 mg, 2.5 mg	
Premarin	N/A	Conjugated equine estrogen	N/A	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg	
Oral Estrogen Progesterone/Progestin Combinations					
Bijuva	Progesterone	Estradiol	N/A	0.5 mg estradiol/100 mg progesterone 1 mg estradiol/100 mg progesterone	
Activella	Norethindrone acetate	Estradiol	N/A	0.5 mg estradiol/0.1 mg norethindrone acetate 1 mg estradiol/0.5 mg norethindrone acetate	
Angeliq	Drospirenone	Estradiol	N/A	0.5 mg estradiol/0.25 mg drospirenone 1 mg estradiol/0.5 mg drospirenone	
Prempro	Medroxyprogesterone	Conjugated equine estrogen (CEE)	N/A	0.3 mg CEE/1 mg medroxyprogesterone 0.45 mg CEE/1.5 mg medroxyprogesterone 0.625 mg CEE/2.5 mg medroxyprogesterone 0.625 mg CEE/5 mg medroxyprogesterone	
Premphase	Medroxyprogesterone	CEE	N/A	0.625 mg CEE daily days 1 -14 with 0.625 mg CEE estrogens/ 5 mg medroxyprogesterone daily days 14 - 28	
Femhrt	Norethindrone acetate	Ethinyl estradiol	N/A	2.5 mcg/0.5 mg, 5 mcg/1 mg	
Duavee	Bazedoxifene	CEE	N/A	0.45 mg CEE/20 mg bazedoxifene	

Brand Name[a]	Progesterone	Estrogen	Testosterone[b]	Available Dosages	Notes

Estrogen Patch					
Minivelle	N/A	Estradiol	N/A	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg (per day)	Twice weekly
Vivelle-Dot	N/A	Estradiol	N/A	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg (per day)	Twice weekly
Climara	N/A	Estradiol	N/A	0.025 mg, 0.0375 mg, 0.05 mg, 0.06 mg, 0.075 mg, 0.1 mg (per day)	Weekly
Menostar	N/A	Estradiol	N/A	0.014 mg (per day)	Weekly
Estrogen-Progestin Patch					
Combi-patch	Norethindrone	Estradiol	N/A	0.05 mg estradiol/0.14 mg norethindrone (per day) 0.05 mg estradiol/0.25 mg norethindrone (per day)	Twice weekly
Climara Pro	Levonorgestrel	Estradiol	N/A	0.045 mg estradiol/0.015 mg levonorgestrel (per day)	Weekly
Estrogen Transdermal Gel/Spray					
EstroGel	N/A	Estradiol	N/A	0.75 mg/pump	
Elestrin	N/A	Estradiol	N/A	0.52 mg/pump	
Divigel	N/A	Estradiol	N/A	0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.25 mg/pouch	
EvaMist	N/A	Estradiol	N/A	1.53 mg/spray	
Estrogen Intravaginal Ring					
Femring	N/A	Estradiol	N/A	0.05 mg, 0.1 mg (per day)	*Systemic* not to be confused with Estring
Progesterone Oral					
Prometrium	Micronized Progesterone	N/A	N/A	100 mg, 200 mg	
Provera	Medroxyprogesterone acetate	N/A	N/A	2.5 mg, 5 mg, 10 mg	
Levonorgestrel-Containing IUDs					
Mirena, Liletta	Levonorgestrel 52 mg IUD	N/A	N/A	52 mg dose IUDs only and for duration of up to 5 yrs	Off-label use of 52 mg IUD for endometrial protection when

					systemic estrogens are used.
Testosterone Transdermal Gel					
Androgel	N/A	N/A	1% testosterone	One tenth of 50 mg tube (5 mg or ~0.5 mL) per day	Off-label use of male product intended for symptoms of FSIAD. One tube should last 10 days. Appropriate monitoring is recommended.[c, d]

*Consistent with recommendations from ACOG, the Menopause Society, and the Endocrine Society, the Work Group supports using FDA-approved products whenever they are available, rather than compounded alternatives.

[a] Brand names listed where applicable; generic equivalents may be available and/or required.

[b] Esterified estrogens/methyltestosterone (Estratest) is a non-FDA-approved combination MHT product with no clear advantage over alternatives for hot flashes. Even though there may be a modest benefit in sexual desire, oral testosterone/methyltestosterone is generally not recommended due to concern for adverse lipid effects and lack of long-term safety in women. In VA, non-FDA-approved products are not part of the medical benefits package.

[c]Androgen therapy monitoring is recommended to ensure physiological premenopausal levels. Serum testosterone monitoring is recommended. Additionally, lipids and liver function should be assessed at baseline and for the duration of therapy. Consider labs every six months. Injectable and implantable "pellet" formulations are not advised.

[d]See VA Formulary Advisory on Transdermal Testosterone for Hypoactive Sexual Desire Disorder (HSDD) in Postmenopausal Females. Available at: https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Testosterone_HSDD_Clinical_Summary_Mar_2025.pdf

Abbreviations: CEE: conjugated equine estrogen; FSIAD: Female Sexual Interest and Arousal Disorder; IUD: intrauterine device; mcg: microgram; mg: milligram; mL: milliliter

B. Menopausal Therapy for GSM

Generic Name	Brand Name[a]	Usual Dosing	Notes
Vaginal Cream			
Estradiol 0.01%	Estrace	0.5- 1 g vaginally daily for 2 weeks, then 0.5- 1 g 1-3 times per week	Reusable applicator (cleanse with warm water and mild soap)
Conjugated equine estrogen 0.625 mg/g	Premarin Vaginal	0.5- 1 g vaginally daily for 2 weeks, then 0.5- 1 g 1-3 times per week	Reusable applicator (cleanse with warm water and mild soap)
Vaginal Ring			
Estradiol	Estring	2 mg ring (releases 7.5 mcg per day) inserted every 90 days	*Low dose vaginal estrogen*; not to be confused with Femring

Vaginal Insert			
Estradiol	Vagifem	10 mcg tablet vaginally daily for 2 weeks, then 10 mcg 2 times per week	Individual applicator for each tablet
Estradiol	Imvexxy	4 mcg or 10 mcg (1 insert) vaginally once daily for 2 weeks, then 4 mcg or 10 mcg 2 times per week	Soft gel vaginal insert; no applicator; insert ~2 inches into vagina with smaller end up
Prasterone	Intrarosa	6.5 mg insert vaginally at bedtime	Dehydroepiandrosterone (DHEA); converted to active androgens and estrogens in the vaginal tissue; single-use applicator
Oral tablet			
Ospemifene	Osphena	60 mg orally once daily	Oral, systemic SERM with estrogen agonist effect in the vaginal tissue; indicated for vaginal dryness and dyspareunia

[a] Brand name listed where applicable; generic equivalents may be available and/or required.

Abbreviations: DHEA: Dehydroepiandrosterone; g: gram; GSM: genitourinary syndrome of menopause; mcg: microgram; mg: milligram; SERM: Selective Estrogen Receptor Modulator

C. Non-Hormonal Treatment of Symptomatic Menopause

Generic Name[a]	Medication Class	Available Dosages	Notes
Fezolinetant	Neurokinin 3 Receptor Antagonist	45 mg	
Elinzanetant	Neurokinin 1, 3 Receptor Antagonist	60 mg	Available as 60 mg capsules, though 120 mg typical dose
Paroxetine Mesylate	SSRI	7.5 mg	
Paroxetine	SSRI	10 mg, 20 mg, 30 mg, 40 mg	Off-Label
Paroxetine ER	SSRI	12.5 mg, 25 mg, 37.5 mg	Off-Label
Citalopram	SSRI	10 mg, 20 mg, 40 mg	Off-Label
Escitalopram	SSRI	5 mg, 10 mg, 20 mg	Off-Label
Venlafaxine	SNRI	37.5 mg, 50 mg, 100 mg	Off-Label
Venlafaxine ER	SNRI	37.5 mg, 75 mg, 150 mg, 225 mg	Off-Label
Effexor XR	SNRI	37.5 mg, 75 mg, 150 mg	Off-Label
Desvenlaxfaxine	SNRI	25 mg, 50 mg, 100 mg	Off-Label
Gabapentin	GABA Analog	100 mg, 300 mg, 400 mg, 600 mg, 800 mg	Off-Label
Gabapentin ER	GABA Analog	300 mg, 600 mg	Off-Label
Oxybutynin XR	Anticholinergic	2.5 mg, 5 mg	Off-Label

[a] Brand name listed where applicable; generic equivalents may be available and/or required.

Abbreviations: CEE: Conjugated Equine Estrogen; ER or XR: extended release; GABA: Gamma-aminobutyric acid; mg: milligram; SNRI: Serotonin-norepinephrine Reuptake Inhibitors; SSRI: Selective Serotonin Reuptake Inhibitor

Appendix I: Abbreviation List

Abbreviation	Definition
5-HT2 receptor antagonist	Serotonin 5-HT2 receptor antagonist
ACOG	American College of Obstetricians and Gynecologists
AE	Aerobic exercise
AHRQ	Agency for Healthcare Research and Quality
AHRQ-EPC	Agency for Healthcare Research and Quality Evidence-based Practice Center
AI	Aromatase Inhibitor
AMH	Anti-Müllerian Hormone
AMI	Acute myocardial infarction
ASRM/ESHRE	American Society for Reproductive Medicine/European Society of Human Reproduction and Embryology
BMD	Bone mineral density
BMI	Body mass index
BZA	Bazedoxifene
CA	Cancer
CAC	Coronary artery calcium
CBT	Cognitive Behavioral Therapy
CBT-Meno	Cognitive Behavioral Therapy for Menopause
CDC	Centers for Disease Control and Prevention
CE	Conjugated estrogen
CE/BZA	Conjugated estrogen/bazedoxifene
CEE	Conjugated Equine Estrogen
CI	Confidence Interval
CIH	Complementary and Integrative Health
cm	Centimeter
CO2	Carbon dioxide
COI	Conflict of interest
CPG	Clinical Practice Guideline
CR	Controlled release
CV	Cardiovascular
CVD	Cardiovascular disease
CYP1A2	Cytochrome P450 family 1 subfamily A member 2
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 family 3 subfamily A member 4
DCIS	Ductal carcinoma in situ
DEXA	Dual-energy X-ray absorptiometry
DHEA	Dehydroepiandrosterone
dL	Deciliter
DOD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
E	Estrogen
E2	17 β-estradiol

Abbreviation	Definition
EBPWG	Evidence-Based Practice Work Group
ECE	Endometrial Cavity Evaluation
EIN	Endometrial Intraepithelial Neoplasm
ELITE	Early versus Late Intervention Trial with Estradiol
ER	Estrogen receptor
ER or XR	Extended release
FDA	Food and Drug Administration
FMP	final menstrual period
FSFI	Female Sexual Function Index
FSH	Follicle-Stimulating Hormone
FY	Fiscal year
GABA	Gamma-aminobutyric acid
GCS	Greene Climacteric Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSM	Genitourinary syndrome of menopause
HDI	Human Development Index
HDL	High-density lipoprotein
HELPP	Hemolysis, elevated liver enzymes, low platelet count
HER2	Human Epidermal Growth Factor Receptor 2
HERS	Heart and Estrogen/progestin Replacement Study
HIIT	High Intensity Interval Training
HR	Hormone receptor
HRT	Hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
HSDD	Hypoactive Sexual Desire Disorder
I^2	I-squared (measure of heterogeneity)
IR	Immediate release
IU	International unit
IUD	Intrauterine device
IV	Intravenous
KEEPS	Kronos Early Estrogen Prevention Study
kg	Kilogram
KQ	Key question
L	Liter
LDL	Low-density lipoprotein
LNG IUD	Levonorgestrel intrauterine device
LOOP	Luteal Out-Of-Phase
MA	Meta-analysis
MACE	Major adverse cardiovascular events
MAOI	Monoamine Oxidase Inhibitor
MBCT	Mindfulness-based Cognitive Therapy
MBE	Mind-body exercise
MBSR	Mindfulness-based Stress Reduction
mcg	microgram

Abbreviation	Definition
MD	Mean difference
MDD	Major Depressive Disorder
ME	Multicomponent exercise
MENQOL	Menopause-related quality of life
MESA	Multi-Ethnic Study of Atherosclerosis
mg	Milligram
MHT	Menopausal hormone therapy
MI	Myocardial infarction
ml	milliliter
MoCA	Montreal Cognitive Assessment
MP	Micronized progesterone
MPA	Medroxyprogesterone acetate
MRS	Menopause Rating Scale
MSCP	Menopause Society Certified Provider
MsFLASH	Menopause Strategies: Finding Lasting Answers for Symptoms and Health
NAM	National Academy of Medicine
NDRI	Norepinephrine–Dopamine Reuptake Inhibitor
NHANES	US National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NK1RA	Neurokinin-1 Receptor Antagonist
NK3RA	Neurokinin-3 Receptor Antagonist
NMDA	N-Methyl-D-Aspartate
NPV	Negative predictive value
NS	Not-significant
NSTEMI	Non-ST-elevation myocardial infarction
OBGYN	Obstetrician-Gynecologist
OR	Odds ratio
P	Progestogen
pg	picograms
PICOTS	Population, intervention, comparison, outcome, timing, and setting
POI	Primary Ovarian Insufficiency
PPV	Positive predictive value
PR	Progesterone receptor
PROGEST	Effects of Progesterone on Vasomotor Symptoms in Postmenopausal Women
PTSD	Post-Traumatic Stress Disorder
QOL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
rUTI	Recurrent urinary tract infection
SAE	Serious adverse events
SERM	Selective Estrogen Receptor Modulators
SLUMS	Saint Louis University Mental Status
SMART	Selective estrogens, Menopause, And Response to Therapy
SMD	Standard mean difference

Abbreviation	Definition
SNRI	Serotonin-norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SR	Sustained release
SR	Systematic review
STRAW	Stages of Reproductive Aging Workshop
SWAN	Study of Women's Health Across the Nation
TCA	Tricyclic Antidepressant
TIA	Transient ischemic attack
U.K.	United Kingdom
ULN	Upper limit of normal
U.S.	United States
USPSTF	United States Preventive Services Task Force
VA	Veteran Affairs
VA ESP	Veteran Affairs Evidence Synthesis Program
VAS	Visual Analogue Scale
VHA	Veterans Health Administration
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
WHI	Women's Health Initiative
WH PCP	Women's Health Primary Care Provider
WMD	Weighted mean difference
Y/O	Years old
YAG	Yttrium Aluminum Garnet

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