**Disclosures**

- Consultant (Fees to UVA)
  - Pfizer, DepoMed, Noven, Shionogi, NovoNordisk
- Multicenter Research
  - DepoMed, Endoceutics, Bionova
- Travel fees: Pfizer, DepoMed, Noven, Shionogi, NovoNordisk

**Beyond Hormone Therapy: Innovative Options for Treatment of Hot Flashes**

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University of Virginia

NAMS, Past President

Hot Flashes—More than a Minor Annoyance

NAMS  October 10, 2013  Dallas, Texas

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**Learning Objectives**

- Describe the management of menopausal hot flashes in women who are not candidates for systemic hormone therapy
  - Phytoestrogens
  - Acupuncture
  - Off-Label Prescription therapies
    - Antihypertensives
    - Antidepressants
      - SSRIs
      - SSNRs
    - Gabapentin
    - FDA approved - Low dose Paroxetine Salt
  - Future- possibly Bazedoxefine/CE

**Pathophysiology of Hot Flashes**

- **Asymptomatic**
  - Thermoneutral Zone
  - Shivering Threshold

- **Symptomatic**
  - Thermoneutral Zone
  - Shivering Threshold

Freedman, RF. Seminars Reproductive Med. 2005;23:2117-125

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**Hot Flashes last longer than we thought...**

<table>
<thead>
<tr>
<th>Cohort: duration of follow-up</th>
<th>Cohort: HT use</th>
<th>No. with flashes</th>
<th>Duration start-to-finish, y</th>
<th>Mean (SD)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 y</td>
<td>Including HT users</td>
<td>131</td>
<td>5.5 (4.0)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8 y</td>
<td>Including HT users</td>
<td>213</td>
<td>3.4 (2.3)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8 y</td>
<td>Excluding HT users</td>
<td>68</td>
<td>5.2 (3.8)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8 y</td>
<td>Excluding HT users</td>
<td>117</td>
<td>3.5 (2.3)</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**HT, hormone therapy**

- **50% of women have hot flashes > 4 years**
- **23% of women still have hot flashes after 13 years**


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**HT Relieves Hot Flashes**

- **HT highly effective for the relief of hot flashes relative to placebo**
  - Placebo reduces hot flash frequency ~50% (95% CI 41.7-58.5)
  - Hot-flash frequency reduced ~77% (95% CI 58.2-87.5)
  - Hot-flash severity reduced (OR 0.13, CI 0.08-0.22)
  - Onset of effectiveness within days
    - May take up to 4-6 wk to see full effect
    - Lower doses take longer to achieve maximal efficacy
  - Adding progesterone protects uterus against cancer
    - ET used in women without a uterus

Estrogen Therapy Reduces Vasomotor Symptoms

(N = 30; Mean Age, 52 Years)

6-month, double-blind, placebo-controlled, crossover study of oral CEE on hot flushes


A significant (P < .05) reduction in number of hot flushes was reported for women taking estrogen compared with placebo.

A significant (P < .05) reduction in number of hot flushes was reported for women taking estrogen compared with placebo.

VMS Unmet Medical Need

- Hot flashes/night sweats can pose enormous burden for some women
- Main reason menopausal women seek medical care
- Many women unable or unwilling to take hormone therapy (HT)
- Many unproven and risky options in use
- Well-studied, approved options needed

Clinical Case 1
Carol

A 52-year-old female G3P3 last menstrual period 6 months ago
- FH negative for breast cancer, osteoporosis, VTE
- She has a FH of mother breast cancer
- She has tried an over-the-counter soy supplement, but her symptoms are unchanged
- Worried about prevention of osteoporosis, heart disease and cognitive decline

Non-Rx treatment options for mild hot flashes: black cohosh
- Clinical trial data mixed with 40-80 mg/day
  - Overall felt to be similar to placebo
  - May take 8-12 weeks before benefit, if any, is evident
- Binds to serotonin receptor, not estrogen receptor
- No discernable effect on vaginal epithelium or endometrium
- Lack of effect on objective measures and hot flashes
- Risks long-term black cohosh (liver toxicity)
- Supplements not regulated as drugs

Carol’s history

- “I thought menopause was going to be a breeze”
  - Increasing hot flashes
    - Currently 6 to 8 hot flashes a day
    - 1 to 2 soaking night sweats a week
    - Early morning awakening, can’t go back 3-4 times/week
    - Emotional lability
    - Fatigue
    - Decreased concentration/mental fog
    - Vaginal dryness and pain with intercourse
    - Reduced sexual satisfaction
    - Urinary urgency

Phytoestrogens modestly effective for mild HF

- More benefit higher proportions genistein or S(Y)-equol
  - Different effects in equol producers vs nonproducers
  - 50 mg/day or higher for at least 12 weeks
- Soy food consumption felt safer than supplements
  - lower risk breast/endometrial cancer observational studies
  - 1-2 servings/day or 25 g soy protein
- Efficacy on bone not been proven
- Efficacy on CV benefits still evolving-positive on lipids
- Low incidence of side effects
- Long-term safety not confirmed
Non-Prescription Therapies: Acupuncture vs oral estradiol 2 mg

24-Week Follow-up period

<table>
<thead>
<tr>
<th>Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Week 1 Week 4 Week 6 Week 8 Week 12 Week 24</td>
</tr>
<tr>
<td>Estrogen (n = 15) Superficial Needle Insertion (n = 13) Acupuncture (n = 15)</td>
</tr>
</tbody>
</table>

Clinical Case 2

56 yr old MWF on low dose combination EPT HT since age 52
Mother breast cancer diagnosed at age 68
One month ago, her screening mammogram showed linear calcifications
She stopped her hormone therapy
off about 4 weeks

Clinical Case 3

52 yr old MWF LMP 1 year ago referred on combination HT for 6 months oral EPT
One month ago, developed VTE following a prolonged airplane flight
Her 19 yr son had PE after football injury
diagnosed-Factor V Leiden homozygote
She stopped her hormone therapy
off about 4 weeks

Clinical Scenario #3

A 55 YO G0 patient with a history of invasive ER+ breast cancer 6 years ago, is experiencing frequent, severe hot flashes.
What therapeutic options are available to her?

Nonhormonal Therapies
Tested in large RCT >50 HF per day better than placebo
- Desvenlafaxine 100 mg
- Escitalopram-10 to 20 milligrams
- Low dose paroxetine salt 7.5 mg
- Gabapentin G-ER 1800 mg asymmetrically dosed
SSRI/SNRI for Vasomotor Symptoms

Percent Hot Flash Reduction 95% CI

- Loprinzi, fluoxetine 20 mg/d
- Stearns, paroxetine 10 mg/d
- Stearns, paroxetine 20 mg/d
- Stearns, paroxetine 12.5 mg/d
- Paroxetine total
- Gordon, sertraline 50 mg/d
- Kimmick, sertraline 50 mg/d
- Grady, sertraline 100 mg/d
- Sertraline total
- Loprinzi, venlafaxine 37.5 mg/d
- Loprinzi, venlafaxine 75 mg/d
- Loprinzi, venlafaxine 150 mg/d
- Venlafaxine total
- Paroxetine total
- Sertraline total
- Venlafaxine total

Study Design for Both Pivotal Studies

Run binge

Randomization 1:1

Placebo Run-in

LDMP

Co-primary Endpoints Study 3 and 4

Persistence Study 4 Only

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>12-Week Study</th>
<th>24-Week Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>Paroxetine (n = 101)</td>
<td>Placebo (n = 98)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Black</td>
<td>White/Caucasian</td>
</tr>
<tr>
<td>Menopause onset type, n (%)</td>
<td>Natural</td>
<td>Surgical</td>
</tr>
<tr>
<td>12-Week Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.70 (4.67)</td>
<td>2.10 (0.50)</td>
<td>1.85 (0.49)</td>
</tr>
<tr>
<td>23.70 (4.67)</td>
<td>2.10 (0.50)</td>
<td>1.85 (0.49)</td>
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</table>

Reduction in Frequency and Severity of HFs:

12-Week Study

Low-Dose Mesylate Salt of Paroxetine (LDMP)

- Paroxetine mesylate 7.5 mg capsules
- For moderate to severe vasomotor symptoms (VMS) associated with menopause
- Selective serotonin reuptake inhibitor (SSRI)
- Mechanism of action in VMS thought to be related to potentiation of CNS neurotransmitters which impact regulation of body temperature
- Dosed orally, once daily at bedtime
- Substantially lower than approved doses for psychiatric use
- No up or down titration

FDA approved Non hormonal Tx Low dose Mesylate Salt of Paroxetine (LDMP)

- 2 DB RCT -Phase 3 studies LDMP 7.5 mg/day
- Moderate to severe vasomotor symptoms
- Weekly reductions freq/severity HF Week 4 + 12
- 24-wk-statistical significance co-primary endpoints
- 12-week study-statistical significance co-primary endpoints
- except for severity of VMS symptoms at Week 12.
- AE- nausea, fatigue, dizziness
- One suicide, 3 suicidal ideations on Rx, none placebo
Reduction in Frequency and Severity of HFs: 24-Week Study

**Treatment-emergent Adverse Events**

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>Paroxetine 7.5 mg (n = 586)</th>
<th>Placebo (n = 589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>206 (34.3)</td>
<td>275 (46.7)</td>
</tr>
<tr>
<td>NAs occurring in ≥2% of the paroxetine 7.5 mg arm and 2-fold more frequently than in the placebo arm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (3.8)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (3.4)</td>
<td>9 (1.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (2.0)</td>
<td>5 (0.8)</td>
</tr>
</tbody>
</table>

**Sexual Dysfunction and Weight Neutral**

<table>
<thead>
<tr>
<th>Treatment-emergent sexual dysfunction events, %</th>
<th>Mean weight change from baseline, lbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libido decreased</td>
<td>Paroxetine 7.5 mg (n = 635)</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>0.2%</td>
</tr>
<tr>
<td>Anorgasmia</td>
<td>0.2%</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>0.2%</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Escitalopram-10 to 20 mgs**

205 women RCT 10-20 mg/ day of escitalopram or placebo for eight weeks. Avg age 54, daily diaries
- Escitalopram-5.26 hot flashes/day, a decline of 47% or 4.5 fewer a day
  - Compared to placebo 6.43 hot flashes/day, a decline of 33% or three fewer/day
  - Doesn’t meet ‘gold standard’ 2 fewer HF/day over placebo
- Significant decrease in severity for SSRI over placebo

- 55% on escitalopram decreased at least 50% in HF frequency at 8 weeks vs 36% of placebo

**Desvenlafaxine 100 mg**

- Significantly reduced number HF at 4 and 12 weeks
- Significantly reduced severity of HF at 4 and 12 weeks
- Provided symptom relief within 1 week of treatment
- Significantly reduced nighttime awakenings due to hot flashes
- One trial but not a further 12 month trial increased CV events


**Desvenlafaxine (DVS)**

Approved for Depression; Not approved for Hot Flashes
Nonhormonal Rx Therapies: Gabapentin

- **Hot-flash Frequency**
  - Placebo
  - 300 mg gabapentin
  - 600 mg gabapentin

- **Hot-flash Severity**
  - Placebo
  - 300 mg gabapentin
  - 600 mg gabapentin

**Gabapentin-ER Study Population**
- Moderate to severe VMS
  - Average age: 54 (34-70)
  - Over 95% under 65
  - Surgical menopause – (around 28%)
  - Frequency: 11 hot flashes/day
  - Severity: 2.5 (mixture of moderate-severe)
  - High sleep disturbance at baseline
  - Not on hormone therapy

**Change from Baseline to Week 12**
- Frequency and Severity of Mod.-to-Severe HF

- **GABA**
- **Placebo**

- **SEVERITY**
- **FREQUENCY**

<table>
<thead>
<tr>
<th>LS Mean Difference (G-ER minus Placebo)</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABAPENTIN-ER (1800 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megestrol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (vs MPA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA 400 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA 500 mg x 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black Cohosh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 420)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine (n = 75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (vs MPA) (n = 94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA 400 mg (n = 74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA 500 mg x 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Efficacy of Therapies for Hot Flashes**

- Courtesy of C.L. Loprinzi, MD.

- **Dizziness and Somnolence Over Time**

- **Percentage**
- **End of Week**

- **1** p < 0.05 Reduction in HF frequency was statistically significant at all time points through Week 12.
Conclusions

- HF may persist for 4 years or more in symptomatic menopausal women.
- Consider non-hormonal treatment for VMS if HT risks outweigh benefits or if patient is reluctant to start HT.
- Only FDA approved non-hormonal option is low dose paroxetine salt.
- Off label options include desvenlafaxine, venlafaxine, escitalopram, gabapentin, paroxetine, zoloft; fluoxetine.

Bazedoxefine and Conjugated Estrogen Study Design

- Randomized, double-blind, placebo-controlled trial.
- Inclusion criteria: Healthy postmenopausal women at least 50 moderate to severe hot flushes per week.
- Treatment groups:
  - BZA 20 mg/CE 0.45 mg
  - BZA 20 mg/CE 0.625 mg
  - Placebo (PBO)

Daily Number of Moderate to Severe HF MITT LOCF

- *BZA/CE 20/0.45: Statistically different from placebo from week 3 onward.
- †BZA/CE 20/0.625: Statistically different from placebo from week 2 onward.

BZA/CE: Summary of Benefits

- Significant improvement in HRQoL.
- Significant reduction in number and severity of hot flushes.
- Significant improvement in sleep.
- Low rates of breast pain similar to those with placebo.
- Low rates of endometrial hyperplasia similar to those with placebo.
- Preservation of bone mineral density and reduction in bone turnover.

Non-Prescription Remedies for mild hot flashes

- Vitamin E - not clinically significant.
- No improvement compared with placebo.
- Dong quai.
- Ginseng.
- Evening primrose oil.
- Red clover - 5 trials.
- Lack long-term safety and efficacy data.
- Side effects and drug interactions occur.

References

- Santen R J Clin Endocrinol Metab. 2010;95:s1-s66.
**Nonhormonal Treatments for Vasomotor Symptoms**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Study Design*</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMs (black cohosh, St. John’s Wort, red clover, acupuncture, exercises)</td>
<td>Duration: 4-52 wk, OL and RPL trials</td>
<td>Mixed results, mostly with no sustained improvement</td>
</tr>
<tr>
<td>SSRIs (paroxetine, fluoxetine, sertraline, citalopram, escitalopram, desvenlafaxine)</td>
<td>Duration: 4-38 wk, RPL trials with all agents N = 20/active arms</td>
<td>Reduction in VMS (frequency, composite scores) 28-55%</td>
</tr>
<tr>
<td>SNRIs (venlafaxine, desvenlafaxine)</td>
<td>Duration: 12-52 wk, RPL trials with all agents N = 20/active arms</td>
<td>Reduction in VMS (frequency, composite scores) 55-68% for VEN 55-68% for DVS</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Duration: 4-12 wk, OL and RPL trials, N = 20-100</td>
<td>Reduction in VMS (frequency, composite scores) 50-70%</td>
</tr>
</tbody>
</table>

**Notes:**
- SSRIs = selective serotonin reuptake inhibitors.
- SNRIs = serotonin and norepinephrine reuptake inhibitors;
- CAMs = complementary and alternative medicines.

**Key Inclusion/Exclusion Criteria**

**Inclusion:**
- 18–70 years
- ≥7 moderate-to-severe HF’s/day (or ≥50/week)
- Menopausal, nondepressed women
- VMS ≥14 HF’s/week with ≥40 mIU/mL FSH
- ≥6 weeks post-surgical bilateral oophorectomy
- RPL trials

**Exclusion:**
- Creatinine clearance <60 mL/min
- Current treatment with hormone therapy (washout permitted)

**Therapeutic Class: Menopausal Symptoms**

**Antidepressants:**
- SSRIs: Citalopram, 10-30 mg/d
- Escitalopram, 10-20 mg/d
- Fluoxetine, 20 mg/d titrated to 60 mg/d
- Sertraline, 50-150 mg/d
- Venlafaxine, 37.5-75 mg/d
- Duloxetine, 60-120 mg/d
- Paroxetine (controlled release), 12.5-25 mg/d
- Escitalopram, 10-20 mg/d

**Antihypertensives:**
- Methyldopa (250 mg 3 times/d)
- Hydralazine (25 mg 3 times/d)
- Nifedipine (30 mg 3 times/d)

**Antiseizure Agents:**
- Gabapentin, 100-300 mg titrated to 900 mg/d

**Relaxation Approaches:**
- Acupuncture
- Acupressure
- Yoga
- Exercise
- Water-based lubricants and bioadhesive moisturizers
- Relaxation therapies

**Study Design**

<table>
<thead>
<tr>
<th>Screeni ng Period</th>
<th>Double-blind Treatment (paroxetine 7.5 mg or placebo)* Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>OL and RPL trials</td>
<td>12-week study: 84 days</td>
</tr>
<tr>
<td>Entry criteria</td>
<td>24-week study: 168 days</td>
</tr>
<tr>
<td>Entry criteria</td>
<td>N = 20-65 in VEN; N = 120-200 in DVS</td>
</tr>
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<td>Entry criteria</td>
<td>Follow-up 7 days after last dose of study drug</td>
</tr>
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**Notes:**
- *Menopausal, nondepressed women
Conclusion

G-GR may provide a non-hormonal alternative for post-menopausal women troubled by moderate-to-severe HF who are unable or unwilling to take hormone therapy.