Current Perspectives on the use of Menopausal Hormonal Therapy (MHT)

A Guideline and Case-Based Approach to Management

This Group Learning program has been certified by the College of Family Physicians of Canada for up to 1.25 Mainpro+ credits.
## Dr. Susan Goldstein Disclosure

### Relationships with commercial interests:

<table>
<thead>
<tr>
<th>Item</th>
<th>Company / Other</th>
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<tbody>
<tr>
<td>Grants/Research Support:</td>
<td></td>
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<tr>
<td>Speakers Bureau/ Honoraria:</td>
<td>Merck, iMedicus, Pfizer</td>
</tr>
<tr>
<td>Consulting Fees / Advisory:</td>
<td>Actavis, Merck, Pfizer</td>
</tr>
<tr>
<td>Other:</td>
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</table>
Mitigating Potential Bias

• The potential for bias in the program has been mitigated by submitting the program content to a full content review by the national office of the CFPC.

• This review ensured that the program content was limited to evidence-based recommendations and patient care recommendations that conform to currently accepted standards (Health Canada, National and International Guidelines, other evidence based resources).

• Planning committee members were responsible for all content decisions. Each committee member has a special interest in the subject area are (credentialed) Certified Menopause Practitioners recognized by the North American Menopause Society (NAMS)
Planning Committee Members

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After participating in this group learning activity participants will be better able to:

1. Employ relevant guidelines for the management of menopausal patients

2. Counsel patients about the risks and benefits of menopausal hormone therapy

3. Formulate individual, evidence-based management strategies for symptomatic menopausal women
Introduction
Largest Cohort of Women Now Entering Menopause

Breakdown of Canadian Female Population by Age

Source: Statistics Canada, Canadian Population 2013, Women

51 is the average age for menopause
Menopause Can Seriously Impair QOL

Results of a 2012 Endocrine Society survey
69% of women with menopausal symptoms said symptoms negatively affect their QOL

Even mild symptoms impact on QOL
Moreover, severe symptoms affect ~20% of women and are perceived to have equivalent effects on QOL as chronic dialysis

QOL: quality of life.

# Defining Menopause: STRAW+10 Staging System

## Terminology

<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>
</tr>
</thead>
<tbody>
<tr>
<td>STAGES</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
<td>POSTMENOPAUSE</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Terminology</td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Variable</td>
<td>Variable</td>
<td>1-3 yrs</td>
<td>2 yrs (1+1)</td>
<td>3-6 yrs</td>
<td>Remaining lifespan</td>
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</tbody>
</table>

## Principal Criteria

**Menstrual cycle**
- Variable to regular
- Regular
- Regular
- Subtle changes in flow / length
- Variable length
- Persistent ≥7-day difference in length of consecutive cycles
- Interval of amenorrhea of ≥60 days

## Supportive Criteria

**Endocrine**
- FSH
- AMH
- Inhibin B
- Low
- Low
- Variable Low
- Variable Low
- >25 IU/L
- *Stabilizes Very low*
- Stabilizes Very low

**Antral Follicle Count**
- Low
- Low
- Low
- Low
- Very low
- Very low

## Descriptive Characteristics

**Symptoms**
- Vasomotor symptoms likely
- Vasomotor symptoms most likely
- Increasing symptoms of genitourinary syndrome of menopause (GSM)

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

Menopause = More Than Hot Flashes

<table>
<thead>
<tr>
<th>Common menopause-related symptoms</th>
<th>Other symptoms associated with menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes and night sweats</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>Mood changes</td>
</tr>
<tr>
<td>Irregular menses</td>
<td>irritability</td>
</tr>
<tr>
<td></td>
<td>anxiety</td>
</tr>
<tr>
<td></td>
<td>depression not responsive to antidepressants</td>
</tr>
<tr>
<td></td>
<td>Urogenital symptoms</td>
</tr>
<tr>
<td></td>
<td>recurrent urinary tract infections</td>
</tr>
<tr>
<td></td>
<td>urinary urgency and/or incontinence</td>
</tr>
<tr>
<td></td>
<td>Dyspareunia</td>
</tr>
<tr>
<td></td>
<td>Breast symptoms*</td>
</tr>
<tr>
<td></td>
<td>Cognitive disturbances</td>
</tr>
<tr>
<td></td>
<td>concentration difficulties</td>
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<tr>
<td></td>
<td>forgetfulness</td>
</tr>
<tr>
<td></td>
<td>Physical symptoms</td>
</tr>
<tr>
<td></td>
<td>stiffness/soreness/joint pain</td>
</tr>
<tr>
<td></td>
<td>headaches/migraines/backaches</td>
</tr>
<tr>
<td></td>
<td>weight gain</td>
</tr>
<tr>
<td></td>
<td>fatigue</td>
</tr>
<tr>
<td></td>
<td>palpitations</td>
</tr>
<tr>
<td></td>
<td>Loss of libido</td>
</tr>
</tbody>
</table>

*Breast tenderness decreases in late perimenopause/postmenopause vs. before and in early perimenopause.

Genitourinary Syndrome of Menopause (GSM)*

GSM is defined as a collection of symptoms and signs associated with reduced estrogen and involving changes to the labia major/minora, clitoris, vestibule/introitus, vagina, urethra and bladder.

This new term replaces the older terminology, which separated vulvovaginal atrophy and urogenital atrophy.

Start the Conversation Early

• Menopause provides a window of opportunity for various counselling issues

• Women could benefit from education about:
  ➢ Hormonal changes and expected symptoms
  ➢ The varied treatment options
  ➢ Preventive health care recommendations and lifestyle modifications

• Much of how women respond to menopause and their decision-making process around treatment options is based on conversations they have with family members, friends and their health care provider

How do you “get the conversation going” with your menopausal and/or perimenopausal patients?

What do you feel are some of the “barriers” to starting this important dialogue with our patients?
General Consideration: Address Lifestyle Issues

• Perimenopause is an opportune time to educate women about healthy lifestyle changes

• Women often do not raise issues around menopausal symptoms so health care providers should proactively ask them

• Lifestyle modifications such as smoking cessation and limiting alcohol intake are appropriate for ALL menopausal women

• A combination of environmental, diet and behavioural modifications may be needed
Consider Nonhormonal Options

Menopausal hormone therapy (MHT) is the most effective treatment for moderate to severe VMS.

However, MHT is not always desired or it may be contraindicated in some situations.

So... which types of nonhormonal treatments are effective?
## Nonhormonal Treatments for VMS

<table>
<thead>
<tr>
<th>Recommended (good evidence)</th>
<th>Recommend with caution (may benefit, further studies required)</th>
<th>Not Recommended (negative, insufficient, or conflicting data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SSRI/SNRI</td>
<td>• Weight loss</td>
<td>• Exercise/yoga</td>
</tr>
<tr>
<td>• Gabapentinoids</td>
<td>• Soy Isoflavones: S-equol derivatives</td>
<td>• Cooling techniques</td>
</tr>
<tr>
<td>• Clonidine</td>
<td>• Mindfulness based stress reduction</td>
<td>• Avoiding triggers</td>
</tr>
<tr>
<td>• Cognitive Behavioural Therapy</td>
<td>• Stellate ganglion block</td>
<td>• Paced respiration</td>
</tr>
<tr>
<td>• Hypnosis</td>
<td></td>
<td>• OTC supplements/herbals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acupuncture</td>
</tr>
</tbody>
</table>

**Rationale:**
Some interventions may have health benefits but may be unlikely to help VMS and **may delay appropriate treatment**

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; VMS, vasomotor symptoms

## Menopausal Hormone Therapy (MHT)

<table>
<thead>
<tr>
<th>Evidence for:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional Systemic ET and EPT</strong></td>
</tr>
<tr>
<td>• VMS</td>
</tr>
<tr>
<td>• Vulvo-vaginal atrophy (GSM)</td>
</tr>
<tr>
<td>• Prevention of osteoporotic fractures</td>
</tr>
<tr>
<td>• Sleep, mood</td>
</tr>
<tr>
<td><strong>Tissue Selective Estrogen Complex (TSEC)</strong></td>
</tr>
<tr>
<td>• VMS</td>
</tr>
<tr>
<td>• Vulvo-vaginal atrophy (GSM)</td>
</tr>
<tr>
<td>• Bone protection</td>
</tr>
</tbody>
</table>

MHT, menopausal hormone therapy; ET, estrogen therapy; EPT, estrogen + progestogen therapy; GSM, genitourinary syndrome of menopause; VMS, vasomotor symptoms; VVA, vulvovaginal atrophy

IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
What is a Tissue Selective Estrogen Complex (TSEC)?

- Pharmacology that is distinct from CE or SERM components alone
- CE demonstrates tissue-selective estrogen receptor agonist activity
  - Maintains efficacy on VMS, VVA and bone
- BZA is a SERM that displays both tissue-selective estrogen receptor agonist and antagonist activity
  - Antagonizes CE stimulation of the breast or endometrium

**TSEC**: Tissue Selective Estrogen Complex; **CE**: Conjugated estrogens; **SERM**: Selective Estrogen Receptor Modulator; **VMS**: Vasomotor symptoms; **VVA**: Vulvovaginal atrophy.

Different SERMs Have Different Sites of Action

Bone
- Antagonist
  - BZA
  - OSP*
  - RLX
- Agonist
  - Estrogens

Endometrium
- Antagonist
  - BZA
  - OSP*
  - Tamoxifen
- Agonist
  - Estrogens

Breast
- Antagonist
  - BZA
  - OSP*
  - RLX
- Agonist
  - Estrogens

SERM: selective estrogen receptor modulator; BZA: bazedoxifene; OSP: ospemifene*; RLX: raloxifene.


*not available in Canada
Rationale Behind TSEC

- Maximize established benefits / evidence of ET while minimizing potential problems associated with progestogens, including:
  - Unscheduled bleeding
  - Breast pain/tenderness
  - Increase in breast density
    - Reduces sensitivity of screening mammograms
    - Independent risk factor for breast cancer

TSEC: tissue selective estrogen modulator; ET: estrogen therapy.

• “CE/BZA has shown to suppress VMS, alleviate vulvovaginal atrophy, and prevent postmenopausal bone loss while having a favourable safety profile with respect to breast and endometrium”

• “Obviates the need for progestin co-therapy in women using systemic estrogen, thus simplifying therapy and avoiding progestin associated adverse effects”

TSEC: tissue selective estrogen complex; VMS: vasomotor symptoms; VVA: vulvovaginal atrophy; CE/BZA: conjugated estrogens/bazedoxifene.
Current Guidelines: So what do the current guidelines state about the use of MHT in women?
Guideline Support for Prescribing MHT Today

MHT: menopausal hormone therapy
Recommendations for MHT

In conjunction with MHT counselling: Lifestyle interventions should be addressed

- Smoking cessation
- Limited alcohol & caffeine
- Healthy diet / weight control
- Regular physical exercise

MHT: menopausal hormone therapy

IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
General Considerations for MHT

• Assess for menopausal symptoms
• Evaluate comorbidities
• Counsel on risk/benefit of treatment options
• Individualize treatment
• Dose and duration of MHT should be consistent with treatment goals

MHT: menopausal hormone therapy
Why Use MHT?

• **IT IS** the most effective treatment for VMS (systemic therapy) and GSM (local therapy)

• **COULD** be initiated for bone protection

• **SHOULD** be initiated in premature ovarian insufficiency/early menopause

• **MAY** improve mood, joint pain, sleep, sexuality and quality of life

VMS: vasomotor symptoms; GSM: genitourinary syndrome of menopause

IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
### Contraindications To Systemic MHT

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Progestogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unexplained vaginal bleeding</td>
<td></td>
</tr>
<tr>
<td>• Acute liver dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Estrogen-dependent cancer (endometrial, breast)</td>
<td></td>
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<tr>
<td>• Coronary heart disease</td>
<td></td>
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<tr>
<td>• Previous stroke</td>
<td></td>
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<tr>
<td>• Active thromboembolic disease</td>
<td></td>
</tr>
<tr>
<td>• Unexplained vaginal bleeding</td>
<td></td>
</tr>
<tr>
<td>• Breast cancer</td>
<td></td>
</tr>
<tr>
<td>• Peanut* allergy (micronized progesterone therapy only)</td>
<td></td>
</tr>
</tbody>
</table>

* Refers to generic version. Name brand made with sunflower oil and soy.

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MHT: menopausal hormone therapy  
Can MHT be used in Special Populations?

- Diabetic women (individual assessment required)
- Hypertensive patients
- Start women at increased risk of breast cancer with appropriate counselling and surveillance
- Continuation of MHT in older postmenopausal women (>60 years old and >10 years since menopause) with appropriate counselling and surveillance
  - Address CV risk factors
  - Low- or ultralow-dose ET is preferred

MHT: menopausal hormone therapy; CV: cardiovascular; ET: estrogen therapy
Other Forms of MHT

- Progestogens or low-dose oral contraceptives can be offered as alternatives during the menopausal transition

- Use local vaginal estrogen if local symptoms only
  - No uterine protection (progestogen, SERM) required at appropriate doses
  - Vaginal estrogen can be used in women with contraindications to systemic ET (stroke, thromboembolic disease)
  - Can be combined with systemic MHT when bothersome symptoms of GSM persist

MHT: menopausal hormone therapy; SERM: selective estrogen receptor modulator; ET: estrogen therapy; GSM: genitourinary syndrome of menopause

Current Perspectives on Safety of MHT

• Risk/benefit differs with age and years from final menstrual period (FMP)

• Safest when INITIATED under age 60 or within 10 years of FMP

• Risk/benefit may differ with
  - Dose
  - Formulation (oral vs transdermal)
  - Choice of progestogen
  - Regimen (continuous vs cyclic)

IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
2017 NAMS Menopause Consensus Guidelines Statement, Publication in press
Duration of VMS

HOW LONG DO VMS LAST?
Duration of VMS

- **Median duration:** 7.4 years (4.5 years post FMP)
- **If VMS earlier in transition,** median duration 11.8+ years (9.4 years post FMP)
- **If VMS onset post FMP:** duration 3.4 years

No mandatory time limit for duration of MHT provided that it is consistent with treatment goals

MHT: menopausal hormone therapy; VMS: vasomotor symptoms; FMP: final menstrual period


IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
MHT and Patient Queries

1. Breast Cancer
2. Stroke & VTE
3. Weight Gain
4. Bio-identicals (custom compounded)

MHT: menopausal hormone therapy; VTE: venous thromboembolism
MHT and Breast Cancer

• In the WHI study, risk was associated with:
  ➢ Use of synthetic progestin plus estrogen (EPT arm) but not CE alone arm
  ➢ Duration of use

• Risk is 0.08% per year and almost returns to baseline after discontinuation of MHT

• Observational data suggests less risk with:
  ➢ Micronized progesterone (or dydrogesterone)
  ➢ Lower doses of estrogen

• Rule out lifestyle co-factors (weight, exercise, alcohol, smoking)

EPT: estrogen + progestin therapy; CE: conjugated estrogens; MHT: menopausal hormone therapy; WHI: Women’s Health Initiative
IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
MHT and Risk of Stroke or VTE

• Risk of ischemic stroke and VTE are age-related
  
  ➢ Increases with oral MHT when initiated in women >60 years
  
  ➢ No effect on stroke risk when MHT is Initiated in women under age 60 or within 10 years of FMP

• Observational data suggests lower risk with different progestogens

• Low or ultra-low dose estrogen is preferred when continuing MHT in older women

MHT: menopausal hormone therapy; VTE: venous thromboembolism; FMP: final menstrual period

IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
MHT and Menopausal Weight Gain

- Average weight gain in midlife is 5-10 lb/decade and not attributable to menopause
  - Hormonal changes during menopause increase total and abdominal fat

- Menopausal abdominal fat accumulation is ameliorated by estrogen therapy

- TSEC not associated with weight gain above baseline gain for age

MHT: menopausal hormone therapy; TSEC: tissue selective estrogen complex

IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
Black et al. Menopause 2016;23:376-82
Custom Compounded BHT

• Custom compounded BHT is not recommended
  - Lack of evidence of efficacy
  - Lack of quality control, regulatory oversight

• Salivary hormone level testing has no clinical utility

• Recent reports of endometrial cancer in women on custom compounded hormones (none on EPT)

Pharmaceutical grade ‘bio-identical hormones’ are available: β-estradiol and micronized progesterone

BHT: bio-identical hormone therapy; EPT: estrogen + progestogen therapy
1. IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2): 109-50
2. Gaudard et al. Cochrane Database Syst Rev 2016 Aug 1; CD010407
3. Davis et al. J Womens Health 2014;23:642-8
### Approved MHT Products Available in Canada

<table>
<thead>
<tr>
<th>ORAL MHT</th>
<th>TRANSDERMAL MHT</th>
<th>VAGINAL MHT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E only</strong>*</td>
<td><strong>E only</strong>*</td>
<td><strong>E only†</strong></td>
</tr>
<tr>
<td>CE 0.3, 0.625, 1.25 mg/d <em>(Premarin)</em></td>
<td>E2 patch 25, 37.5, 50, 75, 100 mcg, 1-2/wk <em>(Climara, Estraderm, Estradot, Oesclim)</em></td>
<td>CE cream 0.625 mg/g (0.5 to 2 g/d for 21 d) <em>(Premarin cream)</em></td>
</tr>
<tr>
<td>E2 0.5, 1.0, 2.0 mg/d <em>(Estrace)</em></td>
<td>E2 gel 0.06%, 1 pump <em>(Estrogel)</em></td>
<td>Estrone cream 0.1% (2-4 g/d for 21 d) <em>(Estragyn)</em></td>
</tr>
<tr>
<td><strong>P only (as part of EPT)</strong></td>
<td>E2 gel 0.1% (0.25, 0.5, 1.0 g/d) <em>(Divigel)</em></td>
<td>E2 ring 2 mg/90 days <em>(Estring)</em></td>
</tr>
<tr>
<td>MP 200 mg/d x 14 d <em>(Prometrium)</em></td>
<td><strong>E + P combo products</strong></td>
<td>E2 tablet 10 mcg 1x/d x 2w then 1x/2w <em>(Vagifem)</em></td>
</tr>
<tr>
<td>MPA 2.5 mg/d x 14 d <em>(Provera)</em></td>
<td>E2 45 mcg + 15 mcg LNG/d <em>(Climara Pro)</em></td>
<td></td>
</tr>
<tr>
<td>NETA 2.5 mg/d x 20 d <em>(Norlutate)</em></td>
<td>E2 50 mcg + NETA 140-250 mcg/d <em>(Estalis)</em></td>
<td></td>
</tr>
<tr>
<td><strong>E + P combo products</strong></td>
<td>E2 0.06% gel (1 pump) for 21-25 d/m + MP 200 mg/d for 14 d/m <em>(Estrogel ProPak)</em></td>
<td></td>
</tr>
<tr>
<td>CE 0.625 mg/d + MPA 2.5-5 mg/d <em>(Premplus)</em></td>
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<tr>
<td>E2 0.5-1.0 mg + NETA 0.1-0.5 mg/d <em>(Activelle, Activelle LD)</em></td>
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<tr>
<td>E2 0.5-1 mg/d + DRSP 0.25-1 mg/d <em>(Angeliq)</em></td>
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<tr>
<td><strong>TSEC‡ (combo product)</strong></td>
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<tr>
<td>0.45 mg CE + 20 mg BZA /d <em>(Duavive)</em></td>
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</table>

*Progestogen is indicated for women with an intact uterus to provide endometrial protection*

† No progestogen required when used at recommended doses.

MHT: menopausal hormone therapy; CE: conjugated estrogens; E2: estradiol; EE: esterified estrogens; MP: micronized progesterone; MPA: medroxyprogesterone acetate; NETA: norethindrone acetate; LNG: levonorgestrel; DRSP: drospirenone; TSEC: tissue selective estrogen complex

Adapted from NAMS http://www.menopause.org/docs/default-source/professional/nams-ht-tables.pdf and Individual product monographs.
Monitoring Therapy: Clinical Considerations

- Monitor blood pressure at baseline and follow-up
- Monitor lipids and glucose as indicated
- Follow current mammography and Pap guidelines
- Measure bone mineral density per local guidelines
- Endometrial surveillance in women at higher risk of endometrial cancer or if persistent unscheduled bleeding
- Review treatment annually

# Counselling on the Risks and Benefits of MHT

## Benefits

- Symptom relief: VMS, GSM
- Prevention of osteoporosis and related fractures
- May benefit mood, sleep
- Improves joint pain

## Risks

- Increased breast cancer risk after 5 years of EPT
- Heart disease & stroke: no significant increase in women aged 50-59 years
- VTE: occurs rarely even in first 1-2 years

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MHT: menopausal hormone therapy; VMS: vasomotor symptoms; GSM: genitourinary syndrome of menopause; EPT: estrogen + progestogen therapy; VTE: venous thromboembolism.
Practical Applications:
Sharing Knowledge through Case-based Learning

Reflective practice
The Menopause Quick 6 (MQ-6):

- Brief screener to identify menopause-related symptoms amenable to therapy
- Questionnaire can be self-rated or clinician-administered
- Developed in accordance with SOGC recommendations on the evaluation of perimenopausal women
The Menopause Quick 6 Screen (MQ-6)

A Simple Approach for Family Practice:

1. Any changes in your periods?
2. Are you having any hot flashes?
3. Any vaginal dryness or pain or sexual concerns?
4. Any bladder issues/ incontinence?
5. How’s your sleep?
6. How’s your mood?

The Menopause Quick 6 Screen can help determine treatment strategies and future planning

Goldstein, S, Canadian Family Physician, Vol. 63, April 2017
Individualized Approach Using the MQ-6

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual pattern</td>
<td>VMS</td>
<td>Vag pain/dry/sexual concerns</td>
<td>Urinary: incontinence/OAB</td>
<td>Sleep issues</td>
<td>Mood issues</td>
</tr>
</tbody>
</table>

MHT Indicated?

CONTRAINDICATIONS to MHT
- Unexplained vaginal bleed
- Known or suspected BrCA
- Acute liver dx
- Active thromboembolic dx
- Acute CVS dx
- Recent CVA
- Pregnancy

COMORBIDITIES?
- DM
- Hypertension
- Smoker
- Obesity
- High LIPIDS or CVS risk
- Gallstones

Non-hormonal management of vasomotor symptoms
- Gabapentin/Pregabalin
- SSRI/SNRI
- Clonidine
- CBT/Hypnosis

VMS
- ++

GSM
- ++
- +/-

Sleep
- +++

Mood
- +++

Any Estrogen

EPT or TSEC

Cyclic regimen

LMP > 1 yr ago?

Hysterectomy?

ET

Continuous regimen

Consider adding additional Vaginal ET (cream/tablet/ring)

GSM Symptoms?
- Vaginal dryness, pain/dyspareunia, urinary symptoms, frequent UTIs
- AND
Lower dose of Estrogen to be prescribed:
- <= CEE 0.625 po, E2 1.0mg po or E2 50 ug Tdg

Goldstein, S, Canadian Family Physician, Vol. 63, April 2017
Vanessa, Age 53, G1P1

- **MQ-6 Results:**
  - FMP 15 months ago
  - VMS severity 7/10 x 1 year
  - Occasional dyspareunia
  - Sleep OK, irritable mood
- **FHx:** aunt breast cancer, father MI age 75
- **EtOH:** 2/night
- **P/E:**
  - BMI 29 kg/m\(^2\)
  - Genitourinary: mild atrophy
  - Mammogram and Pap: up to date, normal
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Is MHT indicated?</td>
</tr>
<tr>
<td>2</td>
<td>Are there contraindications?</td>
</tr>
<tr>
<td>3</td>
<td>Are there comorbidities?</td>
</tr>
<tr>
<td>4</td>
<td>Does patient have a uterus?</td>
</tr>
<tr>
<td>5</td>
<td>When was FMP?</td>
</tr>
<tr>
<td>6</td>
<td>Is vaginal ET needed?</td>
</tr>
</tbody>
</table>

* Derived from MQ6 treatment algorithm
Indications for MHT:

- Moderate to severe VMS
- Treatment of VVA/GSM
- Bone protection
- Treatment for premature ovarian insufficiency and early menopause

Vanessa is a candidate for MHT:
- She has moderately severe VMS and mild vulvovaginal atrophy -
Vanessa, Age 53, G1P1

- MHT is the most effective therapy for VMS and GSM
- However, Vanessa does not want to take hormones

**What else could you recommend?**

### Nonhormonal Treatments for VMS

<table>
<thead>
<tr>
<th>Recommended (good evidence)</th>
<th>Recommend with caution (may benefit, further studies required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SSRI/SNRI</td>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Gabapentinoids</td>
<td>• Soy Isoflavones: S-equol derivatives</td>
</tr>
<tr>
<td>• Clonidine</td>
<td>• Mindfulness based stress reduction</td>
</tr>
<tr>
<td>• Cognitive Behavioural Therapy</td>
<td>• Stellate ganglion block</td>
</tr>
<tr>
<td>• Hypnosis</td>
<td></td>
</tr>
</tbody>
</table>

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; VMS, vasomotor symptoms

1. Is MHT indicated?
Vanessa, Age 53, G1P1

- Vanessa declined gabapentin due to risk of sedation and potential weight gain
- Trial of venlafaxine XR 37.5 mg
  - No significant relief even after titrating up to 75 mg
- She is now ready to try MHT, but she requests custom-compounded “bio-identical hormones”
Custom Compounded BHT

• BHT is not recommended
  ➢ Lack of evidence of efficacy
  ➢ Lack of quality control, regulatory oversight
• Salivary hormone level testing has no clinical use
• Case reports of endometrial cancer in women on BHT (none on EPT)

Pharmaceutical grade ‘bio-identical hormones’ are available:
β-estradiol and micronized progesterone

BHT: bio-identical hormone therapy; EPT: estrogen + progestogen therapy
1. IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy, Climacteric, 2016 Apr; 19(2) : 109-50
2. Gaudard et al. Cochrane Database Syst Rev 2016 Aug 1; CD010407
3. Davis et al. J Womens Health 2014;23:642-8
Are there contraindications?

- MQ-6 Results:
  - FMP 15 months ago,
  - VMS severity 7/10 x 1 year,
  - Occasional dyspareunia,
  - Sleep OK, irritable mood
- FHx: aunt breast cancer, father MI age 75
- EtOH: 2/night
- P/E:
  - BMI 29 kg/m²
  - Genitourinary: mild atrophy
  - Mammogram and Pap: up to date, normal

MHT is not contraindicated
Are there comorbidities?

• **MQ-6 Results:**
  - FMP 15 months ago,
  - VMS severity 7/10 x 1 year,
  - Occasional dyspareunia,
  - Sleep OK, irritable mood

• **FHx:** aunt breast cancer, father MI age 75

• **EtOH:** 2/night

• **P/E:**
  - **BMI 29 kg/m²**
  - Genitourinary: mild atrophy
  - Mammogram and Pap: up to date, normal

Comorbidities? Risk factors?
Vanessa has a uterus… what are her MHT options?

- Intact uterus requires uterine protection:
  - Tissue Selective Estrogen Complex (TSEC)
  - CE + BZA
  - Estrogen + Progestogen (E + P)
  - Higher dose of progestogen may be needed in obese women
# Clinical Considerations for Women With a Uterus

<table>
<thead>
<tr>
<th>Target</th>
<th>SERM</th>
<th>ET</th>
<th>EPT</th>
<th>TSEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Density</td>
<td>+</td>
<td>↔</td>
<td>-</td>
<td>↔</td>
</tr>
<tr>
<td>Uterus</td>
<td>↔</td>
<td>-</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Hot Flash</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vagina</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Legend:** ↔ Neutral, + Favourable effects, - Need for improvement

SERM: selective estrogen receptor modulator; ET: Estrogen Therapy; EPT: Estrogen Progestogen Therapy; TSEC: tissue selective estrogen complex.


4. Does patient have a uterus?
Vanessa is >1 year post-FMP and 53 years old

- If FMP within 1 year: use cyclic regimen
- If FMP >1 year: use continuous regimen
- Consider fertility; contraception not required if:¹,²
  - 2 years post-FMP and age <50
  - 1 year post-FMP and age <55
  - Age >55

EPT: estrogen + progestin therapy  FMP: final menstrual period.

• When ET is considered solely for treatment of GSM, local ET is advised

• Some low-dose systemic regimens may be inadequate for relief of vaginal symptoms
  ➢ Addition of local ET may be needed to achieve adequate vaginal symptom relief

ET: estrogen therapy; GSM: genitourinary syndrome of menopause
Vanessa: Management Planning

Applying what we have discussed, what treatment(s) would you recommend for Vanessa?

- **MQ-6 Results:**
  - FMP 15 months ago,
  - VMS severity 7/10 x 1 year,
  - Occasional dyspareunia,
  - Sleep OK, irritable mood

- **FHx:** aunt breast cancer, father MI age 75

- **EtOH:** 2/night

- **P/E:**
  - BMI 29 kg/m²
  - Genitourinary: mild atrophy
  - Mammogram and Pap: up to date, normal
# Approved MHT Products Available in Canada

<table>
<thead>
<tr>
<th>ORAL MHT</th>
<th>TRANSDERMAL MHT</th>
<th>VAGINAL MHT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E only</strong>*</td>
<td><strong>E only</strong>*</td>
<td><strong>E only†</strong></td>
</tr>
<tr>
<td>CE 0.3, 0.625, 1.25 mg/d <em>(Premarin)</em></td>
<td>E2 patch 25, 37.5, 50, 75, 100 mcg, 1-2/wk <em>(Climara, Estraderm, Estradot, Oesclim)</em></td>
<td>CE cream 0.625 mg/g (0.5 to 2 g/d for 21 d) <em>(Premarin cream)</em></td>
</tr>
<tr>
<td>E2 0.5, 1.0, 2.0 mg/d <em>(Estrace)</em></td>
<td>E2 gel 0.06%, 1 pump <em>(Estrogel)</em></td>
<td>Estrone cream 0.1% (2-4 g/d for 21 d) <em>(Estragyn)</em></td>
</tr>
<tr>
<td><strong>P only (as part of EPT)</strong></td>
<td><strong>E + P combo products</strong></td>
<td>E2 2 mg/90 days <em>(Estring)</em></td>
</tr>
<tr>
<td>MP 200 mg/d x 14 d <em>(Prometrium)</em></td>
<td>E2 45 mcg + 15 mcg LNG/d <em>(Climara Pro)</em></td>
<td>E2 tablet 10 mcg 1x/d x 2w then 1x/2w <em>(Vagifem)</em></td>
</tr>
<tr>
<td>MPA 2.5 mg/d x 14 d <em>(Provera)</em></td>
<td>E2 50 mcg + NETA 140-250 mcg/d <em>(Estalis)</em></td>
<td><strong>E + P combo products</strong></td>
</tr>
<tr>
<td>NETA 2.5 mg/d x 20 d <em>(Norlutate)</em></td>
<td>E2 0.06% gel (1 pump) for 21-25 d/m + MP 200 mg/d for 14 d/m <em>(Estrogel ProPak)</em></td>
<td><strong>E + P combo products</strong></td>
</tr>
<tr>
<td><strong>E + P combo products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CE 0.625 mg/d + MPA 2.5-5 mg/d <em>(Premplus)</em></td>
<td>CE 0.625 mg/d + MPA 2.5-5 mg/d <em>(Premplus)</em></td>
<td></td>
</tr>
<tr>
<td>E2 0.5-1.0 mg + NETA 0.1-0.5 mg/d <em>(Activelle, Activelle LD)</em></td>
<td>E2 0.5-1 mg + NETA 0.1-0.5 mg/d <em>(Activelle, Activelle LD)</em></td>
<td></td>
</tr>
<tr>
<td>E2 0.5-1 mg/d + DRSP 0.25-1 mg /d <em>(Angeliq)</em></td>
<td>E2 0.5-1 mg/d + NETA 0.1-0.5 mg/d <em>(Activelle, Activelle LD)</em></td>
<td></td>
</tr>
<tr>
<td><strong>TSEC† (combo product)</strong></td>
<td><strong>TSEC† (combo product)</strong></td>
<td><strong>TSEC† (combo product)</strong></td>
</tr>
<tr>
<td>0.45 mg CE + 20 mg BZA /d <em>(Duavive)</em></td>
<td>0.45 mg CE + 20 mg BZA /d <em>(Duavive)</em></td>
<td>0.45 mg CE + 20 mg BZA /d <em>(Duavive)</em></td>
</tr>
</tbody>
</table>

*Progestogen is indicated for women with an intact uterus to provide endometrial protection
† No progestogen required when used at recommended doses.

MHT: menopausal hormone therapy; CE: conjugated estrogens; E2: estradiol; EE: esterified estrogens; MP: micronized progesterone; MPA: medroxyprogesterone acetate; NETA: norethindrone acetate; LNG: levonorgestrel; DRSP: drospirenone; TSEC: tissue selective estrogen complex

Adapted from NAMS http://www.menopause.org/docs/default-source/professional/nams-ht-tables.pdf and Individual product monographs.
Vanessa 1 Year After EPT was Initiated

One year later...

• Complains of breast tenderness
• She is worried about breast cancer
• How might you counsel Vanessa regarding her concerns / complaints?
• How would you and Vanessa make a decision about treatment / next steps?

• MQ-6 Results:
  ➢ FMP 15 months ago,
  ➢ VMS severity 7/10 x 1 year,
  ➢ Occasional dyspareunia,
  ➢ Sleep OK, irritable mood
• FHx: aunt breast cancer, father MI age 75
• EtOH: 2/night
• P/E:
  • BMI 29 kg/m²
  • Genitourinary: mild atrophy
  • Mammogram and Pap: up to date, normal
Vanessa, 5 Years After EPT was Initiated

Five years later...

- Vanessa still has occasional VMS
- She does not want to stop MHT
- Does she need to?

• MQ-6 Results:
  - FMP 15 months ago,
  - VMS severity 7/10 x 1 year,
  - Occasional dyspareunia,
  - Sleep OK, irritable mood

• FHx: aunt breast cancer, father MI age 75

• EtOH: 2/night

• P/E:
  - BMI 29 kg/m²
  - Genitourinary: mild atrophy
  - Mammogram and Pap: up to date, normal
Duration of MHT Use

No mandatory time limit for duration of MHT provided it is consistent with treatment goals

- Evidence supports safe use for at least 5 years in healthy women initiating treatment before age 60
- Decision to continue therapy at discretion of well-informed woman and her health professional
- Dosage should be titrated to the lowest effective dose

Use of MHT should be individualized and not discontinued based solely on a woman’s age or her duration of use
Pearls for Practice

- Systematically assess perimenopausal women
  - Using the MQ-6 may be helpful
- Address relevant lifestyle factors
- Individualize treatment based on all currently available options (non-hormonal & MHT)
- Reassess risk/benefit of MHT on an annual basis
“Having nine lives is cool, but if I have to go through menopause again, forget it!”