Primary Care Women’s Health Forum

Getting Comfortable with the Uncomfortable Symptoms of Menopause: The VVA Dialogue

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Educational Objectives
By the end of this activity, the participant should be better able to:
1. Proactively identify and diagnose VVA in postmenopausal women while maintaining a high level of sensitivity for patient’s discomfort.
2. Describe the efficacy and safety of available and emerging therapies for the management of vulvar vaginal atrophy.
3. Exercise informed clinical decision making with respect to therapeutic selection and duration, considering the benefits, risks, and unique needs of each individual patient.
4. Implement effective patient-centric counseling strategies that increase patients’ knowledge of vaginal health and address any concerns or misperceptions they may have regarding VVA and its therapies.

Speaker Disclosure
Dr. Levine has disclosed that he is on the advisory board for Bayer Healthcare Pharmaceuticals and Pfizer, has received an educational training grant from Pfizer, and is on the speaker’s bureau for Merck & Company.
INTENDED LEARNERS
This activity is designed for primary care physicians, nurses, nurse practitioners, and physician assistants who treat female patients.

Independent Clinical Reviewers: Cari Benbasset-Miller, MD, Physician, Family Medicine, Cambridge, MA; Brian McDonough, MD, Clinical Professor of Family Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania; William C. Torrey, MD, Medical Director, DHPA, Associate Professor of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; Lorena A. Wright, MD, Clinical Assistant Professor Metabolism, Endocrinology and Nutrition, University of Washington Medical Center/Roosevelt, Harborview Medical Center, Seattle, Washington.
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PLANNING COMMITTEE
The planning committee comprises of Cari Benbasset-Miller, MD, Pamela Ellsworth, MD, Deborah Friedman, MD, Susan Hutchinson, MD, W. Clay Jackson, MD, DIPTH, Cheryl L. Lambing, MD, FAAFP, Jeffrey Levine, MD, MPH, Brian McDonough, MD, William C. Torrey, MD, Lorena A. Wright, MD; Susie Seaman, MSN, NP, CWOCN; Celeste Collazo, MD, MaryEllen Fama, Raquel Gaerlan, Michael Kearney, Michelle Montgomery, Randy Robbin, and John Savage, NACCME.

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Getting Comfortable with the Uncomfortable Symptoms of Menopause: The VVA Dialogue

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Jeffrey P. Levine, MD, MPH: Advisory Committee—Bayer, Pfizer; Implant Trainer—Merck

Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

Why are Menopausal Symptoms Relevant for Primary Care Clinicians?

Menopausal Age and Life Expectancy


What is Menopause?
• Final menstrual period
  - Confirmed by 12 months of no menstrual bleed
• Result of loss of ovarian follicular function
  - Usual cause is aging
• Mean age 51 to 52 years
  - Natural age range of 45 to 55 years
• Premature menopause: age <40 years
  - Usually caused by medical intervention
    (i.e., bilateral oophorectomy, chemotherapy)
  - 1% of women – primary ovarian insufficiency

Menopausal Symptoms
• Menstrual bleeding changes
• Vasomotor symptoms
  - Hot flushes, night sweats
• Urogenital symptoms
  - Dryness, itching, dysuria, urgency, incontinence
• Sexual dysfunction
  - Dyspareunia, decreased sexual desire
  - Sleep disturbances
  - Mood disorders
  - Cognitive changes
  - Bone loss / Osteoporosis
  - Skin tone changes

VVA and Primary Care
• 25% to 50% of all postmenopausal women will experience symptoms of VVA beginning 4 to 5 years after menopause
• Many postmenopausal women continue to engage in sexual activity (62% aged 57-64 years; 40% aged 65-74 years; and 17% aged 75-85 years)
• ~4 out of 10 postmenopausal women never discussed symptoms of VVA with a provider
• Only 13% of providers initiated the conversation about symptoms of VVA

References:
Learning Objectives

• Proactively identify and diagnose vulvar and vaginal atrophy (VVA) in postmenopausal women while maintaining a high level of sensitivity for patients' discomfort
• Describe the efficacy and safety of available and emerging therapies for the management of VVA
• Exercise informed clinical decision making with respect to therapeutic selection and duration, considering the benefits, risks, and unique needs of each individual patient
• Implement effective patient-centric counseling strategies that increase patients' knowledge of vaginal health and address any concerns or misperceptions they may have regarding VVA and its therapies

Urogenital Symptoms

New terminology: “Genitourinary Syndrome of Menopause”

• Symptoms of vaginal dryness, vulvovaginal irritation and itching, and dyspareunia
• Accompanied by increase in recurrent UTIs, incontinence
• Occurs in 10% to 40% of postmenopausal women
• Unlike hot flushes, vaginal atrophy is typically progressive and unlikely to resolve on its own

UTI = urinary tract infection.

Vaginal Changes in Menopause

• Loss of labial and vulvar fullness
• Labial/vaginal dryness
• Intromital stenosis
• Vaginal epithelial pallor
• Loss of vaginal elasticity and rugal folds
• Cervical petechiae
• Friable vagina and cervix


Vaginal Atrophy

• Loss of glycogen-rich superficial cells - Loss of acid-producing Lactobacilli
• pH increases (>5.0)
• Increased parabasal cells


Hormone Therapy

Hormone therapy (HT) encompasses both estrogen-alone and estrogen-progestogen therapies

• Estrogen therapy (ET)
  - Unopposed estrogen is prescribed both systemically for women who do not have a uterus, and locally in very low doses for any woman with vaginal symptoms
• Estrogen-progestogen therapy (EPT)
  - Progestin is added to ET to protect women with a uterus against endometrial cancer, which can be caused by estrogen alone


History of Hormone Therapy

1942 - Conjugated estrogen is isolated from horse urine and marketed as Premarin
1950s-60s - Premarin and other ET gains popularity among American women
Clinical studies published showing link between ET and increased risk of endometrial cancer
1975 - Studies showed addition of progestin helped protect women from endometrial cancer
1980s - HT continued to increase in popularity to a peak of 12 million women
Women’s Health Initiative findings published with HT associated with increased health risks
2010s - Continued RCTs of HT clarify risks and benefits of HT for subgroups of women

RCT = randomized controlled trials.
Women’s Health Initiative
• 2 randomized placebo-controlled clinical trials looking at EPT for women with uterus and ET for women without uterus
• 161,809 postmenopausal women between the ages of 50 and 79 years
• Looked at impact of HT on major outcomes including
  - CHD
  - Invasive breast cancer
  - Stroke
  - Pulmonary embolism
  - Endometrial cancer
  - Colorectal cancer
  - Hip fracture
• Planned for 12 years but terminated early after findings showed increased health risks for women on HT

CHD = coronary heart disease.

Women’s Health Initiative Findings
• No change in all-cause mortality
• EPT associated with increased risk:
  - CHD, breast cancer, stroke, VTE
• EPT associated with decreased risk:
  - Colorectal cancer, hip fracture
• ET associated with no change in CHD
  - Increased risk of stroke
  - Decreased risk of hip fracture
  - Non-significant trend toward decreased CHD and breast cancer

VTE = venous thromboembolism.

What Have We Learned Since WHI?
• Limitations of WHI data:
  - WHI studied women several years postmenopause, with multiple additional risk factors for morbidities, and with standardized doses of HT
  - Subsequent studies have looked at age, years since menopause, and/or duration of use
  - Symptomatic women are more likely to be younger, closer to onset of menopause
  - HT formulation, route of administration, and timing of initiation produce different effects
  - Absolute risks for HT use in healthy women ages 50 to 59 years are low, but can include thrombosis, stroke, and cardiovascular events. HT initiation in older women carries greater risks
  - Breast cancer risk increases with EPT beyond 3 to 5 years


Menopausal Hormone Therapy
"MHT is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause"

• 2013 Global Consensus Statement, endorsed by multiple international organizations
  - The American Society for Reproductive Medicine
  - The Asia Pacific Menopause Federation
  - The Endocrine Society
  - The European Menopause and Andropause Society
  - The International Menopause Society
  - The International Osteoporosis Foundation
  - The North American Menopause Society

MHT = menopausal hormone therapy.

Patient Evaluation
• Review relative contraindications to HT
  - History of breast cancer (absolute contraindication)
  - History of CHD, VTE, CVA, active liver disease
  - Age >60 years, >10 years past menopause entry
• Evaluate for most bothersome symptoms
  - Vasomotor symptoms vs urogenital symptoms vs both
• Rate severity of symptoms and impact on QoL
  - For mild symptoms, consider non-HT
  - Menstrual history
    - Perimenopausal women may benefit from contraceptive doses
    - Not necessary to check LH/FSH labs prior to treatment*  
  - Physical exam
    - Before local estrogen, do external genital exam
    - Check pH paper, no need for internal exam
  - For mild symptoms, consider non-HT
  - Menstrual history
    - Perimenopausal women may benefit from contraceptive doses
    - Not necessary to check LH/FSH labs prior to treatment*

*For suspicion of abnormal uterine bleeding or primary ovarian insufficiency. CVA = cerebrovascular accident; FSH = follicle-stimulating hormone; LH = luteinizing hormone; QoL = quality of life.
Treatment for Menopause Symptoms

Systemic Therapy

Indicated for:
- Vasomotor symptoms
- Symptoms of urogenital atrophy

- Women should be treated with lowest effective dose of HT
- Women with a uterus should be treated with a concurrent progestin/progesterone
- Transdermal preparations may decrease risk of VTE and ischemic stroke
- The need for treatment should be re-evaluated with an individualized approach to risks and benefits after 3 to 5 years of treatment


Estrogen Therapy

- **Oral Estrogens**
  - Conjugated equine estrogen (CEE)
  - 17β-estradiol
  - Estradiol acetate
  - Estropipate
  - Esterified estrogens
  - Ethinyl estradiol

- **Transdermal Estrogens**
  - 17β-estradiol
  - Multiple dosing options, weekly/biweekly application
  - Caution if adhesive allergy

- **Vaginal Estrogens**
  - Estradiol acetate ring
  - Delivers systemic dose of estrogen over 3 months
  - Treats both vasomotor and urogenital symptoms

ET Products

- **Oral Estrogens**
  - Conjugated estrogens
  - Synthetic conjugated estrogens
  - 17β-estradiol
  - Estradiol acetate
  - Estropipate
  - Esterified estrogen

- **Transdermal Estrogens**
  - Patches
    - 17β-estradiol – applied 1 to 2 × weekly
    - Gels, Sprays, Emulsions
  - 17β-estradiol – applied daily

- **Vaginal Estrogens**
  - Estradiol acetate – inserted for 3 months

Progestin / Progesterone Products

- **Progestins (Synthetic)**
  - Generic medroxyprogesterone acetate (MPA)
  - Generic norethindrone acetate
  - Levonorgestrel intrauterine system
  - Not FDA approved for postmenopausal endometrial protection

- **Progesterones (Natural)**
  - Oral
    - Caution with peanut allergy
  - Vaginal cream
  - Vaginal ovules
  - Yarn cream
  - Not effective for endometrial protection

EPT Oral Products

- Conjugated estrogen + MPA
- Ethinyl estrogen + norethindrone
- 17β-estradiol + norethindrone
- 17β-estradiol + drospirenone
EPT Transdermal Products

- Estradiol + levonorgestrel
  - Weekly patch
  - 1 standard EPT dose
- Estradiol + norethindrone
  - Biweekly patch
  - 1 estradiol dose / 2 norethindrone dosing options
  - May be used continuously or cyclically

CE/SERM Oral Product

- Conjugated estrogen + bazedoxifene
- Indicated in women with a uterus for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis
- Not FDA approved for symptoms of VVA due to menopause

Local ET

Indicated only for symptoms of urogenital atrophy

- Dosing: cream, ring, tablet
- Effective for atrophy symptoms, may also reduce risk of urinary urgency and recurrent UTIs
- May increase risk for endometrial cancer for women who have a uterus
- Presumed lower risk than commonly used doses of systemic ET
  - Serum estrogen levels reported with use are within postmenopausal range
  - No recommendation to give progestin opposition

Local Vaginal ET Products

- Conjugated equine estrogen
  - Vaginal cream
    - Biweekly
  - 17β-estradiol
    - Vaginal cream
      - 1 to 3×/week
  - Estradiol hemihydrate
    - Vaginal suppository
    - Biweekly
  - Estradiol acetate
    - Vaginal ring
    - Quarterly

Bioidentical Hormones

- Compounded combinations of hormones
- May combine several hormones, some non-FDA approved
- May contain non-hormonal ingredients causing harm (e.g., dyes, preservatives)
- May use nonstandard routes of administration (e.g., subdermal implants)
- Often prescribed with salivary hormone testing (inaccurate and unreliable)
- No evidence for greater safety or efficacy than FDA approved preparations (NAMS, AACE, ACOG)

Non-HT for Urogenital Atrophy Symptoms

- First-line treatment of lubricants and moisturizers may significantly improve symptoms for many women
- Increasing foreplay and changing positions during sex may improve dyspareunia
- Prescription therapies of low dose vaginal ET should be considered for continuing symptoms


Prescription Non-HT Product

- Ospemifene: SERM approved to treat moderate-to-severe dyspareunia, a symptom of VVA, due to menopause
- Daily 60 mg oral therapy, taken with food
- **Black Box Warning** regarding endometrial cancer and cardiovascular disorders


Surveillance and Discontinuation

- Mammograms per standard guidelines
- Discuss symptoms annually
- Consider trial tapering medication after 2 years
- If continuing treatment, review individual risks and benefits of treatment after 5 years

Take Home

- Menopausal symptoms can have large impact on quality of life via both vasomotor and urogenital manifestations
- HT is the most effective treatment option for both menopausal vasomotor and urogenital symptoms
- Perceived risks of HT are often inflated for many symptomatic women who are younger, more recently entered into menopause, and have fewer comorbidities
- Many doses and routes of administration are available for HT
- Individualized assessment of risk and benefit ratios for HT should be done by women and their providers regularly

Resources

- **MenoPro from NAMS**
  - Free, targeted to both women and health care providers
  - [www.menopause.org/for-women/-i-menopro-i-mobile-app](http://www.menopause.org/for-women/-i-menopro-i-mobile-app)
- **“The Truth about Bioidentical Hormone Therapy”**
  - Available from NAMS as patient handout
  - [www.menopause.org/docs/professional/tpbio0812.pdf?sfvrsn=2](http://www.menopause.org/docs/professional/tpbio0812.pdf?sfvrsn=2)
- **“Hormone Therapy and Menopause FAQs”**
  - Available from NAMS Web site as patient resource
  - [www.menopause.org/for-women/expert-answers-to-frequently-asked-questions-about-menopause/hormone-therapy-menopause-faqs](http://www.menopause.org/for-women/expert-answers-to-frequently-asked-questions-about-menopause/hormone-therapy-menopause-faqs)

NAMS = North American Menopause Society.
Medication Index
Primary Care Women's Health Forum: Getting Comfortable with the Uncomfortable Symptoms of Menopause: The VVA Dialogue

The following medications were discussed in this presentation. The table below lists the generic and trade name(s) of these medications.

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