The Role of SERMs in Managing the Most Bothersome Symptoms of Vulvovaginal Atrophy: Dyspareunia and Dryness

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Identified or perceived conflict of interest has been resolved in accordance with ACCME guidelines.

Disclosures

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Salary and Stockholder: Sermonix Pharmaceuticals

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Objectives

- Describe the pathophysiology underlying dyspareunia and dryness associated with VVA
- Define the underlying mechanisms of action of the various available SERMS
- Identify the indications and usage of the available SERMS
- Cite the scientific data regarding the benefits and risks of oral versus topical therapy for the management of dyspareunia and dryness associated with VVA

Anatomic Correlates to Estrogen Deficiency

NAMS Menopause 2007;14:357-369.
Photos courtesy Dr Murray Freedman

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(ARS Polling Question #1) Unlike vasomotor symptoms, vulvovaginal symptoms of menopause:

1. Last only 2 years or less
2. Only occur in the perimenopause
3. Can occur several years before menopause, and last indefinitely
4. Not sure

Onset of Vasomotor Symptoms vs. Vulvovaginal Symptoms

VVA/GSM Incidence and Unmet Need

- VVA, a component of genitourinary syndrome of menopause (GSM), is prevalent and bothersome in postmenopausal women
- GSM symptoms will affect 50-70% of the >64 million US postmenopausal women at some point
  - Dyspareunia and vaginal dryness most common symptoms
- Chronic condition with symptoms worsening over time and do not improve without treatment
- Many women remain unaware that vulvar and vaginal changes can be a direct result of the menopausal transition
- Communication challenges result in underdiagnosis, undertreatment or delays in seeking treatment

Unmet Need (con’t)

- Although quite common and bothersome, most women fail to get treatment (~93%) due to:
  - Embarrassment
  - Lack of knowledge about VVA
  - Lack of knowledge of approved treatment options
  - Negative attitudes regarding hormone therapy
- Women who do seek treatment are often dissatisfied with the safety, convenience, and efficacy of current approved products

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Impact of GSM Symptoms on Sexual Function (REVIVE)

- Vaginal dryness (55%); dyspareunia (44%); vaginal irritation (37%)

REVIVE, Real Women’s Views of Treatment Options for Menopausal Vaginal Changes Survey.


Vaginal Histology

- Premenopause: Epithelium well-estrogenized, multi-layered with good blood supply, superficial cells rich in glycogen
- Postmenopause: Estrogen-deficiency atrophy with marked thinning of epithelium, reduced blood supply, and loss of glycogen
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Bazedoxifene: Effects on Endometrium in Postmenopausal Women with Osteoporosis


Effects of Bazedoxifene (BZA) and Conjugated Estrogen (CE) on the Endometrium of Women in SMART-1


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Lasofoxifene

Self-Assessment of Moderate to Severe Vaginal Symptoms - Change From Baseline at Week 12 (Pooled Phase 3 Studies)

Presented at the 26th Annual Meeting of the North American Menopause Society, September 30-October 3, 2015, Las Vegas, NV

Lasofoxifene, mg/day

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<tr>
<th></th>
<th>0.35</th>
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<th>Placebo</th>
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<tbody>
<tr>
<td><strong>DYSpareunIA</strong></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
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<td>218</td>
<td>217</td>
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<tr>
<td>LS Mean change</td>
<td>-1.3 (0.07)</td>
<td>-1.3 (0.07)</td>
<td>-1.3 (0.07)</td>
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<td>LS Mean diff from PBO</td>
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<td>-0.4</td>
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<td>p-value</td>
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<td>0.002</td>
<td>0.001</td>
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<tr>
<td><strong>Vaginal DRYNESS</strong></td>
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<td></td>
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<td>307</td>
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<tr>
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<td>-1.2 (0.07)</td>
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<td>-0.3</td>
<td>-0.4</td>
</tr>
<tr>
<td>p-value</td>
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<td>0.004</td>
<td>0.002</td>
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<tr>
<td><strong>Dysuria</strong></td>
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<td></td>
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<tr>
<td>N</td>
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<td>130</td>
<td>115</td>
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<tr>
<td>LS Mean change</td>
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<td>-0.9 (0.08)</td>
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<tr>
<td>p-value</td>
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<td>0.023</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Vulvar &amp; Vaginal ITCHING</strong></td>
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<td></td>
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<tr>
<td>N</td>
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<td>93</td>
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<td>-1.1 (0.09)</td>
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<tr>
<td>p-value</td>
<td>0.011</td>
<td>0.002</td>
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Ospemifene: Preclinical

- Ospemifene: triphenylethylene originally in clinical development for osteoporosis
  - Induced mucification and a beneficial shift of the maturation index in rat model
  - Reduced bone turnover, increases bone strength
  - Prevented growth of pre-malignant lesions and progression to invasive carcinoma in adenoma/mammary intraepithelial neoplasia mouse model
  - Slowed down the tumor growth of MCF-7 xenografts and cancer development, progression in MTag.Tg model


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Long-term Safety of Ospemifene: Dyspareunia

- 40-week extension of 12-week study of ospemifene vs placebo for the treatment of VVA in postmenopausal women (n=180) with intact uterus
  - Hot flushes most frequently occurring TEAE (7.2 vs. 2.0 ospemifene vs. PBO)
  - Endometrial findings
    - At week 52, more than 95% of endometrial biopsies atrophic, inactive or insufficient tissue
    - Mean endometrial thickness ↑ 1.1 mm after 1 yr over PBO
    - Bleeding/spotting rate of 1.7%, similar to PBO
    - No cases of endometrial hyperplasia or carcinoma


<table>
<thead>
<tr>
<th>Variable</th>
<th>Ospemifene 60mg/d (n=364)</th>
<th>Placebo (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic Characteristics</td>
<td>Baseline</td>
<td>Week 52</td>
</tr>
<tr>
<td>Tissue insufficient for dx</td>
<td>59 (16.2)</td>
<td>27 (8.7)</td>
</tr>
<tr>
<td>Atrophic</td>
<td>300 (82.4)</td>
<td>267 (86.1)</td>
</tr>
<tr>
<td>Inactive</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Weakly proliferative</td>
<td>1 (0.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Active proliferative</td>
<td>0 (0)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Goldstein, Bachmann, Koninckx, Lin, Portman, Ylikorkala Climacteric 2013
Summary

• SERMs have unique tissue selectivity profiles
• Endometrial and vaginal effects vary widely
• VVA and sexual function are prevalent and important issues for menopausal patients and their providers
• Ospemifene—an FDA-approved SERM with estrogen receptor antagonist effects in some tissues and agonist effects in the vulvovaginal tract manages the 2 most common complaints of VVA: dyspareunia and dryness

Common Questions Regarding Clinical Use of SERMS

• Do I need to add a progestin when using SERMs in patients with a uterus?
• Can I use SERMs in combination with topical estrogens or prasterone?
• Can SERMs be used concurrently, for example raloxifene with ospemifene?
• Why use a systemic drug to treat a local condition?
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