Clinical Dilemmas in Menopause Management: A Case Based Approach

Judith M.E. Walsh, MD, MPH
Professor of Medicine
UCSF Women’s Health Center of Excellence
Conflicts of Interest: None

Overview

• Natural history of menopause
• Hormone therapy: Risks and Benefits
• Menopausal symptoms
• Current role of hormone therapy for menopausal symptoms
• Non-hormonal treatment of menopausal symptoms

MENOPAUSE IS NOT A DISEASE

“Feminine Forever”

• Dr. Robert Wilson, 1966
• Replacing estrogen is like diabetics replacing insulin
• Women “will be much more pleasant to live with and will not become dull and unattractive.”
• Wyeth-Ayerst funded all expenses
Menopause Is A Positive Step

• Gallup poll 1997: Most middle aged American women “welcome menopause as a new and fulfilling life stage.”
• Goal: Support women in achieving a successful transition

Natural History of Menopause

• Average age is 51
• Predictors of age at menopause
  – Genetics
  – Family history
  – Ethnicity
    • Earlier in Latino and later in Japanese American compared to Caucasians
  – Smoking: about two years earlier
  – Reproductive history
    • Never having children and shorter cycle length associated with earlier menopause

Menopausal Symptoms: Prevalence

• Hot flushes (50% or more)
  • Often with perspiration
• Night sweats (50% or more)
• Sleep disturbance (40-60%)

OTHER SYMPTOMS

• Other symptoms happen at the time of menopause but are less clearly related to menopause
  – Mood changes
  – Cognition
  – Changes in sexual function
  – Urinary complaints
  – Joint pain
Vasomotor Symptoms

- Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She is still having hot flashes and awakens at least twice a night with them. She is considering taking estrogen but wants to know how much longer this will last. What do you tell her?

What do you tell her about when they will go away?

1. Average duration is about 2 years and so they should be gone in about 6 months.
2. Average duration is about 4 years
3. They will never go away

Background

- Treatment for menopausal symptoms is based on their transitory nature
- Many clinical guidelines suggest that symptom duration is approximately 2 years
  - Many studies do not follow women more than 2 years
- Risks and benefits of hormone therapy depend on duration of use
  - "Use lowest dose for shortest duration"
Duration of Vasomotor Symptoms

• Objective: to estimate the natural progression of menopausal symptoms

Results

• Percent of women with symptoms increased in the two years before the final menstrual period (FMP), peaked one year after the FMP and did not return to premenopausal levels until 8 years after the FMP
• 50% of women had symptoms during the 4 years after FMP
• 10% of women had symptoms up to 12 years after FMP

Vasomotor symptoms

• Rigorous meta-analysis included 10 studies with over 35,000 participants
• Clear definition of vasomotor symptoms
• Assessed prevalence of symptoms and “bothersome symptoms”
Results: Bothersome Symptoms

Duration of Hot Flushes

- Most prior studies examined populations of older women
- Newer evidence suggests that these durations might be longer when younger women are included
- Counseling regarding duration of hot flushes may inform clinical decision making

The News

- Duration of menopausal hot flushes and associated risk factors
  - Freeman, EW et al. Obstetrics and Gynecology, May 2011

- Aim: To estimate the duration of moderate-to-severe menopausal hot flushes and identify potential risk factors for hot flush duration.

Methods

- Penn Ovarian Aging Study - 436 premenopausal women, ages 35-47 years (not using hormonal therapy of any type); followed for 13 years
  - Analytic Subsample: 259 women did not report hot flushes at baseline but did experience mod/severe sx during follow-up
- Measures: validated menopausal symptom list embedded in structured interview, hormones
- Assessments made at 9-month intervals during study years 0-5, then annually until year 10, every other year until study completion
Menopausal stages

- Premenopause: regular menstrual cycles 22-35 days long
- Late premenopause: change of more than 7 days in cycle length
- Early transition: changes in cycle length of 7 days or more in either direction for 2 consecutive menstrual cycles OR 60 days amenorrhea
- Late transition: 90 d to 11 months amenorrhea
- Postmenopause: 12 months or more amenorrhea


Results

Results – Hazard Ratio for Likelihood of Hot Flashes Ending

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal</td>
<td></td>
</tr>
<tr>
<td>Pre/late premenopausal</td>
<td>Ref.</td>
</tr>
<tr>
<td>Early Transition</td>
<td>3.26 (1.78-5.97)</td>
</tr>
<tr>
<td>Late transition/postmenopausal</td>
<td>5.14 (2.70-9.77)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>39 or younger</td>
<td>0.33 (0.14-0.78)</td>
</tr>
<tr>
<td>40-44</td>
<td>0.52 (0.30-0.91)</td>
</tr>
<tr>
<td>45-49</td>
<td>Ref.</td>
</tr>
<tr>
<td>50 or older</td>
<td>1.00 (0.54-1.87)</td>
</tr>
<tr>
<td>White Race (Ref: African American)</td>
<td>1.73 (1.11-2.68)</td>
</tr>
<tr>
<td>BMI 30 or more (Ref: BMI under 30)</td>
<td>1.94 (1.25-3.02)</td>
</tr>
<tr>
<td>Estradiol (mean)</td>
<td>0.82 (0.64-1.05)</td>
</tr>
</tbody>
</table>

Take Home Message

- In this population-based cohort, median duration of moderate-to-severe hot flushes was…10.2 years!
  - Adding mild hot flushes…duration was 11.6 years
- Younger, thinner, African-American women are likely to have longer hot flush duration
- Effect of hormone therapy on hot flush duration was not evaluated
- Clinicians counseling patients about hot flash duration should be mindful that the earlier the hot flashes start, the longer they are likely to last!
Minnie Pause….continued

• Now that Minnie knows that the symptoms could last for a while more, she definitely wants to do something about her intolerable hot flashes. Her only medical history is hypertension well controlled on lisinopril. She would like to hear your thoughts on hormones and whether they are a safe option for her.
• What do you tell her?

What do you tell her?

1. Why don’t you try black cohosh- that will work just as well
2. Venlafaxine is as effective as hormones and it is a lot safer
3. Hormone therapy is probably ok, if you don’t take it for too long
4. Absolutely not- no one takes hormones any more

Should I use hormones?

• Ok, so they may help my symptoms……but are they safe?

Background

• WHI trials designed to determine benefit/risk of hormone therapy when taken for chronic disease prevention
  – Primary efficacy outcome: CHD
  – Primary safety outcome: invasive breast cancer
• Combination trial stopped early due to increased breast cancer risk and unfavorable risk-to-benefit ratio
The News

- Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women’s Health Initiative Randomized Trials

- Aims:
  - Provide a comprehensive, integrated overview of findings from the 2 WHI hormone therapy trials with extended post-intervention follow-up and stratification by age and other important variables

Methods

- Post-intervention follow up through Sept 30, 2010 based on 81.1% surviving participants
- Utilized time to event methods based on intention-to-treat, global index calculated
  - CHD, invasive breast cancer, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death

Intervention


Extension phase

2005-2010

Initial WHI: Randomized to CEE/MPA (or CEE alone) or placebo

Post-intervention

Post-stopping WHI: Follow up for those providing additional consent

Data in this study

Post-stopping WHI: Follow up for those providing additional consent

Instructed to stop study medication

Original trial completion date

Results

<table>
<thead>
<tr>
<th>Post-Intervention</th>
<th>CEE + MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diff/10,000 PY</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CHD</td>
<td>2 1.04 (0.89-1.23)</td>
</tr>
<tr>
<td>Breast CA</td>
<td>10 1.32 (1.08-1.61)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0 1.01 (0.91-1.11)</td>
</tr>
<tr>
<td>Global index</td>
<td>4 1.03 (0.95-1.11)</td>
</tr>
</tbody>
</table>

- Global index HR was not modified by age (p>0.99 for trend)
  - Absolute risks of adverse events were lower in younger than older women
**Results**

<table>
<thead>
<tr>
<th>Post-Intervention</th>
<th>CEE Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff/10,000 PY</td>
</tr>
<tr>
<td>CHD</td>
<td>-4</td>
</tr>
<tr>
<td>Breast CA</td>
<td>-7</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>-7</td>
</tr>
<tr>
<td>Global index</td>
<td>-6</td>
</tr>
</tbody>
</table>

- Women in 50s had fewer events per 10,000 PY compared with women in 70s (p for trend, 0.02)

**Conclusions**

- Neither CEE + MPA nor CEE alone significantly affected all-cause mortality during or after the intervention phase
  - HT has a harmful effect on CHD risk among older women, results in younger women are inconclusive
- Risk–benefit ratio of HT is most favorable when initiated in younger menopausal women
  - Most risks and benefits from hormone therapy dissipate after stopping

**Key Article**

- Management of Menopausal Symptoms, ACOG Practice Bulletin #141, January 2014
  - ACOG. Obstet Gyne. 2014
  - Level A Evidence:
    - Systemic HT is the most effective therapy for vasomotor symptoms, low dose has better side effect profile
    - Risks of combined systemic HT include VTE and breast cancer
    - It is recommended that providers individualize care and treat women with lowest effective dose for the shortest duration needed to relieve vasomotor symptoms

**Take Home Messages**

- For women early in menopause, risks are lowest for hormone therapy and once therapy is stopped these risks wane
- Minnie is young and healthy and would be a candidate for hormone therapy for her vasomotor symptoms; would recommend revisiting the use of hormones annually for her
Minnie, continued…

• Minnie decides she wants to use hormone therapy and asks what she should start. You have heard that transdermal methods might be safer, but are not entirely sure what to recommend beyond that…

Transdermal Estrogen: Background

• Avoids hepatic first pass metabolism
  – Decreased effect on serum coagulation factors, triglycerides, CRP
• Associated with a lower VTE risk
  – Canonico, 2007
• Associated with a lower risk of stroke
  – Renoux BMJ 2010
• No RCT comparisons of differing HT regimens and clinical CVD outcomes

The News

• *Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women’s Health Initiative Observational Study*

  • Aims
    – Compare different estrogen dose/formulation and risks for major CHD, stroke, CVD mortality, total CVD and all-cause mortality

Methods

• Prospective cohort study of 93,676 postmenopausal women aged 50-79
  – Clinic visit at baseline and 3 years
  – Annual mailed self-administered questionnaires
  – CVD events confirmed by medical record review
• Mean follow up time, 10.4 years
• Adjusted for age, race, smoking, activity, BMI, HTN, diabetes, use of lipid-lowering medication, hysterectomy, oophorectomy, education, income
**Results**

<table>
<thead>
<tr>
<th>Event</th>
<th>Transdermal HT vs Oral CEE</th>
<th>Oral estradiol vs Oral CEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Major CHD</td>
<td>0.63 (0.37-1.06)</td>
<td>1.13 (0.79-1.61)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.87 (0.55-1.38)</td>
<td>0.64 (0.40-1.02)</td>
</tr>
<tr>
<td>Total CVD</td>
<td>0.82 (0.59-1.14)</td>
<td>0.93 (0.71-1.23)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>0.94 (0.50-1.74)</td>
<td>1.33 (0.84-2.12)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.06 (0.78-1.44)</td>
<td>1.09 (0.83-1.43)</td>
</tr>
</tbody>
</table>

**Conclusions**

- CVD risk did not differ substantively among different formulations/routes of administration
  - Overall absolute risk of CVD in younger women was lower as compared with older women
- Only a small percentage of women were using transdermal estrogen—not powered to fully see differences

**Key Article**

- *Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens*
- Retrospective case-control study comparing CV event risk associated with current CEE compared with estradiol use in a large HMO

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjusted Odds Ratio (95% CI) [reference: estradiol use]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>2.08 (1.02-4.27)</td>
<td>0.045</td>
</tr>
<tr>
<td>MI</td>
<td>1.87 (0.91-3.84)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.13 (0.55-2.31)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**Key Article**

- *ACOG Committee Opinion: Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism*
  - ACOG Committee Opinion #556, April 2013
- Prothrombotic effect of estrogen is possibly related to high concentrations of estrogen in the liver due to first pass effect
- Transdermally administered estrogen has little or no effect in elevating prothrombotic substances
Take home messages

• Observational evidence suggests a possible increase in risk of MI with CEE compared with estradiol use
  – Did not reach statistical significance
• Transdermal estrogen has been associated with decreased risks of VTE compared with oral forms
• For Minnie, transdermal estrogen is safest, and it may be better to recommend estradiol over CEE
  – And she needs a progestin as she still has a uterus

HT for Symptomatic Relief

• Any form of estrogen is highly effective
• Generally can be taken for a few years and gradually stopped
• A progestin should be added for women with a uterus
• Therapy can be tailored to a woman’s preference
• “Lowest dose for shortest duration”

Effective Dose Equivalents

• Dose that stops hot flashes in 80% of women
  – 1 mg micronized 17 beta estradiol
  – 50mcg/day transdermal 17 beta-estradiol
  – 0.625 mg conjugated equine estrogens
  – 1.25 mg piperazine estrone sulfate

Lower dose hormone therapy

• Effective in some trials
• Estimates of efficacy after 12 weeks
  – 38% placebo
  – 63% low dose estrogen
  – 83% standard dose estrogen
• Lower doses may take longer for maximal symptom relief
  – 12 weeks vs 4-8 weeks
• Less bleeding and breast tenderness and may require less progestin
Estee Jenn

- Estee Jenn is a 60 year old woman who has been on HT for 10 years. You have been trying to encourage her to stop it for a while but she has not wanted to do it. Her best friend has recently developed breast cancer; she has now decided to stop, and wants your advice on the best way to do it. What do you recommend?

Discontinuing hormone therapy

- Symptoms will recur in up to 25% of women with stopping therapy
- Unclear if it is best to stop “cold turkey” or to taper
- Taper can be by daily dose or number of days per week
- Taper until mild symptoms
  - Maintain that dose until symptoms resolve

QUESTION

1. Taper by decreasing the daily dose over 6-12 months
2. Taper by decreasing the number of days a week HT is used over 6-12 months
3. Just stop

QUESTION

Estee has a resumption of her hot flashes after she stops her estrogen. What pharmacologic alternative do you suggest?

1. Paroxitene
2. Escitalopram
3. Venlafaxine
4. Clonidine
5. Gabapentin
OTHER DRUG TREATMENTS

• SSRIs
• Venlafaxine
• Desvenlafaxine
• Clonidine
• Progestin
• 50-67% reduction in hot flash frequency with these regimens
• Placebo effects generally large

Progestins

• High doses
• Oral megestrol (20-80 mg) has shown efficacy
  – Some weight gain
    – Goodwin J Clin Oncology 2008
• High dose depo-MPA (400 mg) is also effective
  – More effective than venlafaxine
    – Loprinzi J Clin Oncol 2006
• May be transient increase in hot flashes for one to two weeks after initiation

Paroxitene

• Paroxitene CR led to a significant decrease in hot flash score
  – 62% in 12.5 mg group
  – 65% in 25 mg group
  – 38% in placebo group
• Avoid in women receiving tamoxifen
  – Decreases active metabolite of tamoxifen
  – Cytochrome P450 CYP2D6

Brisdelle

• First non-hormonal treatment approved for treatment of menopausal symptoms
  – Paroxitene 7.5 mg
• Efficacy?
  – Reduced hot flashes/severe hot flashes compared with placebo
  – 1 to 1.7 fewer severe hot flashes per day at different time points
  – Proportion with >50% reduction in moderate to severe hot flashes at 24 weeks
    • 48% vs 36%
Escitalopram
- Reduction in hot flash frequency
  - 55% in escitalopram group
  - 36% in placebo group
- Effective in African American and Caucasian women
- Effective regardless of coexisting anxiety or depression
  - Freeman, JAMA 2011

Venlafaxine
- Significant reduction in hot flashes
  - 61% vs 27% in placebo (p<0.01)
- 150 mg no more effective than 75 mg
  - Lopinzi, Lancet 2000

Desvenlafaxine
- Industry sponsored trial of metabolite of venlafaxine
  - 700 women with severe hot flashes
- 64% reduction in hot flashes at 12 weeks
  - Vs 51% with placebo
- Hot flashes less severe in desvenlafaxine group
- Not currently FDA approved for this indication
  - Speroff, 2008

Clonidine and Gabapentin
- Clonidine
  - Start with 0.1 mg/day transdermal patch
  - 40% reduction in hot flashes
  - Side effects can be limiting
- Gabapentin
  - 45% reduction in hot flashes vs placebo (29%)
  - 900 mg a day more effective than placebo
  - 300-600 mg at bedtime may help with hot flashes that awaken patients from sleep
Bazedoxifene/conjugated estrogen

- Duavee® approved for treatment of menopausal symptoms and prevention of osteoporosis
  - CEE 0.45 mg
  - Bazedoxifene 20 mg
- Bazedoxifene has estrogen agonist effects on bone and antagonist effects on uterine tissue
- Theoretic advantage
  - Relieve estrogen deficiency symptoms while possibly avoiding increased risks of endometrial and breast cancer

Bazedoxifene/conjugated estrogen

- Medication improved indices of vaginal atrophy and reduced daily number of hot flashes compared with placebo
  - (-9 vs -2.4)
- Similar incidence of VTE between groups

Alternatives for treatment of hot flushes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage (mg/day)</th>
<th>Efficacy (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>0.625 CEE</td>
<td>80% vs 20-30%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>12.5 or 25</td>
<td>62% vs 38%</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 to 20</td>
<td>55% vs 36%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5</td>
<td>37% vs 27%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 or 150</td>
<td>61% vs 27%</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>100</td>
<td>64% vs 51%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1</td>
<td>38% vs 20%</td>
</tr>
</tbody>
</table>

Question

Estee is tired of medications and would like to try an herbal therapy for treatment of her hot flashes. What treatment do you recommend?

1. Black Cohosh
2. Evening primrose
3. Ginseng
4. Dietary soy
5. Wild yam
6. None of the above
Background

• Soy products have been proposed to provide comparable benefits to estrogen for treating menopausal symptoms, without the risks
• Epidemiologic studies on Asian women suggest that soy-containing foods are of benefit to the skeleton
  – Limited by short duration, low dose of soy isoflavones, few participants
• Rapid bone loss occurs during the first 2 years of menopause

SPARE Study: Soy Isoflavones

• SPARE study (Soy Phytoestrogens As Replacement Estrogen) – parallel group, placebo controlled, double blind trial
• 248 women (early menopause) were randomly assigned to receive 200mg soy isoflavones or placebo
• Measures:
  – BMD change
  – Menopausal symptoms
  – Vaginal Maturation
  – Lipids and thyrotropin
  – Assessed at baseline, 12 mo, & 24 mo

Results

• No significant differences between soy and placebo group:
  – Spinal BMD
  – Total hip BMD
  – Femoral neck BMD
  – NTx (N-telopeptide type I bone collagen)
• Subgroup analyses by: race, BMI, estradiol, 25-OH Vit D
  – Women with low 25-OH vit D at baseline – soy group had lower decrease in spinal BMD than placebo
• Rate of hot flashes actually increased in soy isoflavone group
  – (48% vs 32%; p=0.02)

Black Cohosh

• One of the most widely used alternative therapies
• Some small trials of short duration have suggested benefit but others have not
HALT Trial

- Herbal Alternatives for Menopause Trial
  - 5 groups
    - Black cohosh alone
    - Black cohosh with multibotanical regimen
    - Black cohosh, multibotanical and dietary soy counseling
    - Estrogen (CEE 0.625) ± MPA
    - Placebo
  - Main outcome: Reduction in vasomotor symptoms

HALT: Results

- Estrogen reduced vasomotor symptoms more than placebo
- None of the black cohosh regimens reduced symptoms more than placebo
- Effect of dietary soy intake could not be assessed because most subjects did not increase soy intake to target level
  - Newton, Ann Intern Med 2006

Summary Of Herbal Evidence

- Evidence: no benefit
  - Red Clover
  - Dong quai
  - Ginseng
  - Evening primrose
  - Wild yam
  - Vitamin E
  - Acupuncture
- Evidence mixed
  - Soy
  - Black cohosh
  - No data
  - Chasteberry
  - Licorice

Lifestyle and Complementary Modalities

- Cooling body temperature
- Exercise
- Avoiding hot and spicy foods
- Relaxing therapies
  - Yoga, massage, mediation, slow breathing, baths
- Mind-body therapies
  - Relaxation, biofeedback, paced respiration, hypnosis
    - NAMS
- Some evidence that weight loss is beneficial
Hot Flash: Self Help - Be Cool!

- Keep house cool
- Avoid caffeine, alcohol, spicy foods, hot drinks
- Dress in layers, cotton
- Light bed linens
- Use fan, cool drinks
- Exercise

Relaxation

- Relaxation therapy
  - 73% reduction HF
- Diaphragmatic breathing
  - Simple deep breathing when sense HF
  - > 50% reduction HF
- Not all studies have shown a benefit

Guidelines for Hormone Therapy Use

- USPSTF: Harmful effects are likely to exceed the chronic disease prevention benefits in most women
- ACOG, AHA, and Canadian Task Force recommend against use of HT for prevention of chronic disease
- NAMS 2012: When alternative therapies not appropriate, extended use of HT appropriate for women at high risk of fracture
NAMS 2012 Recommendations

- Focuses on emerging differences between ET and EPT as varying ages and time intervals since menopause
- Individualization in decision to use HT: consider individual health, personal risk factors and quality of life priorities
- ET has a more favorable risk benefit profile which allows for more flexibility in duration of use
- EPT associated with an increased risk of breast cancer incidence and mortality after 3-5 years
- Premature menopause: HT until median age of natural menopause and then reassess

Menopause 2012:257-71

Donna

- Donna is a 67 year old woman with significant vaginal atrophy. She has not been sexually active for some time and when asked if this is bothersome to her she admits it causes difficulties in her relationship with her husband. She is very hesitant to use hormones in any form because she reads a lot of articles about them and doesn’t think they are safe. She has significant pain with intercourse, no other major symptoms.

- What recommendations do you have?

What do you tell her?

1. Vaginal moisturizers
2. Estrogen crème will work and it is safer than the pills
3. Why don’t you try an estrogen vaginal ring? It’s safer than the crème
4. There is a new medication called ospemifene that could help

Background

- VVA is associated with physical discomfort, sexual dysfunction, emotional distress, and reduced quality of life
- Incidence of VVA can be ~60%
- Current treatment options are only estrogen or vaginal moisturizer

Vaginal moist... Estrogen crème... Why don't you... There is a new medication... 42% 45% 10% 3%
Treatment Options

• Vaginal moisturizers are used several times a week and vaginal lubricants are used for sexual intercourse
  – Moisturizers: Replens, Vagisil
  – Lubricants: Astroglide, K-Y Jelly, Elegance Women’s
• Can improve symptoms of vaginal dryness or coital comfort but do not reduce vaginal atrophy

Local Estrogen

• Most effective treatment for moderate to severe symptoms of vaginal atrophy
• Can also reduce UTIs and symptoms of overactive bladder
• Typically given daily initially and then twice a week

Local Estrogen Preparations

• Creams
  – Estradiol (100 µcg/g) or CEE (0.625 mg/g)
    – 1 applicator qd for 7 days
    – Then ¼ to ½ applicator twice a week
• Tablet
  – Vagifem (10 µcg estradiol)
    – 1 tab vaginally for two weeks then one tab twice a week
• Ring
  – Estring
  – Releases 7.5 µcg estrogen daily for 90 days

The News

• Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy
• Aims
  – Assess the efficacy and safety of ospemifene for the treatment of dyspareunia
Methods

**P**: 605 women aged 40-80 postmenopausal women who self-reported mod-severe dyspareunia as most bothersome symptom

**I**: 60mg oral ospemifene daily for 12 weeks (N=303)

**C**: placebo daily for 12 weeks (N=302)

**O**: Change from baseline in:
- % parabasal cells and % superficial cells in maturation index
- Vaginal pH
- Severity of dyspareunia

• Details: all study personnel, participants, and clinicians were blinded; analysis was done on an intention-to-treat basis (took at least 1 dose); vaginal exam done at week 4 and 12 along with symptom questionnaire

Results

• All 4 endpoints showed statistically significant improvement in both ITT and PP analysis

• Severity of vaginal pain improved by 2-3 levels in 52.8% of ospemifene, 38.8% of placebo

<table>
<thead>
<tr>
<th>Treatment-emergent AE</th>
<th>Ospemifene (n=303)</th>
<th>Placebo (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>20 (6.6)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17 (5.6)</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>14 (4.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>14 (4.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Vulvar/vaginal mycotic infection</td>
<td>13 (4.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Results

- Mean (SD) change from BL in MBS (dyspareunia) severity score

Conclusions

• Ospemifene induced beneficial improvement in vaginal epithelium and vaginal pH
  - Superior efficacy in reducing vaginal pain associated with sexual intercourse

• Hot flushes were the most common AE
  - only 4.6% in treatment group discontinuing due to AE
Key Article

- One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus
- 40wk extension after a 12wk Phase 3 efficacy and safety trial
  - 180 women enrolled
  - Most common adverse event was hot flushes (7.2%)
  - No cases of VTE or endometrial hyperplasia occurred in the study

Key Article

- Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society
  - NAMS. Menopause, 2013.
- <10% of women report their provider initiated a conversation about VVA
- 1st line therapy: lubricant with intercourse and vaginal moisturizer [Level A]
- Mod-severe VVA: low dose vaginal estrogen or ospemifene [Level A]

Take Home Messages

- Screen women for dyspareunia and VVA—it’s common and distressing for women
- Ospemifene is a SERM with apparent positive effects on VVA without endometrial or VTE events
  - Vasomotor symptoms are the most common side effect
  - Not for use in women with a history of breast cancer
  - FDA approved for moderate-severe dyspareunia

Treatment of Vaginal Atrophy

- Regular sexual activity helps maintain vaginal health
- Start with moisturizers and lubricants
- Vaginal Estrogen if moisturizers and lubricants are insufficient
  - Type of estrogen dependent on patient preference
- Ospemifene if a woman can’t (arthritis, obesity, vulvodynia) or prefers not to use vaginal product
Women with Breast Cancer

• Topical estrogen has minimal systemic absorption but it is not zero
• Start with non-hormonal options
• Women on aromatase inhibitors
  – Probably best to avoid
• Women with low risk of recurrence
  – Probably ok
  – In concert with oncologist and with discussion of pros and cons

Summary

• Average duration of menopausal symptoms is approximately 4 years but seems to be longer in younger women
• Estrogen either alone or with a progestin is not recommended for chronic disease prevention in postmenopausal women
• Risks and benefits of estrogen treatment may differ in older and younger women

Summary

• Estrogen works best for menopausal symptoms
  – Use lowest dose for shortest duration
• Best method for discontinuation is not known
• Start with lifestyle modifications and nonprescription remedies
• Drug alternatives include SSRIs, SNRIs, gabapentin, clonidine and combined estrogen/SSRI

Vaginal Atrophy

• Regular sexual activity, moisturizers and lubricants
• Topical estrogen: start with higher dose and then decrease to maintenance dose
• Ospemifene: for women who can’t or won’t use estrogen
• Women with breast cancer
  individualized decision
“Having nine lives is cool, but if I have to go through menopause again, forget it!”

Questions?