The Seven Dwarfs of Menopause

Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful & Psycho
MENOPAUSE: An Update

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MENOPAUSE: An Update

• Financial Disclosure: No conflict of interest
• Learning Objectives
  – Define Menopause and the effects it has on the female patient
  – Describe prescription hormonal therapies
  – Describe complementary and alternative medical therapy
  – Describe non-prescription therapy
What is MENOPAUSE?

• Menopause is a normal, natural event, defined as the final menstrual period (FMP), confirmed after 1 year of no menstrual bleeding

• Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually due to aging
When is MENOPAUSE?

• Naturally (spontaneously) average age 51
• Prematurely from medical intervention (eg, bilateral oophorectomy, chemotherapy, radiation)
• At any time from impaired ovarian function
What do women think about Menopause

• In a survey of 12,275 perimenopausal women about their attitudes toward menopause, the mean score for all ethnic groups studied was positive.

• In a Gallup survey of 752 women concerning life changes since menopause, a strong majority thought the following were either unchanged or improved: role at work, family life, partner/sexual relationship, friendships, self-fulfillment, and physical health.
Menopausal symptoms & signs

Classic symptoms:
• Change in menstrual cycle pattern (during perimenopause)
• Vasomotor symptoms (hot flashes & night sweats)
• Vulvovaginal symptoms, dyspareunia
• Sleep disturbances

Other symptoms sometimes associated with menopause:
• Cognitive concerns (memory, concentration)
• Psychological symptoms (depression, anxiety, moodiness)

➤ There is no one universal menopausal syndrome
Perimenopause

- The time around the FMP, also called “the menopause transition”
- Begins with variation in the menstrual cycle length of >7 days associated with a rise in follicle-stimulating hormone (FSH) and ends 1 year after the FMP
- Often the most symptomatic phase for women
Millions of Women Undergo Menopause Each Year

• >50 million women in the United States are ≥50 years old\textsuperscript{1}
  – Median age of natural menopause is 51.3 years\textsuperscript{2}
  – 75% of women aged 50 to 55 are postmenopausal\textsuperscript{3}
• Early menopause
  – 1% of women <40 years old experience premature menopause\textsuperscript{3}
  – 5% of women aged 40 to 45 experience natural early menopause\textsuperscript{3}
• Induced menopause
  – >500,000 US women undergo hysterectomies each year, and oophorectomy is performed in 70% of these women\textsuperscript{4}
  – >360,000 US women undergo oophorectomy and salpingo-ooophorectomies each year\textsuperscript{4}
Menopause Definition

• In 2001, the Stages of Reproductive Aging Workshop (STRAW) established a nomenclature for reproductive aging

• In 2011, STRAW+10 updated and modified the model
## STRAW+10

<table>
<thead>
<tr>
<th>Stage</th>
<th>Terminology</th>
<th>REPRODUCTIVE</th>
<th>MENOPAUSAL TRANSITION</th>
<th>POSTMENOPAUSE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td>Variable</td>
<td>variable</td>
<td>1-3 years</td>
<td>2 years (1+1)</td>
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</table>

### PRINCIPAL CRITERIA

<table>
<thead>
<tr>
<th>Menstrual Cycle</th>
<th>Variable to regular</th>
<th>Regular</th>
<th>Subtle changes in Flow/Length</th>
<th>Variable Length</th>
<th>Persistent ≥7- day difference in length of consecutive cycles</th>
<th>Interval of amenorrhea of ≥60 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variable</td>
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### SUPPORTIVE CRITERIA

<table>
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<tr>
<th>Endocrine</th>
<th>FSH</th>
<th>AMH</th>
<th>Inhibin B</th>
<th>Antral Follicle Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

### DESCRIPTIVE CHARACTERISTICS

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

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard**
Menopausal Transition is Associated with Symptoms Lasting up to 10 Years or Longer

• Among women who have hot flashes (HFs), 25% report that these symptoms remain for longer than 5 years,¹ and 10% report that they remain for longer than 10 years¹-³

• **VMS in postmenopausal women include HFs⁴**
  • **Mild HFs**: sensation of heat without sweating
  • **Moderate HFs**: sensation of heat with sweating, able to continue activity
  • **Severe HFs**: sensation of heat with sweating, causing cessation of activity
Vasomotor Symptoms Definition

• Recurrent, transient episodes of flushing accompanied by a sensation of warmth to intense heat on the upper body and face/head

• Commonly referred to as “hot flashes” by day and “night sweats” by night

• Hot flashes can sometimes involve the whole body (eg, inside of elbows, back of knees)
Hypothesis of Thermoregulatory Dysfunction

• The precise pathophysiology of VMS is unknown; however, a hypothesis exists\textsuperscript{1,2}

- Estrogen levels are reduced during menopause
- Neurotransmitter levels are altered in the hypothalamus
- Thermoregulatory set point in the hypothalamic regulatory nucleus is lowered, triggering inappropriate heat loss

Women with VMS are theorized to have a narrowed thermoneutral (Comfort) zone

- Women without VMS have normal temperature thresholds\(^1,2\)
  - Small changes in core body temperature remain in the thermoneutral zone and do not elicit shivering or sweating

Women with VMS have a narrowed thermoneutral zone\(^1,2\)

- HFs are triggered by core body temperature elevations acting within a greatly reduced thermoneutral zone

Core body temperature threshold for shivering was significantly higher in symptomatic postmenopausal women, suggesting narrowing of the thermoneutral zone


Figure from Rossmanith WG, *Gynecological Endocrinology*, 2009;25(5):303-314. Copyright © 2009 Informa Healthcare. Adapted with permission of Informa Healthcare.
Cognitive changes

- There is evidence that psychomotor speed and to a lesser extent verbal memory can decline slightly in perimenopause.
- Although depression and anxiety are related to cognitive decline, neither mood nor age account for these cognitive changes experienced by some women.
- Any transient issue with cognition appears to resolve after menopause.
Normal cognitive aging vs dementia

• People with dementia have cognitive impairment, but not everyone with cognitive impairment has dementia
• Dementia represents a decline in memory and at least one other cognitive domain
• The decline interferes with occupational and/or social functioning
Vulvovaginal changes

• At menopause, loss of estrogen, and possibly inflammation and tissue changes in the vaginal microbiome, increase vaginal pH from an acidic environment to an alkaline one
• Research has now found that some beneficial microbial communities are associated with a higher pH
• This research questions the earlier belief that the menopausal vagina is abnormal and not healthy
Vulvovaginal symptoms

• Symptoms such as vaginal dryness, vulvovaginal irritation/itching, and dyspareunia are experienced by ~10%-40% of postmenopausal women

• Unlike vasomotor symptoms, which abate over time, vaginal atrophy can be progressive and is unlikely to resolve on its own

• Treatments include: regular sexual activity, lubricants and moisturizers, and local vaginal estrogen
Vaginal atrophy illustration

- Vaginal atrophy as illustrated by contrast of vaginal epithelium in a well-estrogenized premenopausal state (left panel) with a low-estrogen postmenopausal state (right panel)
Urinary complaints

• Urinary complaints are common in women throughout life

• Incontinence is the most common
  – Among 3,302 women, mean age 46 years, 57% reported incontinence with 15% moderate and 10% severe symptoms

• Mild incontinence in early perimenopause tends to decline after menopause

• Other complaints include frequency, urgency, dysuria, and rarely, hematuria
Sexual health

• Libido generally decreases with age
• Distressing sexual problems peak during midlife (ages 45-64) and are lowest from age 65 onward
• Decreased estrogen can result in loss of vaginal moisture and elasticity
• Decline in androgens may contribute to a decline in sexual desire, arousal, and vaginal lubrication
• Vaginal sexual activity and lubricants may help keep vaginal tissue more moist and elastic
Effect of perimenopause on parameters of sexual functioning

- Importance of sexuality remains relatively constant
- Sexual desire declines
- Pain with intercourse increases
- Frequency of sexual activity remains relatively constant despite reports of dryness/discomfort
Sexually transmitted infections

• Clinicians should inform peri- and postmenopausal women that they are still at risk for sexually transmitted infections (STIs)
• Vaginal atrophy increases the risk for contracting an STI
• Older women may not be as knowledgeable as younger women about infection risks or steps to take to reduce those risks
PRESCRIPTION TREATMENTS

Doc, I know you said she’d be crying a lot through this transition, but while she’s watching QVC???
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage/Regimen</th>
<th>Evidence of Benefit*</th>
<th>FDA Approved</th>
</tr>
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<tbody>
<tr>
<td><strong>Hormonal</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Estrogen-alone or combined with progestin</td>
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<td></td>
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<tr>
<td>• Standard Dose</td>
<td>Conjugated estrogen 0.625 mg/d</td>
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<td>Yes</td>
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<tr>
<td></td>
<td>Micronized estradiol-17β 1 mg/d</td>
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<td>Yes</td>
</tr>
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<td></td>
<td>Transdermal estradiol-17β 0.0375–0.05 mg/d</td>
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<td>Yes</td>
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<tr>
<td>• Low Dose</td>
<td>Conjugated estrogen 0.3–0.45 mg/d</td>
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<td>Yes</td>
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<tr>
<td></td>
<td>Micronized estradiol-17β 0.5 mg/d</td>
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<td>Yes</td>
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<tr>
<td></td>
<td>Transdermal estradiol-17β 0.025 mg/d</td>
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<tr>
<td>• Ultra-Low Dose</td>
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<td>Progestin</td>
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<td>Tibolone</td>
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<td><strong>Nonhormonal</strong></td>
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<td>SSRIs and SSNRLs</td>
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<td>Sertraline</td>
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<td>Iproniazine</td>
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<td>Taperapentin</td>
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<td>Exercise</td>
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<td>Reflexology</td>
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<tr>
<td>Tellelate-ganglion block</td>
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</tbody>
</table>

Abbreviations: FDA, U.S. Food and Drug Administration; SSRIs, selective serotonin reuptake inhibitors; SSNRLs, selective serotonin norepinephrine reuptake inhibitors. Compared with placebo.
PRESCRIPTION TREATMENTS

• Estrogen (alone or in combination with Progestin)
  – Cochrane meta-analysis of 24 RCT with 3229 participants 75% reduction in frequency and severity
    A. Combination contraception (pill, ring or patch)
      – The average monthly probability of conception declines by 50% at age 43 but up to 80% of women between 40 and 43 are still able to conceive
      – By age 44 only 1.9 % of women can become pregnant using their own eggs
      – When to stop contraception is confusing topic. NAMS recommends that either at Menopause defined as 12 months without menses, or until FSH levels are consistently above 30
Labeling Contraindications for estrogen-containing contraceptives in perimenopausal women (1 of 2)

- Cigarette smoking
- Obesity
- Thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease (current or past history)
- Valvular heart disease with thrombogenic complications
- Thrombogenic arrhythmias
- Hereditary or acquired thrombophilias
- Major surgery with prolonged immobilization
- Diabetes mellitus
- Migraine headaches
- Hypertension
- Known or suspected carcinoma of the breast or personal history of breast cancer
Labeling contraindications for estrogen-containing contraceptives in perimenopausal women (2 of 2)

- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
- Hepatic adenomas or carcinomas, or active liver disease
- Known or suspected pregnancy
Noncontraceptive benefits of combined oral contraceptives for perimenopausal women

- Restoration of regular menses
- Decreased dysmenorrhea
- Reduced heavy menstrual bleeding
- Reduced pain associated with endometriosis (continuous use of oral contraceptive)
- Suppression of vasomotor symptoms
- Enhanced bone mineral density and possible prevention of osteoporotic fractures
- Decreased need for biopsies for benign breast disease
- Prevention of endometrial and ovarian malignancies
- Improvements in acne that may flare up with perimenopause
A. Hormone Therapy (HT) (*HRT not used due to FDA ruling*)
   – Many Options
     » Route of administration: oral, transdermal, topically or vaginally (intranasal and bucal non-us)
   – Insert TABLE 9.14
Potential pros and cons of HT routes of administration
Oral Estrogen

Pros
• Familiar, easy
• Beneficial effect on HDL-C, LDL-C and total cholesterol
• Large amount of data
• Usually relatively low cost

Cons
• Risk of thrombosis, stroke
• Increase in triglycerides, C-reactive protein, other hepatic proteins
• Risk of reducing libido through sex hormone-binding globulin impact
Transdermal or topical estrogen

**Pros**
- Avoids hepatic first-pass effect
- Less increase of triglycerides than oral ET
- Less effect on C-reactive protein than oral ET
- Less risk of reducing libido than oral ET
- Fewer gastrointestinal side effects than oral ET
- Topical emulsion is moisturizing
- Perhaps less risk of thrombosis than oral ET

**Cons**
- Patch-adhesive sensitivity/residue
- Patch is less private
- Usually relatively higher cost
Vaginal (local) estrogen

Pros
• Vaginal benefit at lower dose
• Low-dose therapy typically avoids adverse systemic effects

Cons
• Increase in vaginal discharge
• Some may consider less convenient to use
• Lack of long-term uterine safety data for low-dose products
Progestogens

Pros
• Reduce adverse effect of estrogen on endometrium
• Some progestogens reduce adverse effect of oral estrogen on triglycerides
• Progesterone dosed at night can decrease insomnia, improve sleep

Cons
• Some progestogens increase risk of breast cancer
• Some progestogens reduce beneficial effect of oral estrogen on HDL-C
• Adverse side effects, such as bloating
• Dysphoric effect for some women
HORMONE THERAPY

» Variety of estrogen products
  • Conjungated Estrogens (CE) no generic for Premarin
  • Synthetic conjugated estrogens (Enjuva)
  • Estradoil (Matrix Patches: alora, climara, eslim, estradot, fempatch, menstar, oesclim, Vivelle, Vivelle dot, Transdermal Gels: Divigel, Estrogel, Elestrin, Transdermal Spray: Evamist, Topical Emulsion: Estrasorb
  • Esterfied estrogen (menest)
  • Ethinyl estradiol (Femhrt) – synthetic steriod
Benefits of HT

FDA approved for moderate to severe vasomotor symptoms, some oral and transdermal are approved for prevention, but not treatment of osteoporosis

• May improve sexual desire
• Improve Sleep (not approved but works by reducing night sweats)
• Enhance skin sensation
• Increase vaginal lubrication and elasticity, restore vaginal blood flow, decrease vaginal PH, improve thickness
• Local ET may benefit overactive bladder
• Vaginal ET may decrease recurrent UTI
• ET may reduce CHD and coronary artery calcification risks when initiated in younger, recent post-menopausal woman without uterus (is not recommended for coronary prevention)
• EPT (but not ET) reduces new onset DM, not approved for prevention
Hormone Therapy

• HT contraindication for:
  – history of breast cancer
  – coronary heart disease (CAD)
  – a previous venous thromboembolic event or stroke
  – active liver disease
  – Undiagnosed vaginal bleeding
  – Pregnancy
  – or those at high risk for these complications
Hormone Therapy

• Use for shortest duration as possible
• Use EPT if hx. of supracervical hyst (*or severe endometriosis*)
• Absolute risks in healthy woman 50-59 are low
• Extending EPT acceptable for:
  – Women whom request it and are aware of the risks
  – Prevention of osteoporotic fracture when other therapies are not appropriate
PRESCRIPTION TREATMENTS (HT)

• Women’s Health Initiative (WHI) study
  – Large RCT of healthy menopausal women 50-77.
    • Combined HT = increased risk of breast cancer, coronary heart disease, stroke and venous thromboembolic events and decreased risk of fractures and colon cancer after an average of 5 years of therapy.
    • Estrogen alone = increased risk of thromboembolic events but not an inbreded risk of cardiovascular events or breast cancer
    • HT should not be used for primary or secondary disease prevention.
      – Primary prevention = removing the causes of diseases...immunizations, certain surgery (oophoroectomy)
      – Secondary prevention = detects early disease when it is asymptomatic and when treatment can stop it from progressing...two steps
        » Screening test
        » Follow up diagnosis and treatment...pap smears

  – Tertiary prevention = prevent deterioration or reduce complications after disease has declared itself (beta-blocker after mi)
Age
The average age of the women in the WHI ET and EPT studies were 63.6 and 63.3 years, respectively.

Only about 33% of women in the WHI EPT trial and 31% of women in the ET trial were in the 50-59 year range.

Symptoms
Women who reported mild to moderate symptoms were warned that they could be randomized to placebo potentially allowing them to have symptoms for the duration of the study.

Women with severe symptoms were ineligible for the study.

Dropout Rate and Unblinding
- The dropout rates for the WHI EPT and ET studies were 42% and 53.8%, respectively. The drop in rates were 6.2% and 5.7% for the EPT and ET studies, respectively.

- In addition, 40.5% of the women on active treatment and 6.8% of the placebo group in the EPT study were unblinded, because of vaginal bleeding.

Only 3.5% of study population was 50-54 with moderate to severe symptoms at baseline.
Solidarity Statement by NAMS, ASRM, and the Endocrine Society

“The Experts do agree about WHI”

- Hormone therapy reduces menopausal symptoms
  - Hormone therapy is the most effective treatment for menopausal symptoms such as hot flashes and vaginal dryness
  - If women have only vaginal dryness or discomfort with intercourse, the preferred treatments are low doses of vaginal estrogen
  - Hot flashes generally require a higher dose of estrogen therapy that will have an effect on the entire body
  - Women who have had their uterus removed can take estrogen alone
  - Women who still have a uterus need to take a progestogen (progesterone or a similar product) along with the estrogen to prevent cancer of the uterus
    » Five years or less is usually the recommended duration of use for this combined treatment, but the length of time can be individualized for each woman
Solidarity Statement by NAMS, ASRM, and the Endocrine Society

• “The Experts do agree about WHI”
  – Hormone therapy risks
    • ET and EPT both increase the risk of blood clots in the legs and lungs, similar to birth control pills, patches, and rings
      – the risk is rare in the 50 to 59 age group
    • An increased risk in breast cancer is seen with 5 or more years of continuous estrogen/progestogen therapy, possibly earlier
      – The risk decreases after hormone therapy is stopped.
      – estrogen alone for an average of 7 years in the Women’s Health Initiative trial did not increase the risk of breast cancer
Solidarity Statement by NAMS, ASRM, and the Endocrine Society

• “The Experts do agree about WHI”

The Bottom Line:

• Hormone therapy is an acceptable option for the relatively young (up to age 59 or within 10 years of menopause) and healthy women who are bothered by moderate to severe menopausal symptoms. Individualization is key in the decision to use hormone therapy
PRESCRIPTION TREATMENTS (SERMS)

- Conjugated estrogens/bazedoxifene (Duavee) – approved by FDA to be released in February
  - SERM
    - Activates some estrogen receptors and deactivates receptors in Uterus, therefore being protective for endometrial hyperplasia
    - Indications: after menopause for women with a uterus, to reduce moderate to severe hot flashes and to help reduce the chances of developing osteoporosis.
    - Warnings: do not prescribe with additional estrogens, progestins, or estrogen agonists/antagonists, hx of VTE, liver disorders, hx of breast or uterine cancer, bleeding disorder, pregnant, or breastfeeding...has usual risks associated with Estrogen
      - Evaluate post-menopausal bleeding
PRESCRIPTION TREATMENTS (SERMS)

- Ospemifene (Osphena)
  - FDA approved for the treatment of moderate to severe dyspaurenia in post-menopausal woman with **BLACK BOX** warning for Endometrial Cancer and Cardiovascular Disorders
  - Weak agonist/antagonist on endometrial
  - At the “discretion of provider” if progesterone is needed
    - In clinical trials, no cases of endometrial cancer were seen with exposure up to 52 weeks. There was a single case of simple hyperplasia without atypia. Endometrial thickening equal to 5mm or greater was reported at a rate of 60.1 Osphena vs. 21.2 placebo per 1000 women. Uterine polyps occurred at an incidence of 5.9 Osphena vs. 1.8 placebo per 1000 women, and any type of proliferative endometrium (weakly plus active plus disordered) was 86.1 Osphena vs. 13.3 placebo per 1000 women. –ONLY ONE YEAR OF DATA-Endometrial cancer is slow progression, **BUT we don’t use progesterone with vaginal estrogen**
    - Osphena 60mg rate/thousand woman (placebo)
      - Thromboembolic event 0.71 (1.04)
      - Hemorrhagic Stroke 1.45 (0)
      - DVT 1.45 (1.04)
    - Osphena has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.
PRESCRIPTION TREATMENTS

– PROGESTIN
  • Primarily used in combination with estrogen therapy to prevent endometrial hyperplasia
  • Some studies suggest that when used in combination with estrogen, works better than estrogen alone
  • Some evidence that Progesterone alone is better than placebo for vasomotor
  • ACOG...“because the risk of breast cancer was increased in the conjugated equine estrogen and medroxyprogesterone arm of WHI...there is concern that the risk of breast cancer may be related to progestin use. Therefore, progestin alone is not considered a first line therapy for the management of vasomotor symptoms”

– TESTOSTERONE
  • Alone is not currently approved by FDA for use in women
  • Cochrane met-analysis of 35 trials with 4,768 post menopausal women
    – No benefit for the treatment of vasomotor symptoms and negative impact on lipid, clitoromegaly, hirsuitism and acne
    – When used with HT regimens improved sexual function scores and number of satisfying sexual episodes
    – Nurses Health Study = Showed that estrogen/testosterone had higher breast cancer risk than those whom took combination HT; however the risk showed up in the first few years of treatment and dropped at 5 years of use (suggesting that rather then causing breast cancer it may simply make existing disease present sooner)
PRESCRIPTION TREATMENTS

– **TIBOLONE**
  • Synthetic steroid with tissue specific estrogenic and progestogenic effects
  • NOT FDA approved – not available in US
  • Appears to have beneficial effect on bone density, vasomotor symptoms and vaginal symptoms without estrogenic effects on uterus or breasts

– **SSNRI**
  • Synthetic steroid with tissue specific estrogenic and progestogenic effects
  • NOT FDA approved – not available in US
  • Appears to have beneficial effect on bone density, vasomotor symptoms and vaginal symptoms without estrogenic effects on uterus or breasts
  • Side Effects: Nausea, dizziness, dry mouth, nervousness, constipation, somnolence, sweating and sexual dysfunction
PRESCRIPTION TREATMENTS

- SSRI
  - Effective but probably less so than HT
  - Brisdelle = paroxetine (7.5 mg) is only non-hormonal therapy that is approved by FDA for treatment of moderate to severe vasomotor symptoms
  - Efficacy seen in 7 of 8 co-primary endpoints
  - Not indicated for treatment of any psychiatric condition
PRESCRIPTION TREATMENTS

• Contraindications and precautions for Paroxetine 7.5 mg
  – Black BOX WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
    • Antidepressants including selective serotonin reuptake inhibitors (SSRIs) have been shown to increase the risk of suicidal thoughts and behavior in pediatric and young adult patients when used to treat major depressive disorder and other psychiatric disorders. Because BRISDELLE is an SSRI, monitor patients closely for worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber
Prescription Treatments

– Contraindications and precautions for Paroxetine 7.5 mg continued

• Concern for Serotonin syndrome
  – Concurrent or within 14 days of MAOI’s (Monoamine oxidase inhibitors)
  – Concurrent use of linezoid
  – Concurrent use of IV methylene Blue

• Possible QTc elongation
  – Concurrent use of thioridazin or primozide

• Hypersensitivity to any ingredient in Brisdelle

• Pregnancy

• Tamoxifen
Prescription Treatments

- Clonodine
  - Centrally acting alpha 2-agonist, anti-hypertension
  - Use for vasomotor as off-label
  - Meta-analysis shows slight improvement compared to placebo but less than HT
  - Side effects = dry mouth, insomnia and drowsiness
Prescription Treatments

• Gabapentin
  • Gamma aniobutyric acid analogue, FDA approved as an anti-convulsant agent
  • Use for vasomotor symptoms is off-label
  • RCT = 45% reduction in hot flash frequency and 54% reduction in severity
  • Side effects: dizziness, somnolence and peripheral edema
  • Comparison with venlafaxine (Effexor) and gabapentin – showed patients preferred velafaxine
Prescription Treatments

• Bio identical Hormones
  • Plant derived hormones that are chemical similar or structurally identical to those produced by the body
  • FDA approved: micronized progesterone and estradiol
  • Non FDA approved: compound preparation
  • ACOG committee opinion #532
    – Evidence is lacking to support superiority claims of bio identical...conventional HT is preferred given the available data
Treating the Psychological issues

• Make Diagnosis and refer if needed
  – Non-Pharm: relaxation and stress techniques
  – Pharm:
    • Antidepressants: SSRI effective for depression
    • HT: effective when hot flashes are present
      (PEPI trial suggests that woman whom experience mood changes with synthetic progestin sometimes respond to progesterone)
"The pills put a stop to your hot flashes, Mrs. Bates, but maybe we should reduce the dosage."
COMPLEMENTARY and ALTERNATIVE THERAPY

• Complementary = therapy done in combination with conventional therapy
• Alternative = therapy done instead of conventional therapy
• NIH = 36% use CAM. 62% if use include megavitamins
• Canadians = 20% have consulted an alternative care provider in prior 12 mo. 70% use CAMs
RESOURCES

A. National Center for Complementary and Alternative Medicine (NCCAM)
   – http://nccam.nih.gov/
   – Founded by U.S. Congress in 1998

B. Natural Health Products Directorate
   – Each providence in Canada controls their own regulation of CAMs...leading to a diversity in regulation
HOMEOPATHIC “LIKE CURES LIKE”

• 3 Most Common Treatments
  – Lachesis = derived from venom of South American Bushmaster snake
  – Pulsatilla = wildflower Anemone pulsatilla... found in grasslands of Europe
  – Sepia = Cuttlefish ink...escape mechanism
HOMEOPATHIC TREATMENTS
South American Bushmaster snake
HOMEOPATHIC TREATMENTS
Anemone pulsatilla
HOMEOPATHIC TREATMENTS
Cuttlefish ink
Homeopathic Treatment


• Clinical trials are contradictory and meta-analysis has not proven effective, although generally regarded as safe
CAM TREATMENTS

• Treatment Modalities with significant following but limited randomized controlled trials on menopause treatments
  – Ayurveda – India’s traditional system
  – Mind Body Medicine – 85% success rate of biofeedback for stress incontinence
  – Biofield therapy – Qi gong, Reikle, Therapeutic touch
TRADITIONAL CHINESE MEDICINE

- Often use Acupuncture
- Huang et al found that acupuncture significantly reduces severity of nocturnal hot flashes in a prospective, randomized, placebo controlled study
- Nir Y et al showed that acupuncture decreases the severity of hot flashes but not the frequency
- Vincent et al showed sham acupuncture, while improved, did no better than traditional acupuncture (sham < 5cm from eastern)
- etiology of hot flashes is certainly multifactorial
- Accupuncture – stimulates Beta-Endorphins and other neurotransmitters, including serotonin and norepinephrine....evidence suggesting that decreased Beta-endorphin levels affect the thermoregulatory center in the hypothalamus and allow increases in gonadotropin releasing hormone pulse rates and amplitude.
BIOLOGICALLY BASED PRACTICES

• Herbs
• Foods
• Vitamins
HERBS

• 1972 FDA reviewed all OTC products – many herbs banned due to lack of evidence
  – Now most fall under the 1994 Dietary Supplement and Education Act
  – Manufacturer, not FDA is responsible to ensure labeling is accurate, that claims are substantiated
HERBS

• Demonstrated safety is not required before a dietary supplement is approved for sale
• Can make health claims for “natural conditions” like hot flashes and age related memory loss without providing documentation of safety or efficacy to the government
• Can NOT claim that it treats, prevents or cures a disease unless FDA approves the claim
HERBS

• Few Herbs still government approved as safe and effective for OTC
  – Aloe
  – Capsium
  – Cascara
  – Ipecac
  – Psyllium
  – Witch Hazel
HERBS

• ACOG Practice Bulletin #141 Management of Menopausal Symptoms – January 2014
  – There are currently insufficient data to support the use of herbal remedies for menopausal-vasomotor symptoms
HERBS

• North American Menopause Society
  – Recognizes that non-prescription therapies have not been proven to be as effective as prescription therapies for treating some health condition. However, since the basis tenet of the Hippocratic Oath is do not harm and nonpharmacological treatments typically do little harm, nonpharmacological treatments as “first line” options as they appear to confer minimal risk are often suggested.
HERBS

- ACOG Practice Bulletin #84 Prevention of Deep Vein Thrombosis and Pulmonary Embolism
  - A number of common herbs in addition to non-steroidal anti-inflammatory drugs and antiplatelet medications such as clopidogrel, can potentiate the activity of low molecular weight heparin, unfractionated heparin and vitamin K antagonists and result in excessive bleeding
HERBS & SUPPLIMENTS THAT MAY INTERFERE WITH ANTICOAGULANT THERAPY

- Chinese wolfberry
- Coenzyme Q
- Cranberry Juice
- Curbicin
- Danshen
- Devil’s claw
- Dong quai
- Fenugreek
- Garlic
- Ginger
- Gingko
- Ginseng
- Glucosamine-chondroitin
- Grapefruit juice
- Green tea
- Melatonin
- Omega-3 fish oil
- Papaya extract
- Quilinggao
- St John’s wort
HERBS

• Isoflavones
  – Bind to Estrogen receptors: ER- (beta) > ER (alpha) with both agonist and antagonist properties and a chemical structure similar to estradiol
  – Soy is the most widely used isoflavan Genisttein = daidzen >>> glycerin
  – 30% North American women can metabolize daidzein to equal
HERBS

a) Coronary Heart Disease (aha meta-analysis of 22 RCT – very small reductions in total plasma cholesterol and any benefit would be minimal at best)

b) Vasomotor symptoms (10-20 Asians vs 70-80% of North Americans) – multiple RCT’s with conflicting results for “usual ratio”
   • -30% Americans can metabolize daidzen to equol
   • -60% Asians can metabolize daidzen to equol
   • Asians noted to consume 3 x as much soy in diet
HERBS

• Equol appears to be more effective than the usual mixture of soy isoflavens
  – Soy appears safe for the breast and endometrium (Breast cancer as well per NAMS)
  – Genisttein = daidzen >>> glycerin
  – 30% North American women can metabolize daidzein to equal
OTHER HERBS

• Black Cohosh
  – Most commonly studied as Remifemin, but this is most of older studies
  – Many RCT’s looking at this – much conflicting results
    a. 1989 German Federal Institute for Drugs and Medical Devices approved
  – Case reports of possible link between liver failure and Black Cohosh lead to
    a. Australian Therapeutic Goods Authority and Health Canada to require cautionary statements
    b. US Pharmacopeia – gave cautionary warning
  – Canadian researches found that a product associated with serious adverse events was found to have wrong species of Black Cohosh. Was found to have Asian species Aceta Cimicifuga L.
OTHER HERBS

• Cranberry
  – 6 month study showed that 500 mg of cranberry extract was similar in effectiveness to 100 mg Trimethoprim for prevention of UTI in woman over 45 (NO longer feel it works due to acidification of urine, but instead by preventing bacterial adherence to the urinary epithelia)

• Dong Quai or also known as Agnelica sinensis
  – Efficacy for use as monotherapy has not been confirmed in RCT
  – TCM (Traditional Chinese Medicine) counter it is meant to be used in a cocktail of herbs
  – Side Effects: photosensitivity and anticoagulation
  – Can trigger heavy uterine bleeding and should not be used in women with fibroids, hemophilia or other blood clotting disorders
  – Contraindicated for use with anticoagulants
Other Herbs

• Evening Primrose oil or *Oenothera biennis*
  – Rich in oils containing y-linolenic acid
  – RCT have not shown a benefit over placebo for hot flashes
  – May increase the risk of seizures in patients with schizophrenia taking antipsychotics

• **Gingko or Gingko biloba**
  – Federally funded RCT trial of 3,069 patients failed to show a decline in cognitive in older patients
  – Unclear if causes increase risk of bleeding

• **Ginseng**
  – RCT does not show overall effect on vasomotor symptoms
OTHER HERBS

• **Kava or *Piper methysticum***
  – Cochrane review concluded that, compared with placebo, Kava extract appears to be effective at treating anxiety
  – Linked to severe hepatotoxicity
  – Canada, United Kingdom, Germany, Australia have banned
  – FDA “Kava should not be used before consulting a physician
  – Researches whom have harvested the root alone and processed with water instead of acetone feel the product can be safe. This method, as designed by Pacific Islanders has lead to a history of Kava use without liver toxicity

• **Sage**
  – Teas are safe. Avoid the ethanolic extracts during their production of Thujone. Can cause vertigo, kidney damage and convulsions
• St. John’s Wort or *Hypericum perforatum*
  – Cochrane review of 29 studies involving 6,598 patients concluded that was superior to placebo in patients with major depression and similar effective as standard anti-depressants with fewer side effects. (26% for St John vs 44% for antidepressant)
  – In post-menopausal women, 5-7 studies showed improvement in mood anxiety
  – Do not use with other SSRI – taking with may result in “serotonin syndrome”
  – May decrease levels of warfain, digoxin, therophyline, indinavir, cyclosporine and phenprocoumon
OTHER HERBS

• *Velerian or Valeriana officinalis*
  – A systematic review of RCT for sleep quality shows a statistically significant benefit – Sold in US as “Sedonium”

• *Vitex or Vitex agnus-castus*
  – Approved by German Health Authority for premenstrual syndrome, irregular menses and cyclical mastalgia
  – RCT’s have shown that it improves symptoms of premenstrual syndrome
  – Possible side effect of libido reducing and therefore known as: Chaste-tree berry
NON-PRESCRIPTION THERAPY

Okay... So maybe it wasn't such a good idea to buy your estrogen pills off the internet after all...
NON-PRESCRIPTION THERAPY

• Same issue with Government oversight that was seen with CAM, therefore regulated as supplement

• Vitamins and Minerals
  – Vitamin E
    • Nams “Clinical trials are insufficient to support or refute efficacy for hot flashes; however no side effects in short term use thus oral Vitamin E (400-800 IU/D) is an option to recommend”
    • ACOG “limited data...one less hot flash per day, a marginal reduction, has been reported in the use of Vitamin E (800 IU/D)”
NON-PRESCRIPTION THERAPY

- Vitamin E continued
  » Doses up to 1500 IU/D safe in healthy adults
  » Meta-analysis of 19 trials of patients with chronic disease found a statistical significant deleterious relationship between high dosage (>400 I/D) and all cause mortality in patients with chronic disease
  » Vitamin E does not seem to provide protection against cancer or CVD. Perhaps 600 IU may protect women at high risk for VTE
NON-PRESCRIPTION THERAPY

• Calcium
  – When added to Vitamin D has been shown to reduce or halt bone loss in post-menopausal women (0.14% loss per year compared to 1%)
  – ? – reduce incidence of fracture
  – Potentiate the effect of exercise on BMD
  – NAMS “…been associated with beneficial effects in several non-skeletal disorders, primary colorectal cancer, hypertension, nephrolithlasis and obesity”
  – US Preventive Services Task Force – insufficient evidence – recommend 1,200mg/day
NON-PRESCRIPTION THERAPY

- Calcium Carbonate (TUMS): absorbed better with meals, poorly absorbed in those taking PPI or H2 blocker, natural preparations may have lead
- Calcium Citrate (Calcitrate): absorbed better in fasting state
NON-PRESCRIPTION THERAPY

• Lifestyle Changes
  • Alcohol and caffeine have been associated with increased severity and frequency of vasomotor symptoms therefore reasonable to recommend reduction or avoidance
  • Exercise
    – Improves quality of life and mood in women with vasomotor symptoms but does not actually show significant improvement in vasomotor

• Common sense but without supporting data
  – Layering of clothing, maintaining lower ambient temperature and consuming cool drinks
NON-PRESCRIPTION THERAPY

• Vaginal Lubricants
  • Water soluble products include (Astroglide, Slippery Stuff, and K-Y Jelly)
  • Silicone based lubricants are also available (Pjur Eros, ID Millennium)
  • Oil-based product (Elegance Women’s Lubricant)

• Vaginal Moisturizers
  • Summers Eve (pectin) vs Replens (polycarophil) – RCT comparable relief of dryness with pectin