Medi-Cal Rx

Menopausal Hormone Therapy for Bothersome Vasomotor Symptoms

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Learning Objectives

- Review recommendations provided by The Menopause Society (formerly The North American Menopause Society) on the treatment of menopausal symptoms.
- Identify common symptoms associated with menopause, including vasomotor symptoms and genitourinary symptoms.
- Discuss safety considerations related to menopausal hormone therapy (MHT), including contraindications to treatment and potential risks of therapy.
- Compare recommendations from The Menopause Society to other medical society recommendations on the use of MHT.

Key Points

- According to multiple medical societies, MHT is indicated for treating bothersome vasomotor symptoms (VMS), genitourinary syndrome of menopause (GSM), and primary ovarian insufficiency (POI).
- While not all menopausal women will require or use MHT, it offers the most benefit when prescribed before the age of 60 or within 10 years of menopause onset.
- The most common adverse events found in clinical studies of MHT include nausea, bloating, weight gain, fluid retention, mood swings, breakthrough bleeding, headaches, and breast tenderness.
- Shared decision-making should be used to inform treatment decisions when initiating therapy more than 10 years after menopause onset or in individuals who are older than 60 years of age, and if MHT is continued after the age of 65. Age alone is not a marker for discontinuation.
- Individuals who are not eligible for hormone therapy or who prefer alternative treatment options may be candidates for nonhormonal therapies.
- Many hormonal and non-hormonal therapies for menopausal symptoms are included on the *Medi-Cal Rx Contract Drugs List* (CDL) and are available to Medi-Cal members with a prescription.

Background

Every day in the United States, approximately 6,000 people begin the transition to menopause.[1] Menopause refers to the permanent cessation of menstruation, which typically occurs naturally between 45 and 55 years of age. Menopausal symptoms may appear months to years before the last menstrual period and can significantly impact quality of life. The primary symptoms experienced during menopause include:

- VMS, including hot flashes and night sweats, which commonly co-occur with other disturbances, such as sleep disruption, fatigue, depression, memory loss, and poor concentration.
- GSM, such as dyspareunia, vaginal dryness, vaginal burning, vaginal pruritus, dysuria, urinary urgency, and recurrent urinary tract infections.[2,3]

Nearly 75% of individuals will experience some level of VMS during the menopausal transition period, and more than 50% will have GSM.[2,3] While not everyone will require treatment for menopausal symptoms, individuals with severe VMS, including bothersome hot flashes and chronic sleep disturbances, are the most likely to benefit from starting MHT.[3]

Of note, MHT was formerly called hormone replacement therapy, or "HRT," but the word "replacement" was removed to address the misconception that changing hormone levels during the transition to menopause is inherently pathological and requires replacement. Ovarian hormones (estrogen, progesterone, and testosterone) do not need to be routinely replaced during menopause in the absence of bothersome symptoms.[3]

Recommendations for the Use of MHT

The Menopause Society published the 2022 Hormone Therapy Position Statement, which provides recommendations for the use of hormonal therapies in postmenopausal individuals. The statement includes specific guidance for the treatment of symptoms related to menopause, condition-specific recommendations, mitigating risks associated with MHT, and age-related considerations.[3] Recommendations from several other North American medical societies agree that MHT can be a highly effective treatment for bothersome VMS in appropriately selected patients (refer to **Table 1**).[3-7]

Importantly, no medical societies currently recommend MHT for the primary or secondary prevention of cardiovascular disease (CVD).[4]

Table 1. Selected Recommendations for Menopausal Hormone Therapy[4]

Aspect of Treatment	The Menopause Society[3]	American Association of Clinical Endocrinologists & American College of Endocrinology[5]	Endocrine Society[6]	American College of Obstetricians and Gynecologists[7]
Principal Indication	Menopause symptoms			
Prevention of Heart Disease	Not recommended			
Special Considerations	Consideration of age and time from menopause onset	Consideration of age, time from menopause onset, and all risk factors for cardiovascular disease	Consideration of age, time from menopause onset, and baseline risks of cardiovascular disease and breast cancer	None mentioned
Dose and Route of Administration	Lowest effective dose; shared decision-making to determine formulation, dose, and route	Lowest effective dose; consideration of route to reduce risks of therapy	Shared decision-making to determine formulation, dose, and route	Lowest effective dose; no recommendation on route
Duration	Shortest period based on risk-benefit analysis, with periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy	Recommended for ≤5 years with reduction of dose if continuing	Shortest total duration consistent with the treatment goals and evolving risk assessment of the individual	Individualized based on risk-benefit analysis, recommends against routine discontinuation of therapy based on age alone

In September 2024, The Menopause Society issued The Menopause Society Statement on Misinformation Surrounding Hormone Therapy in response to a significant increase in misinformation and disinformation about the use of hormone therapy for the management of menopause.[8] The statement reaffirmed the indications for MHT, emphasized the importance of discussing the benefits and risks of MHT with patients, and clarified that testosterone therapy is only indicated for sexual desire dysfunction and should not be prescribed for other symptoms or disease prevention.[8]

Management of Bothersome VMS

Adequate treatment of bothersome VMS is important as VMS can significantly affect quality of life.[1,2] The Penn Ovarian Aging Study found that, on average, postmenopausal individuals experience moderate to severe VMS for a median of 10 years.[9] MHT is highly effective for the treatment of VMS and can significantly reduce symptom frequency and severity, thereby improving menopause-related quality of life.[2,3]

Hormone therapy options for the treatment of VMS include estrogen therapy (ET), estrogen-progestogen therapy (EPT), micronized progesterone, or conjugated equine estrogens (CEE) plus bazedoxifene (BZA). ET and EPT have the highest efficacy for VMS and have been shown to reduce VMS symptom severity by up to 75%.[3] To prevent endometrial neoplasia associated with unopposed estrogen therapy, current guidance recommends that all individuals with an intact uterus be prescribed either EPT, micronized progesterone, or CEE plus BZA. Individuals without a uterus can be prescribed ET alone for bothersome symptoms.[3] In some studies, synthetic progestins have demonstrated benefit for treating VMS. However, no long-term study results are available, and the use of progestogens without estrogen is considered off-label.[2,3]

It is important to note that lower doses of ET or EPT may take 6 to 12 weeks to provide adequate symptom relief. Treatment should be reassessed periodically to ensure the optimal hormone product is prescribed at the lowest effective dose that meets treatment goals and minimizes adverse effects. When MHT is discontinued, about 50% of individuals will experience a return of VMS.[3,9] At the time of publishing, no guidance is available regarding tapering of MHT versus abrupt discontinuation of therapy.

For decades, MHT after the age of 65 was considered unnecessary because estrogen withdrawal symptoms rarely persisted beyond the age of 65; however, a growing body of evidence affirms that VMS persists after 60 years of age.[3] While no long-term study results are available assessing the risks and benefits of continued use of MHT after the age of 65, The Menopause Society states that use beyond the age of 65 can be considered in healthy individuals with persistent VMS if it is accompanied by appropriate counseling and regular assessment of risks and benefits. The decision should be informed by the individual's medical history, contraindications to MHT, and the patient's preferences.[3]

The various formulations, doses, strengths, and routes of MHT have comparable efficacy for the treatment of VMS, and include capsules, tablets, transdermal patches, vaginal creams, or vaginal rings. As each route has unique benefits and risks, the decision regarding MHT formulation should be individualized depending on the patient's goals of therapy, patient-specific risk factors, and preferences.[3] In addition to prescribing MHT at the lowest effective dose, using nonoral preparations may minimize the risks of adverse effects.[3,14]

Selected hormonal prescription therapies for VMS that are available on the CDL are listed in **Table 2.**

Table 2. Selected Hormonal Therapies for VMS on the CDL *

Class	Drug Name	Formulation
Estrogens and combinations	Estradiol	• Tablets • Transdermal patches • Vaginal cream or ring
	Conjugated estrogens	• Tablets or capsules • Vaginal cream
	Esterified estrogens	• Tablets or capsules
Progestogens and combinations	Progesterone	• Capsules, micronized
	Norethindrone acetate and ethinyl estradiol	• Tablets

* For current information on covered products, refer to the Contract Drugs & Covered Products Lists page on the Medi-Cal Rx Web Portal.

Safety Considerations for Use of MHT

The Women's Health Initiative (WHI) trial is the largest randomized controlled trial of hormone therapy in women between 50 and 79 years of age. Results from the study found increased risks of cardiovascular disease and breast cancer in individuals who were treated with MHT, leading to a drastic decline in the use of MHT due to safety concerns. Although a large population was studied, the WHI study was limited to the use of CEE and medroxyprogesterone acetate (MPA). The WHI study also had limited enrollment of people with bothersome VMS who were younger than 60 years of age or who were less than 10 years from the time of menopause onset. This population is significant because MHT is U.S. Food and Drug Administration (FDA)-indicated for this population specifically. Since the WHI trial, more evidence has become available that clarifies who is most likely to benefit from MHT, specific MHT treatment regimens and their associated safety risks, and essential steps that can be taken to treat individuals needing MHT while minimizing the risks of therapy.[3,11]

The most common adverse events found in clinical studies of MHT include nausea, bloating, weight gain, fluid retention, mood swings (progestogen-related), breakthrough bleeding, headaches, and breast tenderness.[3] There were a few rare but serious risks that were identified by the WHI study published in 2002, including a higher incidence of breast cancer seen in individuals who were given CEE with MPA compared with placebo, venous thromboembolism (VTE), stroke, and gallbladder disease.[3,7,10,11] As other progestogens and BZA have not been found to increase the risk of breast cancer, out of an abundance of caution, MPA is no longer recommended to avoid any potential increased risk of breast cancer.[3]

Observational data suggest that certain hormone formulations, such as lower-dose estrogens and non-MPA progestogens and specific routes of administration, including transdermal estradiol, are associated with reduced cardiovascular risks when compared to CEE with MPA.[3]

However, it is currently uncertain whether nonoral routes of administration lower the risk of VTE, breast cancer, or cardiovascular events due to the lack of clinical trials designed to assess these outcomes when nonoral agents are prescribed.[3]

Contraindications for oral and transdermal hormone therapy include unexplained vaginal bleeding; liver disease; prior estrogen-sensitive cancer (including breast cancer); coronary heart disease (CHD); prior stroke, myocardial infarction (MI), or VTE; or high risk of thromboembolic disease, including uncontrolled blood pressure greater than 180/110.[3,4]

Compounded bioidentical hormone therapies present safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing from inconsistencies in manufacturing, presence of impurities, sterility issues, insufficient scientific efficacy and safety data, and lack of labeling describing the risks of therapy. Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products.[3] More information on compounded hormonal therapies can be found in the American College of Obstetrics and Gynecology (ACOG) Clinical Consensus on Compounded Bioidentical Menopausal Hormone Therapy.[12]

Individuals who are not eligible for hormonal therapy or prefer alternative treatment options for bothersome VMS may be candidates for nonhormonal therapies. Non-pharmaceutical evidence-based treatments include cognitive behavioral therapy (CBT), clinical hypnosis, weight loss for postmenopausal patients with comorbid obesity, and stellate ganglion blockade for treatment-resistant VMS.[15] The Menopause Society provides guidance on the use of non-hormonal therapies during menopause, as most recently published in the 2023 Nonhormone Therapy Position Statement.[15] Recommended nonhormonal prescription therapies for VMS that are available on the CDL are listed in **Table 3**.

Table 3. Non-hormonal Therapies for VMS on the CDL*

Class	Drug Name	Formulation
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine or desvenlafaxine	• Tablets
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, paroxetine, or escitalopram	• Tablets • Solution, oral
Neurokinin B receptor-3 (NK3) antagonists	Fezolinetant	• Tablets
Urinary antispasmodics	Oxybutynin	• Transdermal patches • Tablets • Syrup
Anticonvulsants	Gabapentin	• Tablets or capsules • Solution, oral

* For current information on covered products, refer to the Contract Drugs & Covered Products Lists page on the Medi-Cal Rx Web Portal.

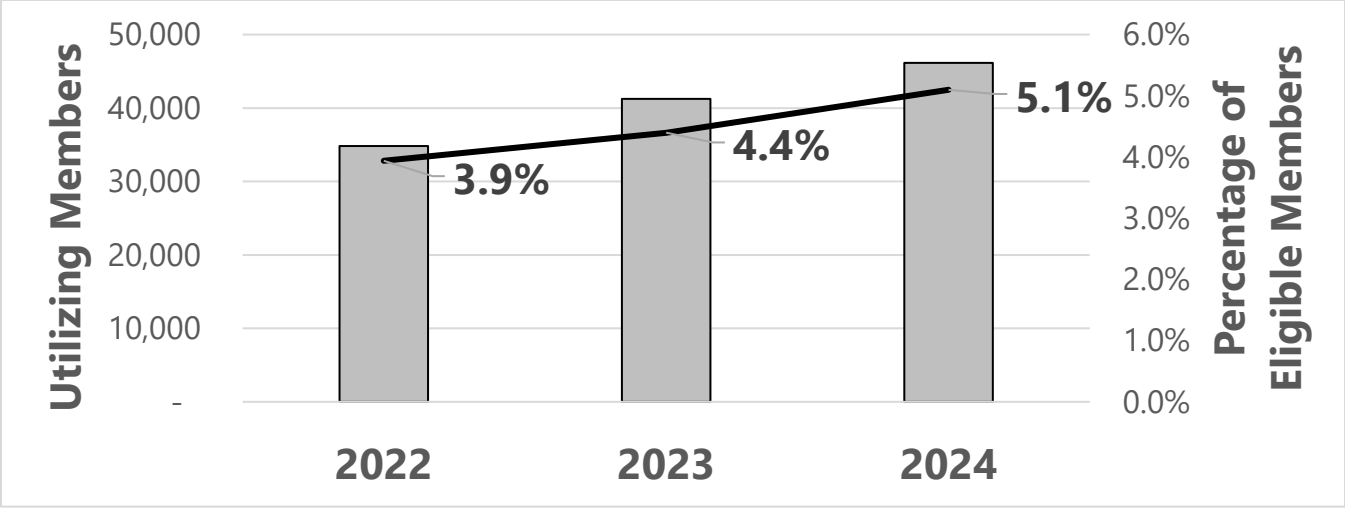
Use of MHT in the Medi-Cal Population

A retrospective administrative claims analysis was conducted to evaluate the recent use of MHT among Medi-Cal members (refer to **Table 2** for all therapies included in the analysis). All paid medical and pharmacy claims were reviewed for eligible Medi-Cal members with a date of service between January 1, 2022, and December 31, 2024. A 90-day lookback period included any pharmacy claims paid before January 1, 2022, to account for any days' supply that overlapped with the measurement year. Inclusion criteria for eligible members included those Medi-Cal members who identified as female and were between 50 and 59 years of age during each measurement year. Members with dual eligibility for Medicare were excluded from the analysis due to the likelihood of incomplete pharmacy claims data for this population.

Results

As shown in **Figure 1**, the use of MHT in the Medi-Cal population is similar to other published data.[8] Importantly, both the total utilizing members and the percentage of eligible members with at least one paid claim for MHT have increased since 2022, with the percentage of eligible members with at least one paid claim for MHT going from 3.9% in 2022 to 4.4% in 2023, then to 5.1% in 2024.

Figure 1. Use of MHT in the Medi-Cal Population between 2022 and 2024.



Similarly, when using member diagnostic codes from medical claims data to determine the presence of menopausal symptoms (*International Classification of Diseases – 10th Revision* [ICD-10] code N95.1), utilization of MHT among these members also increased during this period, going from 12.9% in 2022, 14.6% in 2023, to 15.4% in 2024.

Conclusion/Discussion

Current guidelines encourage a patient-centered approach and shared decision-making when considering therapy for patients experiencing menopausal symptoms. If hormonal therapy is prescribed, providers should thoroughly review the potential risks and benefits associated with the selected treatment and prescribe the lowest effective dose to manage symptoms, with consideration of the route of administration.

Clinical Recommendations

- In postmenopausal patients without contraindications, MHT is the most effective treatment for bothersome VMS.
- The type and duration of MHT should be tailored based on the patient's history, menopausal age, comorbidities, and goals of therapy. If the decision is made to initiate MHT, providers should opt for the lowest effective dose in order to manage symptoms, with consideration given to the route of administration and patient risk profile.
- Risks of hormone therapy differ depending on product type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. A progestogen should be co-prescribed with systemic ET for all people with an intact uterus.
- A risks-benefits discussion and shared decision-making should be used when:
  - Considering initiating MHT after 60 years of age or if more than 10 years have passed since the onset of menopause.
  - Continuing MHT after 65 years of age.
- MHT is not recommended to prevent or treat a decline in cognitive function or dementia.
- Postmenopausal bleeding that occurs while on MHT must be evaluated thoroughly.
- Compounded bioidentical hormone therapies should only be considered due to allergy or if customized dosing is needed.
- Providers may find the following patient resources helpful:
  - Menopause Misinformation Is Everywhere. Here's How to Detect It, available on the ACOG website
  - Menopause Education for Patients, available on The Menopause Society website
  - The Menopause Map™, available on the Endocrine Society website
  - What Is Menopause?, available in both English and Spanish on the National Institute on Aging website

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