Hormone Therapy for Symptoms of the Menopause

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UC San Diego, School of Medicine
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Hormone Therapy for Symptoms of Menopause: Learning Objectives

Review

- Endocrine Society 2015 Clinical Practice Guideline for Treatment of Symptoms of Menopause
- NAMS *Menoapp* tool
- NAMS Position Statement on Nonhormonal Rx VMS
- Treatment Duration: Implications > age 65
- Genitourinary Syndrome of Menopause (GSM)
Treatments of Menopause-Associated Vasomotor Symptoms

- Estrogen
- Prescription Rx
- Nonprescription Remedies
- Mind-Body and Behavior
- Lifestyle Modification

Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Practice Guideline

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Goals of the Guideline

- Focus on treatment of symptoms of menopause
- Emphasize individualized clinical approach
  - Patient symptoms
  - Personal preferences
  - Overall health status
- Suggest baseline risk assessments
  - Contraindications to medical therapies
  - Cardiovascular risks
  - Breast cancer risks
Therapies:

+ Local
+ Systemic

5.0 VVA/GSM

Therapies:
- Local
- Systemic

1.0 Definitions/Diagnosis

Postmenopausal woman
- < 60 y of age or
- < 10 y since menopause
Late perimenopausal

2.0 Health Considerations for All Women

3.0 VMS
Moderate or severe MHT: Patient interest (−) Contraindications

4.0 VMS
Moderate or severe MHT: Patient declines (+) Contraindications

The Stages of Reproductive Aging +10 Staging System for Reproductive Aging in Women

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### Menarche

<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3b</th>
<th>-3a</th>
<th>-2</th>
<th>-1</th>
<th>+1a</th>
<th>+1b</th>
<th>+1c</th>
<th>+2</th>
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<tbody>
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<td>Terminology:</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
<td>POSTMENOPAUSE</td>
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<td>Peak</td>
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<td>Late</td>
<td>PERIMENOPAUSE</td>
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<tr>
<td>Duration:</td>
<td>Variable</td>
<td>Variable</td>
<td>1-3 years</td>
<td>2 years (1+1)</td>
<td>3-6 years</td>
<td>Remaining lifespan</td>
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### Supportive Criteria:

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<th>Endocrine:</th>
<th>FSH</th>
<th>AMH</th>
<th>Inhibin B</th>
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<tr>
<td></td>
<td>Low</td>
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<td>Low</td>
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<td>Variable</td>
<td>↑Variable</td>
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<td>Stabilizes</td>
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<td>&gt;25 IU/L</td>
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<td>Very Low</td>
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<td>Low</td>
<td>Very Low</td>
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<table>
<thead>
<tr>
<th>Antral Follicle Count:</th>
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<td>Low</td>
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### Descriptive Characteristics:

<table>
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<th>Symptoms</th>
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<tbody>
<tr>
<td>Vasomotor symptoms</td>
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<tr>
<td>Vasomotor symptoms</td>
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<tr>
<td>Increasing symptoms of urogenital atrophy</td>
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</tbody>
</table>

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*Blood draw on cycle days 2-5  ↑ = elevated  ** Approximate expected level based on assays using current international pituitary standard67-69

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Harlow et al. STRAW+10 Staging Reproductive Aging Climacteric, Fertil Steril, JCEM, Menopause 2012
WHI 2013 Update: Intervention and Extended Poststopping Phases

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Postintervention</th>
<th>Cumulative</th>
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<tbody>
<tr>
<td>CE + MPA</td>
<td>5.6 y</td>
<td>13 y</td>
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<tr>
<td>CE-alone</td>
<td>7.2 y</td>
<td>13 y</td>
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WHI: Risks and Benefits of MHT ages 50-59

Number of women per 1,000 per 5 years of use

<table>
<thead>
<tr>
<th>Condition</th>
<th>15</th>
<th>12.5</th>
<th>10</th>
<th>7.5</th>
<th>5</th>
<th>2.5</th>
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<th>2.5</th>
<th>5</th>
<th>7.5</th>
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<td>Pulmonary embolism</td>
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<td>Colorectal cancer</td>
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<td>Endometrial cancer</td>
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<td>Lung cancer</td>
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Risks

Benefits

Postmenopausal women (50-59 years of age)
3.0 Hormone Therapy for Menopausal Symptom Relief

3.1 Estrogen and Progestogen Therapy

3.1a. For menopausal women:

- With bothersome VMS ± additional climacteric symptoms
- Who are < 60 yrs of age or < 10 yrs past menopause
- Without contraindications
- Or excess cardiovascular or breast cancer risks
- And who are willing to take MHT

We suggest initiating ET for those without a uterus, and EPT for those with a uterus (Grade 2/⊕⊕○○○)
Approach to Patient with VMS Considering MHT

Assess Patient Criteria
- Symptomatic woman?
  - Age < 60 y or
  - < 10 y since menopause
- Interested in MHT?

If age ≥ 60 y or
≥ 10 y since menopause

CONSIDER OTHER OPTIONS

Approach to Patient with VMS Considering MHT

Consider circumstances where MHT should not be used:
- Contraindications
- Cautions

PRESENT
CONSIDER OTHER OPTIONS

ABSENT

Contraindications to Hormone Therapy

- Possibility of pregnancy
- Undiagnosed vaginal bleeding
- Estrogen sensitive cancers (breast/endometrium)
- History of stroke or MI
- History of deep vein thrombosis or pulmonary embolism
- Liver dysfunction or disease

Approach to Patient with VMS Considering MHT

EVALUATE CARDIOVASCULAR RISK

ACCEPTABLE

HIGH *

CONSIDER OTHER OPTIONS

* Includes known CHD, CVD, PAD, etc.

## Evaluate Cardiovascular Risk

<table>
<thead>
<tr>
<th>10-yr CVD Risk</th>
<th>Years since Menopause Onset</th>
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<tbody>
<tr>
<td></td>
<td>≤ 5 y</td>
</tr>
<tr>
<td>Low (&lt;5%)</td>
<td>MHT ok</td>
</tr>
<tr>
<td>Moderate (5 to 10%)</td>
<td>MHT ok (Choose Transdermal)</td>
</tr>
<tr>
<td>High** (&gt;10%)</td>
<td>Avoid MHT</td>
</tr>
</tbody>
</table>

Approach to Patient with VMS Considering MHT

EVALUATE BREAST CANCER RISK

ACCEPTABLE

HIGH to MODERATE *

CONSIDER OTHER OPTIONS

* Includes calculated level of risk that would qualify for risk-reducing medications

Evaluate Breast Cancer Risk

<table>
<thead>
<tr>
<th>Risk Category***</th>
<th>5-Year NCI or IBIS Breast Cancer Risk Assessment</th>
<th>Suggested Approach</th>
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<tbody>
<tr>
<td>Low</td>
<td>&lt; 1.67 %</td>
<td>MHT ok</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.67-5 %</td>
<td>Caution†</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 5 %</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
“As the impact of severe menopausal symptoms on quality of life may be substantial, however, there are instances in which a woman with a history of coronary heart disease or breast cancer, for example, will choose to accept a degree of risk that might be considered to outweigh the benefits of MHT.

An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances benefits to that individual when weighed against potential risks.”
The MenoPro app from The North American Menopause Society (NAMS) has 2 modes: one for clinicians and one for women/patients, to support shared decision making.

Are you a Health Care Provider or Woman/Patient?

Transdermal Therapy— Metabolically friendlier?

Less effect on:
- Clotting factors
- Blood pressure
- Triglycerides
- C-reactive protein
- Sex hormone binding globulin
Conclusion: Low quality evidence from 15 observational studies suggests that compared to transdermal estradiol, oral estrogen therapy may be associated with increased risk of VTE, DVT, and possibly stroke, but not MI.
Clinical case: Choice of MHT

Relevant Guidelines

Custom-compounded hormones

3.1i We recommend using MHT preparations approved by the FDA and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones.

(Ungraded best practice statement)

FDA approved ‘bioidenticals’

- Estrogen preparations
  - Oral 17-β estradiol
  - Cutaneous 17-β estradiol preparations:
    - Patches, gels, sprays, and emulsions
    - Vaginal estradiol preparations
      - Cream, ring, tablet
  - Vaginal estradiol preparations
  - Oral micronized progesterone
Clinical case: Choice of MHT

Relevant Guidelines

3.1h We suggest a shared decision-making approach to decide about the choice of formulation, starting dose, and route of administration of MHT and to tailor MHT to each woman’s individual situation, risks, and treatment goals. (Ungraded best practice statement)
# Low Dose Estrogen for Treatment of Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Dosage</th>
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<tbody>
<tr>
<td><strong>ORAL</strong></td>
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<tr>
<td>Conjugated equine estrogens</td>
<td>0.3 mg</td>
</tr>
<tr>
<td>Micronized $17$-$B$-estradiol</td>
<td>0.5 mg</td>
</tr>
<tr>
<td><strong>TRANSDERMAL</strong></td>
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<tr>
<td>$17$-$B$-estradiol patch*</td>
<td>25 mcg</td>
</tr>
<tr>
<td>Cutaneous gel*</td>
<td>1-1.25 g</td>
</tr>
<tr>
<td>Estrogen lotion</td>
<td>1 packet</td>
</tr>
</tbody>
</table>

* 14 mcg patch and .25 g gel effective at 12 weeks

Lowest Doses of Progestogens

- 1.5 mg oral MPA
- 0.1 mg oral norethindrone acetate
- 0.5 mg oral drospirenone
- 50-100 mg oral micronized progesterone
Clinical case: Choice of MHT

Relevant Guidelines

*Conjugated equine estrogens with bazedoxifene*

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of CEE/BZA (where available) as an option for relief of VMS and prevention of bone loss.

TSEC: Tissue Selective Estrogen Complex

- Pairs the SERM bazedoxifene 20 mg with conjugated estrogens 0.45 mg
- FDA approved October 3, 2013, for:
  - Treatment of vasomotor symptoms
  - Osteoporosis prevention
- Provides endometrial protection without progestogen therapy


TSEC: Tissue Selective Estrogen Complex

Bazedoxifene 20 mg with CE 0.45 mg

- Relieves vasomotor symptoms\(^1,2\)
- Improves vaginal symptoms\(^1,3\)
- Improves sleep and quality of life\(^4\)
- Decreases bone turnover and bone loss\(^5\)
- Effects breast tenderness,\(^1\) vaginal bleeding,\(^6\) and rates of endometrial hyperplasia\(^7\) similar to placebo
- No changes in mammographic breast density\(^8\)

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Ms. A’s case (continued)

At her annual visit, she continues to report improvement in VMS while taking MHT. She now mentions an older friend who has been taking hormone therapy ‘forever’ and looks and feels great. She wonders how long she should plan to take MHT?

How do you counsel re duration of therapy?
Health Outcomes During Overall Combined Phases: 13y Cumulative

- **Breast cancer**
  - Risk elevated with CE + MPA 1.28
  - With CE alone, risk decreased 0.79

- **Endometrial cancer**
  - Reduced 33 % with CE+ MPA 0.67

- **Hip fracture risk**
  - 19 % reduction with CE+ MPA 0.81

Manson JE, et al. *JAMA* 2013; 310:1353; *All HR statistically significant at least p<.02*
Clinical case: Monitoring during therapy

Relevant Guidelines

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening.
3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman.

(Ungraded best practice statement)
Clinical case: Duration of therapy

Relevant Guidelines

3.4d For young women with primary ovarian insufficiency (POI), premature or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed.

Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years...use of HT and estrogen therapy should be individualized based on each woman’s risk-benefit ratio and clinical presentation.”
The North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65

The 2012 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) states that hormone therapy (HT) is the most effective treatment for symptoms of menopause. To maximize safety, the initiation of HT should be considered for healthy symptomatic women who are within 10 years of menopause or aged younger than 60 years and who do not have contraindications to use of HT. Contraindications are well established and should be considered in making this decision. However, vasomotor symptoms persist for an average of 7.4 years and for more than a decade in many women. Moderate to severe vasomotor symptoms have been documented in 42% of...
Clinical case: Nonhormonal therapies

Relevant Guidelines

4.1a For postmenopausal women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, and without contraindications, we recommend SSRIs/SNRIs or gabapentin or pregabalin.
POSITION STATEMENT


Abstract

Objective: To update and expand The North American Menopause Society’s evidence-based position on nonhormonal management of menopause-associated vasomotor symptoms (VMS), previously a portion of the position statement on the management of VMS.

Methods: NAMS enlisted clinical and research experts in the field and a reference librarian to identify and review available evidence. Five different electronic search engines were used to cull relevant literature. Using the literature, experts created a document for final approval by the NAMS Board of Trustees.

Results: Nonhormonal management of VMS is an important consideration when hormone therapy is not an option, either because of medical contraindications or a woman’s personal choice. Nonhormonal therapies include lifestyle changes, mind-body techniques, dietary management and supplements, prescription therapies, and others. The costs, time, and effort involved as well as adverse effects, lack of long-term studies, and potential interactions with medications all need to be carefully weighed against potential effectiveness during decision making.

Conclusions: Clinicians need to be well informed about the level of evidence available for the wide array of...
Nonhormonal Options for VMS Relief

**Recommend**
- Cognitive behavioral therapy; clinical hypnosis
- Paroxitene salt, SSRI, SNRI, gabapentinoids, clonidine

**Recommend with caution**
- Weight loss, mindfulness based stress reduction, S-equol, stellate ganglion block

**Do not recommend**: cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, over-the-counter supplements and herbal therapies, acupuncture, calibration of neural oscillations, and chiropractic interventions

*Menopause, Vol. 22, No. 11, 2015*
Genitourinary Syndrome of Menopause (GSM)

- A collection of symptoms and signs associated with decreased estrogen levels that can involve the labia majora, labia minora, vestibule, introitus, clitoris, vagina, urethra, and bladder

- Treatment indicated if symptoms are bothersome

- Treatment should be individualized based on severity of symptoms and the woman’s preference after discussion of treatment options and risks/benefits

Portman DJ and Gass M. Presented at NAMS Annual Meeting, October 2013, Dallas; and ISSWSH, February 2014, San Diego
Treatments of Menopause-Associated Vaginal Symptoms

- Vaginal Estrogen
- Systemic HT or SERM
- Nonprescription Remedies
- Lifestyle Modification
Clinical case: Vaginal symptoms

Relevant Guidelines: OTC

5.1 Vaginal moisturizers and lubricants

5.1a For postmenopausal women with symptoms of vulvovaginal atrophy (VVA), we suggest a trial of vaginal moisturizers to be used at least twice weekly.

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants.
Clinical case: Vaginal symptoms

Relevant Guidelines: OTC

5.1 Vaginal moisturizers and lubricants

5.1a For postmenopausal women with symptoms of vulvovaginal atrophy (VVA), we suggest a trial of vaginal moisturizers to be used at least twice weekly.

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants.

Clinical case: Vaginal symptoms

Relevant Guidelines: Vaginal estrogen

5.2a For women without a history of hormone-(estrogen-) dependent cancers who are seeking relief from symptoms of GSM (including VVA), that persist despite using vaginal lubricants and moisturizers, we recommend low-dose vaginal estrogen therapy. (Grade 1/ᵉᵉᵉᵉᵉ)
Clinical Case: Vaginal Symptoms

Estrogen preparations

Vaginal creams
- Conjugated equine estrogens (*Premarin*)
- 17-\(B\)-estradiol (*Estrace*)

Vaginal rings
- 17-\(B\)-estradiol (*Estring*)*

Vaginal tablets
- Estradiol hemihydrate (*Vagifem*)

Progestogen is generally not indicated when low-dose estrogen is administered locally.

*Serum E2 level = 7 pg/mL
Available evidence does not support the boxed warning on low-dose vaginal estrogen regarding an increased risk of CHD, stroke, VTE, dementia, and breast cancer…

…efforts to modify the labeling of these products are in progress.
Treatment of Vaginal symptoms

Relevant Guidelines: Systemic Rx

5.3 Ospemiphene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene.

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene.

Clinical case: Vaginal symptoms

Relevant Guidelines

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to non-hormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET.

(Ungraded best practice statement)

Key Take Home Points: Treatment of Menopausal Symptoms

- MHT is suggested therapy for relief of menopausal symptoms for appropriately selected patients.
- Effective relief of vasomotor symptoms can be achieved with non-hormonal prescription therapies.
- Vaginal and urinary symptoms are undertreated; local estrogen and a systemic SERM therapy are effective.
- Compared to oral estrogen, transdermal estrogen therapy appears to be associated with lower VTE risk.
- Individualize approach to initiation and continuation of MHT.