Overview: Identifying Candidates and Tailoring Treatment

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Disclosures

VMS: Research, Consultant, and/or Speaker

Depomed, Noven, Pfizer, Therapeutics MD,

Vasomotor Symptoms

Hot flashes and night sweats affect 75% of US peri/postmenopausal women

Majority of women are symptomatic from 6 months to 2 years, 25% report symptoms for > 5 years

Penn Ovarian Aging Study found the median duration of moderate-severe VMS was 10.2 years

VMS have been associated with lower health status, work productivity and a reduction in one’s QOL


VMS in Postmenopausal Women

“hot flashes, hot flushes and night sweats”

• Mild HF: sensation of heat without sweating

• Moderate HF: sensation of heat with sweating but able to continue with activity

• Severe HF: sensation of heat with sweating causing the cessation of activity

Majority of women have mild-moderate HF

10-15% of women have severe or very frequent HF


FDA. Guidance for Industry: estrogens and estrogen/progestin drug products to treat vasomotor symptoms and other symptoms and physical changes associated with estrogen deficiency for clinical evaluation, 2003

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2014 NAMS Vasomotor Symptoms Recommendations for Clinical Care

“Treatment for hot flashes should be considered if symptoms are bothersome, disrupt sleep, or adversely affect quality of life. Therapy should be tailored to the individual woman’s medical history, treatment goals, personal attitudes toward menopause and medication use.” (Level 1)

Shifren JL, Gass ML, et al. NAMS Recommendations for Clinical Care of Midlife Women. Menopause 2014;21, No.10 epub

Clinical Evaluation

- Thorough personal and family history can help with counseling about options. i.e. HT vs. CNS meds
- Assess “stage” of menopausal transition, time since LMP, if perimenopausal, could still need contraception
- Physical exam with a special focus on CVD risk, CA screening guidelines, r/o other etiologies for “flushing”
- Evaluate any abnormal bleeding
- Lab Tests: Lipids, CMP (LFTs, FBS), CBC, based on history. Assess CVD risk (low, moderate or high)
- Mammogram

Differential Diagnosis of Autonomic and Vasodilatory Flushing

<table>
<thead>
<tr>
<th>Autonomic-thermoregulatory</th>
<th>Vasodilatory Flushing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal VMS</td>
<td>Medications:</td>
</tr>
<tr>
<td>Exercise</td>
<td>SSRIs, SNRIs, opiates, nitrates</td>
</tr>
<tr>
<td>Fever</td>
<td>Foods:</td>
</tr>
<tr>
<td>Heat exhaustion</td>
<td>Capsaicin, sulfites, MSG</td>
</tr>
<tr>
<td>Emotional</td>
<td>ETOH</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Carcinoid, Mastocytosis, Pheo</td>
</tr>
<tr>
<td>(CNS tumor, epilepsy,</td>
<td>Medullary thyroid CA, Leukemia,</td>
</tr>
<tr>
<td>autonomic dysfunction,</td>
<td>Lymphoma, Renal Cell CA,</td>
</tr>
<tr>
<td>Spinal cord injury, MS,</td>
<td>Dumping syndrome,</td>
</tr>
<tr>
<td>Parkinson’s, headaches)</td>
<td>Pancreatic tumor (VIP)</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis, TB</td>
</tr>
<tr>
<td></td>
<td>Bronchogenic CA</td>
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</table>


Ten Year Risk of CVD, based on ACC/AHA ASCVD Risk Estimator

http://www.imedicalapps.com/2014/04/ascvdriskestimatorapp/

Age, smoking, hypertension, systolic BP, diabetes, total cholesterol, HDL cholesterol

Low < 5% 10-year CVD Risk
Moderate < 5-10% 10-year CVD Risk
High > 10% 10-year CVD Risk

Goff DC et al, Circ 2013;pub,November 12, 2013
Lifestyle Modifications

- Eat a healthy diet, maintain healthy weight
- Get regular exercise, sleep hygiene
- Don’t smoke
- Avoid hot flash triggers (caffeine, alcohol, spicy food)
- Keep cool
  - Dress in layers (light or wicking clothing)
  - Sleep in cool room (fan, thermoregulating pillow)
  - Consume cold drinks
- Try relaxation techniques (yoga, meditation, tai chi, deep breathing)

Herbal Alternatives Comparable with Placebo

<table>
<thead>
<tr>
<th></th>
<th>Mean no. of Vasomotor Symptoms/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh</td>
<td>6.5</td>
</tr>
<tr>
<td>Multibotanical</td>
<td>6.2</td>
</tr>
<tr>
<td>Multibotanical + soy</td>
<td>6.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.0</td>
</tr>
</tbody>
</table>

No statistically significant differences at any time point.
Black cohosh = 160 mg/day; multibotanical = 200 mg black cohosh with alfalfa, boron, chasteberry, dong quai, false unicorn, licorice, oats, pomegranate, ginseng; soy = soy dietary counseling.

A Decade After The Women’s Health Initiative--The Experts Do Agree

Statement published in the journals of North American Menopause Society (Menopause), American Society for Reproductive Medicine (Fertility and Sterility), and The Endocrine Society (Journal of Clinical Endocrinology and Metabolism)

“...the decision to initiate hormone therapy should be for the indication of treatment of menopause-related symptoms...no question that HT has an important role in managing symptoms for women during the menopausal transition and in early menopause.”
Explaining Risk

- Essential to understand basic concepts of risk
- Risk discussion individualized for each woman
- Providing figures for absolute risk is clearer than relative risk
- Put the risk in perspective (i.e., a risk is “rare” if it occurs ≤ 10 per 10,000 patients per year; it’s “very rare” if it occurs ≤ 1 per 10,000 per year)

Explaining HT Risk

HT risk is related to:

- A woman’s baseline disease risks
- Her age
- Age at menopause
- Cause of menopause
- Time since menopause
- Prior use of any hormone
- HT types, routes of administration, dosing
- Emerging medical conditions during treatment

Dose & Route of Administration

- All routes of administration of ET can effectively treat menopausal symptoms
- Non-oral routes may offer both advantages and disadvantages compared with oral route (but no long term RCT outcomes)
  
  See Table 18, pg 279, Chapter 8, NAMS: Menopause Practice: A Clinician’s Guide, 5th ed., 2014

- Transdermal ET may be associated with lower risk of DVT, stroke, and MI
- Multiple progestogen options for endometrial protection
- A SERM (bazedoxifene) with oral conjugated estrogen is also an option for women with a uterus (approved 2013)

NAMS HT Position Statement, Menopause 2012
Stithien JL, Gries ML, et al. NAMS Recommendations for Clinical Care of Middle Women. Menopause 2014;21, No. 10 suppl
Recommendations

Individualization is key in one’s decision to use HT (shared decision making) and should incorporate the woman’s health and QOL priorities as well as her personal risk factors for VTE, CHD, stroke, and breast cancer.

The lowest dose of HT should be used for the shortest duration needed to manage a woman’s menopausal symptoms.

Lower doses have fewer side effects and may have more favorable benefit-risk ratio than standard doses, but they have not been tested in long-term trials.
### Estrogen-Progestogen Therapy Regimens, Terminology

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Estrogen</th>
<th>Progestogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous-cyclic (sequential)</td>
<td>Daily</td>
<td>12-14 d/mo</td>
</tr>
<tr>
<td>Continuous-cyclic (sequential)</td>
<td>Long cycle</td>
<td>Daily</td>
</tr>
<tr>
<td>Continuous-combined</td>
<td>Daily</td>
<td>Daily</td>
</tr>
</tbody>
</table>

### Progestogen “Problems”

- Dysphoria
- Bloating
- Bleeding
- EPT associated with a greater risk of breast CA (concern for length of time to use HT)

### Alternatives:

- Lower estrogen dose and minimize progestogen
- Off label use of local vaginal P or L-IUS
- BZA 20 mg/CE 0.45mg
- Unopposed low/ultralow dose estrogen with monitoring

### Risk/benefit analysis:

Risk/benefit analysis: risk of a therapeutic intervention vs. the risk of not treating, balanced against the possible benefit of a therapy

Reevaluate health status regularly
Discontinuation or Extended Duration

- 50% chance of vasomotor symptoms recurring independent of age and duration of use
- Symptom recurrence similar whether tapered or abrupt
- Decision to continue HT should be individualized
- Extended duration for continued VMS symptoms, patient preference, baseline risks of breast ca, CVD, and osteoporosis

Candidates for Nonhormonal Prescription Therapies

- Treatment Naive
- OTC remedy failures or minimal effect
- Cannot or choose to not use HT
- On HT: desire or need to discontinue, or otherwise appropriate to consider alternatives

Nonhormonal Prescription Therapies for Hot Flashes

- Selective serotonin reuptake inhibitors (SSRIs)
  - Fluoxetine 10-20 mg
  - Paroxetine HCL10-20 mg/d (CR 12.5-25mg/d)
  - Escitalopram 10-20mg/d and Citalopram 10-30 mg/d
- Serotonin–norepinephrine reuptake inhibitors (SNRIs)
  - Venlafaxine 75-150mg/d
  - Desvenlafaxine 50-100mg/d
- Potential limitations:
  - Antidepressant stigma, contraindications/side effects
  - None of the above are government approved for hot flashes, so use would be considered off-label, but........

Nonhormonal Prescription Therapies

- Paroxetine (LDMP)7.5mg
  - First and only FDA approved SSRI for VMS –some patients prefer bedtime dosing, no up or down titration, No affect on weight and libido (NAMS 2013)
  - Cannot be used with Tamoxifen
- Gabapentin-IR (and G-GR) 900-2400mg/d,
  - Start at 100mg/d, slow up-titration to lid dosing
  - Good for sleep and concomitant pain, arthralgias
  - CNS side effects, dizziness, somnolence , tapering advised
- Pregabalin-75-150mg bid, CNS AEs-memory and concentration
- Eszopiclone- 3 mg, helps nighttime VMS, sleep and mood
- Clonidine- 0.05mg -0.1mg bid or 0.1mg/day patch
  - Less effective than SSRIs and gabapentin
  - Low BP, HR arrhythmias, headache

Algorithm and Mobile App for Menopausal Symptom Management and Hormonal/Non-Hormonal Therapy Decision Making:

A Clinical Decision-Support Tool From The North American Menopause Society

MenoPro

**Moderate-to-severe hot flashes and/or night sweats?** (and inadequate response to behavioral/lifestyle modifications)

<table>
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<th>Yes</th>
<th>No</th>
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<tr>
<td>Interested in HT and free of breast cancer, endometrial cancer, DVT/PE, CHD, stroke/TIA, and other contraindications to HT?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Assess CVD risk and time since menopause onset</td>
<td>Moderate to severe (5% to 10%)</td>
<td>Moderate (5% to 10%)</td>
</tr>
<tr>
<td>Years Since Menopause Onset</td>
<td>2</td>
<td>6 to 10</td>
</tr>
<tr>
<td>HT OK</td>
<td>HT OK</td>
<td>HT OK</td>
</tr>
<tr>
<td>HT OK (choose transdermal)</td>
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<tr>
<td>Avoid HT</td>
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**DECISION ABOUT DURATION OF USE**: continue moderate-to-severe symptoms; patient preference; weigh baseline risks of breast cancer, CVD, and osteoporosis.

**CVD Risk Over 10 Years (ACC/AHA Risk prediction score)**
Assess CVD risk and time since menopause onset

**Moderate-to-severe hot flashes and/or night sweats?** (and inadequate response to behavioral/lifestyle modifications)

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<td>Yes</td>
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<td>Moderate (5% to 10%) HT OK</td>
<td>High (&gt;10%) Avoid HT</td>
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**DECISION ABOUT DURATION OF USE**: continued moderate-to-severe symptoms; patient preference; weigh baseline risks of breast cancer, CVD, and osteoporosis.

**Prior Hypertension?**
Yes = HT options (see tables)
No = EPT options (see tables)
CE/bazedoxifene also may be an option

**Low (<5%) HT OK**
Adequate control of hot flashes?

**Moderate (5% to 10%) HT OK (choose transdermal)**
Adequate control of hot flashes?

**High (>10%) Avoid HT**
Adequate control of hot flashes?

**See HT algorithm**

**Interested in HT and free of breast cancer, endometrial cancer, DVT/PE, CHD, stroke/TIA, and other contraindications to HT?**

Yes

**Interested in non-hormonal therapy and free of contraindications to SSRIs/SNRIs?**

Yes

**Avoid SSRIs/SNRIs. Consider gabapentin, pregabalin, or clonidine, if no contraindications.**

No

**Adequate control of hot flashes?**

Yes

**See HT algorithm**

No

**Consider low-dose paroxetine or other well-studied SSRIs/SNRIs (venlafaxine, escitalopram, others), if no contraindications.**

**Avoid SSRIs/SNRIs. Consider gabapentin, pregabalin, or clonidine, if no contraindications.**

**Adequate control of hot flashes?**

Yes

**See HT algorithm**

No

**Adjust dose or consider gabapentin, pregabalin, or clonidine.**
Moderate-to-severe hot flashes and/or night sweats? (and inadequate response to behavior/lifestyle modifications)

Yes

Genitourinary symptoms such as vaginal dryness or pain with intercourse/sexual activity?

Yes

Free of breast cancer, endometrial cancer, and other hormone-sensitive cancers?

Yes

Avoid hormonal therapy

No

Vaginal lubricants and/or moisturizers

No

Yes

Yes

Consider low-dose vaginal estrogen if response is inadequate. Ospemifene may be an option for women who prefer a non-estrogen oral treatment, if no contraindications.