Managing Menopause

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At the end of this presentation, the listener will be able to:

1. Evaluate the stages of reproductive aging to determine a woman’s menopausal status.
2. Prioritize the common symptoms of menopause based upon their likelihood of successful treatment with hormones.
3. Determine a woman’s vulnerability to disease during her menopausal lifespan and appreciate the role of menopause in exacerbating key risk factors.
4. Develop a treatment paradigm based on best practices and current state of the science.
Case Study
Case Presentation - Patient

- 52 years old
- Last menstrual period: 4 months ago
- Drenching night sweats,
- Poor sleep with daytime sleepiness
- “Has a bad attitude”
- Concerned about symptoms/refuses to consider hormones
- Body mass index (BMI)=30 kg/m²
- BP 140/90
Patient Issues

- Obesity +/- metabolic syndrome
- Hot flushes
- Sleep problems
- Possible mood disorder
Is It Aging, Menopause or Something Else?

- Often difficult to disentangle age-related processes (insulin resistance, worsening sleep quality, short term memory impairment) from menopause related processes
- Rule of thumb: the *late* transition associated with the biggest rise in menopause-related symptoms
- Menopause per se appears associated with increased LDL cholesterol and temporary cognitive challenge
Determining Menopausal Status

- Applies only to women who cycle at least once per 3 months in midreproductive life
- Pre-transition: consistent intermenstrual interval
- Early transition: increasing irregularity, at least one period in past 3 months (median age at onset=47)
- Late transition: amenorrhea for 3-11 months
- Menopause: 12 months of amenorrhea after age 45: 90% predictive of permanent amenorrhea (median age=51.4 years)
Symptoms and Morbidity by Menopausal Stage

- Pre: 15% women report hot flashes
- Early transition: 30% report hot flashes
- Late transition: 65% report hot flashes; new onset major depression risk rises 2-3 fold, vaginal dryness becomes more prevalent, sleep complaints increase, bone loss becomes detectable
Patient Workup

- Evaluate obesity/metabolic syndrome:
  - lipid panel, waist circumference, fasting blood sugar
- Treat night sweats
  - treatment (non-hormonal per patient’s request)
- Evaluate sleep problems
  - possibly secondary to night sweats, possibly unrelated (sleep apnea, restless leg syndrome)
- Evaluate mood disorder
  - screen for depression
Results

Patient and spouse deny snoring

Depression screen
  - positive for sadness and anhedonia;
  - negative for recent weight loss or gain
  - negative for suicidal ideation,
  - negative history for depression or other major mood disorder

Negative family history for breast cancer; delivered first child age 28

<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>Total Cholesterol</th>
<th>LDL</th>
<th>HDL</th>
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</thead>
<tbody>
<tr>
<td>150 mg/dl</td>
<td>160 mg/dl</td>
<td>100 mg/dl</td>
<td>35 mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting Blood Glucose</th>
<th>Waist Circumference</th>
<th>Repeat BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 mg/dl</td>
<td>37 inches</td>
<td>140/90</td>
</tr>
</tbody>
</table>
General Recommendations

- Physical activity
  - Weight-bearing exercise, at least 30 minutes, at least 5 days a week
- Healthy diet
  - Limit intake of fats, increase fruits and vegetables
  - Maintain BMI <25 kg/m²
- Stress reduction/control
- Vitamin D₃: 600-1000 IU/day
- Calcium
  - 1000 mg elemental calcium/day if taking hormones
  - OR 1200 mg elemental calcium/day if not on hormones
  - divided doses, taken with food, best taken through dietary sources
- Prevent cognitive impairment
  - Leisure cognitive challenges, exercise and dietary antioxidants are protective
  - Vitamin E ineffective
General Recommendations

- Evaluate breast cancer risk factors and indications for chemoprophylaxis
- Evaluate appropriateness of low-dose aspirin therapy
- Evaluate fracture risk
- Screen for cognitive impairment
- Encourage adherence to screening guidelines (mammography, colonoscopy)
For most symptoms, Menopausal Hormone Therapy (MHT) or Estrogen Therapy (ET) for women without a uterus is the most effective option.

Recommended to use ‘the lowest possible dose for the shortest possible time’ to minimize MHT and ET associated risks.

Nonhormonal alternatives can be used ‘off-label’ and have a reasonable track record of efficacy.

Growing entrepreneurial industry advocating ‘bioidentical hormones’ and promoting them as risk-free.
Indications for Hormone Therapy

- Now called ‘MHT’ (menopausal hormone therapy)
- Lose the ‘replacement’
- Primary indication: symptom control
- Secondary indication: prevention of osteoporosis and fracture
Evolution in Thinking About MHT

- 1990’s ‘global therapy’ for menopause and beyond
- Potential risks of breast cancer and venous thromboembolism outweighed by multiple organ system benefits
- Largest determinant of value of long term MHT: cardiovascular health
- Secondary benefits believed to accrue to women who used MHT:
  - Less stroke and dementia—not supported by RCT
  - Less skin wrinkling and more favorable body fat distribution+/-
  - Fewer cataracts and better dentition
  - Better quality of life +/-
### Absolute Risks and Benefits of MHT

**WHI Cases /10,000 Women-Years**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>E+P</th>
<th>E-Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>+6</td>
<td>-3</td>
</tr>
<tr>
<td>Stroke</td>
<td>+7</td>
<td>+12</td>
</tr>
<tr>
<td>VTE</td>
<td>+18</td>
<td>+8</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>+8</td>
<td>-6</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>-5</td>
<td>-6</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>-6</td>
<td>+1</td>
</tr>
</tbody>
</table>

Statistically significant

WHI Publications; 6/06.
DENIAL IS THE FIRST STAGE OF....

NO, IT ISN'T.
Ultrasound Measurement of CIMT

Hodis HN, et al.

**Thickness of the common carotid artery intima-media layers measured by ultrasound (CIMT).**

*Gray’s Anatomy, 1918, fig. 507*
Changes in Imaging Endpoints, CIMT

CIMT

- o-CEE
- t-E2
- Placebo

p=NS
Would MHT Benefit This Patient?

- Most effective treatment for vasomotor symptoms
- Therapeutic benefit for
  - Poor sleep
  - Adverse mood (mild to moderate depression)
- Possible benefit for sexual dysfunction
Estrogen Versus Placebo

% decrease hot flash score from baseline

0  4  8  12  16

-100 -90 -80 -70 -60 -50 -40 -30 -20 -10  0

E2 25mcg
E2 50mcg
E2 100 mcg
PBO
MHT and Mood

- 12 week trial transdermal E2 (0.1 mg) vs. placebo in 50 perimenopausal women with depression
- Remission of depressive symptoms in 17/25 (68%) on E2 vs. 5/25 (20%) on placebo
- Other trials demonstrate efficacy of 50mcg dose
- Combine with antidepressants or use alone
- Psychiatric backup
- Not effective in postmenopausal women > 1 year beyond the final menstrual period

Source: Arch Gen Psychiatry. 2001 Jun;58(6):529-34.
Anticipated MHT Risk-to-Benefit

**PROS**
- effective for night sweats
- likely to improve sleep
- likely to improve mood (with or without antidepressant medication)
- likely to reduce her risk of acquiring T2DM
- Additional benefit for bone and colon cancer

**CONS**
- likely to increase risk for breast cancer
- likely to increase risk for VTE and stroke
- Additional risks of gall bladder disease, possible risk of dementia later in life
The ‘Lowest Dose for the Shortest Time’

- No other conclusively proven long-term benefits of MHT beyond symptom control
- Symptoms will subside over time for most women
- Many women find partial symptom relief satisfactory
- Allow patient to adjust dose to her level of comfort within safe range of dosing
Belief (not proven) that lower doses have less risk
Clinical end-point=patient satisfaction with symptom relief and ability to tolerate potential risks
Inherent assumption that therapy is not long-term
Low-Dose Estrogen Products

- **Transdermal:**
  - gels 25-100 mcg/day
  - sprays 21-40 mcg/day
  - patches 14-100 mcg/day
- **Vaginal**
  - rings 7.5 mcg/d-100 mcg/day
  - creams - variable
  - tablets 25 mcg 2 times/week
- **Oral**
  - low dose CEE 0.45 mg
  - ultra-low dose 0.3 mg
- **Trend in new drug approvals is towards lower dose products**
Duration of Treatment

- Hot flushes can last for 10 years or more!
- May also be mild, appear and disappear quickly
- No way to know the trajectory an individual woman will follow
- Attempt to wean off hormones periodically:
  - Every 6 months
  - Every year
Successful
- About 75% women wean successfully
- Mild-moderate symptoms
- Natural menopause
- Possibly:
  - Exercising women
  - Women of normal body weight

Unsuccessful
- Surgical menopause
- Severe symptoms when hormones started
- Clear reason for taking hormones
- Symptoms $>10$ years
- Early age at symptom onset
(Grady, Haimov-Kochman)
Is It Better to Gradually Stop Hormones?

- 91 women, mean duration of hormones 8.8 years
- Worse short term hot flushes in women weaned abruptly
- No difference between groups at 9 months

Source: Menopause. 2006 May-Jun;13(3):323-4
What About Those 16% Who Persist?

- When evidence suggests the symptom won’t go away
  - Reinforce risk to benefit of continued MHT
  - Re-assess the risks—they will increase with age and time on hormones
  - Consider new non-hormonal alternatives as appropriate
Nonhormonal Alternatives: Pooled analysis

- 7 trials of selective serotonin reuptake inhibitors (SSRI) and serotonin/norepinephrine reuptake inhibitors (SNRI)
- 3 trials gabapentin
- Additional reduction in hot flash score vs. placebo (24%):
  - Paroxetine 41%
  - Venlafaxine 33%
  - Fluoxetine 13%
  - Sertraline 3-18%
  - Gabapentin 38%

Source: J Clin Oncol. 2009 Jun 10;27(17):2831-7
Gabapentin for Hot Flashes

- Not FDA-approved indication
- Works well for night time symptoms
  - 300-600 mg at bedtime will often relieve night sweats
  - Medication may need to be continued in the daytime for optimal control
- Side effects: daytime drowsiness
- Effective doses can range from as low as 100 mg to as high as 2700 mg per day
CYP2D6 inhibitors: interfere with metabolism of tamoxifen to endoxifen. Concerns about reduction in efficacy of tamoxifen

Paroxetine > fluoxetine > venlafaxine

ASCO 2009: recurrence >> after SSRI use in tamoxifen takers with breast

### SSRI/SNRI Doses and Side Effects

<table>
<thead>
<tr>
<th>Venlafaxine</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 75-150 mg</td>
<td>• 20 mg/day</td>
</tr>
<tr>
<td>• Side effects: Nausea (start low and increase slowly), weight loss, sleeplessness or even drowsiness; loss of libido/anorgasmia</td>
<td>• 12.5-25 mg controlled release</td>
</tr>
<tr>
<td>• DO NOT DISCONTINUE ABRUPTLY</td>
<td>• Can cause increased appetite, weight gain</td>
</tr>
<tr>
<td>• Patients must wean off</td>
<td>• May cause increased anxiety or drowsiness; loss of libido</td>
</tr>
<tr>
<td></td>
<td>• DO NOT DISCONTINUE ABRUPTLY</td>
</tr>
</tbody>
</table>
### Benefit to Risk Ratio for SSRI/SNRIs

<table>
<thead>
<tr>
<th>PROS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Likely to help her night sweats</td>
</tr>
<tr>
<td>• Rapid onset of effect—within days</td>
</tr>
<tr>
<td>• Likely to help her depressed mood</td>
</tr>
<tr>
<td>• May facilitate weight loss</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Possible short term adverse effects: GI, sexual side effects</td>
</tr>
<tr>
<td>• Possible unknown, long term adverse effects</td>
</tr>
</tbody>
</table>
Is the Patient’s Poor Sleep Due to Menopause?

- Sleep quality declines in the 5th decade of life for women and men
- Not all sleep problems are due to menopause
  - Sleep apnea
  - Restless leg syndrome
  - Depression
- Consider a trial of MHT for poor sleep if no other factors are present
Sleep Hygiene

- Keep ambient light low after sundown
- Avoid caffeine, alcohol at night
- Warm drink or bath before bedtime
- Keep extremities warm
- Maintain a consistent sleep-wake cycle
- Sleep enough to avoid daytime sleepiness
Is There Something ‘More Natural’?

• Complementary and alternative medicine (CAM) use

• Advantages of CAM
  ○ no doctor visit required
  ○ patient has control of dosing
  ○ perception of CAM as more ‘user-friendly’ and harmless
  ○ appeal of ‘wellness’ model espoused by CAM therapies and practitioners

• Disadvantages of CAM
  ○ most clinical trials reveal little to no efficacy, potential harm
Red clover isoflavones (n=6)
  - NO BENEFIT

Soy isoflavones (n=11)
  - Inconsistent
  - overall NO BENEFIT

HALT Trial (black cohosh)
  - NO BENEFIT OVER PLACEBO

Vaginal Symptoms

- ~30-40% of women experience dyspareunia or vaginal dryness (apart from intercourse)
- Symptoms persist long after menopause in 26% of women
- No current alternatives to estrogen
- Patients can readily self-titrate to the lowest dose that provides comfort
- Weaning unlikely to be beneficial
  - Reevaluate the need for treatment
  - Reassess the risks annually

Highly prevalent at all ages in women

Distress associated with sexual dysfunction rose in the years around menopause:

- 10.8% women <45
- 14.8% women 45-64
- 8.9% women >64

Sexual Responsiveness Changes with Age

- Longer time to orgasm
- Less intensity of orgasm
- Less lubrication after menopause
- Sexual pain if vaginal dryness is severe
  - Childhood sexual abuse
- Partner sexual dysfunction
  - Medication interactions: antihypertensives, antidepressants
  - Erectile dysfunction
- Partner issues
  - Marital discord
## Testosterone and HSDD* in Surgically Menopausal Women

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Scale</th>
<th>Δ Arousal</th>
<th>Δ Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shifren, 2000</td>
<td>75</td>
<td>BISF</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>Davis, 2006</td>
<td>77</td>
<td>PFSF</td>
<td>16.4 vs 5.98</td>
<td>NS</td>
</tr>
<tr>
<td>Braunstein, 2005</td>
<td>447</td>
<td>PFSF</td>
<td>--</td>
<td>79% satisfying sex</td>
</tr>
<tr>
<td>Simon, 2005</td>
<td>562</td>
<td>PFSF</td>
<td>--</td>
<td>2.19 vs 0.97 more orgasms/month</td>
</tr>
<tr>
<td>Warnock, 2005</td>
<td>102</td>
<td>MSIQ, WHQ</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*HSDD=Hypoactive Sexual Desire Disorder
### RCTs of Testosterone in Natural Menopause

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Scale</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobo, 2003¹</td>
<td>N=218</td>
<td>BISF-W, SIQ</td>
<td>Interest and response doubled, <strong>HDL decreased</strong></td>
</tr>
<tr>
<td>Shifren, 2006²</td>
<td>N=549</td>
<td>PFSF</td>
<td>1.92 vs 0.5 more satisfying sex/month</td>
</tr>
<tr>
<td>Davis, 2008³</td>
<td>N=814</td>
<td>PFSF, PDS</td>
<td>2.1 vs 0.7 satisfying sex/month</td>
</tr>
</tbody>
</table>

Is There a Downside to Testosterone?

- Therapeutic range of testosterone in women is not well known
  - Over-replacement can cause balding, vocal change, clitoromegaly, polycythemia, breast atrophy, low HDL
- Limited long-term safety data
  - Nurses’ Health Study: 77% increase in breast cancer in T+E users
- APHRODITE Study: testosterone alone in postmenopausal women
  - Improved ‘satisfying sex’ by 2.1 episodes/month
  - Excess breast cancer cases seen over 1 year
‘We recommend against making a diagnosis of androgen deficiency in women at present because of lack of a well defined clinical syndrome’

‘We recommend against the generalized use of testosterone by women:’

- Because the indications are inadequate
- Evidence of safety in long-term studies is lacking

Source: J Clin Endocrinol Metab. 2006 Oct;91(10):3697-710.
The Bioidentical Hormone Controversy

- Heavy marketing to public without scientific efficacy and testing
- Be aware of the regulatory issues
- Several societies (The Endocrine Society, NAMS) have position statements against their use
- Increased FDA oversight may occur in the future
- Should not generally be prescribed
### ‘Bioidentical’ Versus Evidence-Based Hormones

<table>
<thead>
<tr>
<th>‘Bioidentical’</th>
<th>Evidence-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compounded E,P,T</strong></td>
<td></td>
</tr>
<tr>
<td>• Steroids are stable</td>
<td></td>
</tr>
<tr>
<td>• Excipients vary widely</td>
<td></td>
</tr>
<tr>
<td><strong>Salivary-based dosing, titration</strong></td>
<td></td>
</tr>
<tr>
<td>• ‘Right’ level when symptoms are the indication?</td>
<td></td>
</tr>
<tr>
<td>• Saliva does not reflect circulating hormones</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmaceutical grade, FDA approved E&amp;P</strong></td>
<td></td>
</tr>
<tr>
<td>• Just as natural!</td>
<td></td>
</tr>
<tr>
<td>• Adjust medication to treat symptoms</td>
<td></td>
</tr>
<tr>
<td>• The patient is the arbiter of success</td>
<td></td>
</tr>
</tbody>
</table>
Avoid misleading terminology

Redirect patient to FDA-approved ‘natural’ hormones

REMEMBER: If you write the prescription you are part of the problem!
The menopausal years are not a monolithic time of life for women

In addition to menopause-related illnesses, the common chronic diseases of aging should be addressed in the health evaluation of menopausal women
Summary

- Menopausal symptoms can be addressed in a variety of ways and the clinician should gain expertise with several methods, including hormones.
- Other disease screening, treatment and healthy lifestyle advice should be performed on a regular basis.
- Patients should be directed towards evidence-based treatments and counseled to avoid unproven and potentially hazardous therapies.
<table>
<thead>
<tr>
<th>Author</th>
<th>Citation</th>
<th>Study</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostick</td>
<td>1999; AJE 149:151</td>
<td>Iowa Women’s Health Study</td>
<td>34,486</td>
<td>Ca++ supplements decreased CVD HR 0.66</td>
</tr>
<tr>
<td>Michaelssoon</td>
<td>2013; BMJ 12:346</td>
<td>Swedish Cohort Study</td>
<td>61,433</td>
<td>&gt;1400mg/day&gt;&gt;&gt;CVD risk HR 2.57</td>
</tr>
<tr>
<td>Chung</td>
<td>2009; AHRQ 09-E0115 8/09</td>
<td>Meta-analysis</td>
<td>200 articles</td>
<td>No association</td>
</tr>
<tr>
<td>Bolland</td>
<td>2011; BMJ 342:d2040</td>
<td>WHI—CT ONLY</td>
<td>36,282</td>
<td>Increased risk with Ca++&gt;1000mg</td>
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<tr>
<td>Prentice</td>
<td>2013; Osteo Intl 24:567</td>
<td>WHI—CT +OS</td>
<td>&gt;100,000</td>
<td>No association</td>
</tr>
<tr>
<td>Wang</td>
<td>Am J Cardiov Drug 12:105</td>
<td>Meta-analysis</td>
<td>Pooled data</td>
<td>No association</td>
</tr>
<tr>
<td>Xiao</td>
<td>JAMA Int Med 2013: 1-8 Feb 4</td>
<td>NIH-AARP diet and health study</td>
<td>388,229</td>
<td>NO increased risk with supplements in women</td>
</tr>
</tbody>
</table>