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

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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

Anatomic Correlates to Estrogen Deficiency

NAMS Menopause 2007;14:357-369.
Photos courtesy Dr Murray Freedman
Signs and Symptoms of Genitourinary Aging

- Dryness and insufficient moistness
- Diminished blood flow
- Dyspareunia
- Itching
- Burning sensation
- Soreness
- Loss of elasticity
- Thinning of the vaginal tissue and alteration of keratinization
- Mucosal defects including petechiae, microfissures, ulceration and inflammation
- Shortening, fibrosis, obliteration of vaginal vault
- Narrowing of vaginal entrance
- Smoothing of fornix, flattening of vaginal rugae

Genitourinary Syndrome of Menopause (GSM)

- A collection of symptoms and signs associated with decreased estrogen and other sex steroids
  - Can involve changes to labia majora/minora, vestibule/introitus, clitoris, vagina, urethra, and bladder
  - Symptoms include, but are not limited to, dryness, pain with sex that may lead to subsequent sexual dysfunction, bladder and urethral symptoms, frequent urinary tract infections, burning, itching, and irritation that are bothersome or distressing
- Symptomatic vulvovaginal atrophy (VVA) is one component of GSM
  - Treatment of symptomatic VVA may improve all components of GSM

Portman D, Gass M et al, Menopause 2014

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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


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.

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ER Distribution in Human Vagina

ER α

ER β


SELECTIVE ESTROGEN RECEPTOR MODULATORS: SERMS

WHAT THEY ARE

HOW THEY WORK

WHICH DOES WHAT and WHERE
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Estrogen Receptors and SERMs

Selective estrogen receptor modulators bind to the ER and the resulting complex undergoes conformational change and dimerization and the bound complex, through genomic (and some non-genomic) mechanisms, interacts with different subsets of coactivators and corepressors, eliciting different activities in different tissues.

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Tamoxifen, Raloxifene and Gynecologic Effects

- **Tamoxifen**
  - Small but significant increases in vaginal symptoms and difficulty in sexual functioning
  - Some studies has shown beneficial shift in VMI
  - Endometrial stimulation

- **Raloxifene**
  - Neutral effect on vaginal mucosa
  - Does not diminish effect of vaginal CEE cream on subjective signs of vaginal atrophy and no negative sexual effects
  - Not protective of endometrium with systemic ET


Bazedoxifene (BZA)

### Vaginal Superficial Cells

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>Week 12</th>
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<tbody>
<tr>
<td>BZA/CE 20 mg</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>BZA/CE 0.45 mg</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>BZA 20 mg</td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
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</tbody>
</table>

*P<0.01 vs. placebo
Both BZA/CE groups: Statistically different from BZA 20 mg at both time points (P<0.001) MITT LOCF

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Bazedoxifene (BZA)

Vaginal pH

*P<0.001 vs. placebo
Both BZA/CE groups: Statistically different from BZA 20 mg at both time points (P<0.001) MITT LOCF

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

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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


Ospemifene and Urogenital Health: FDA Approved Indications

Ospemifene is once-daily, oral, non-hormonal treatment

- Early 2013: for treatment of moderate to severe dyspareunia due to VVA
- Early 2019: for treatment of moderate to severe vaginal dryness due to VVA

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Ospemifene 60mg Phase III - VVA Clinical Trial

Multicenter phase 3 randomized, double-blind 12-week efficacy and safety study
- 919 women 40-80 y.o. (mean age 59 y.o.) with self-reported most bothersome sx of dyspareunia (n=605) or dryness (n=314)
  - Dyspareunia strata
    - Ospemifene 60mg po/d (n=303) vs. Placebo (n=302)
- Co-primary endpoints:
  - pH, parabasal, superficial cells
  - Change in severity using VVA symptom questionnaire for MBS of dyspareunia


Ospemifene and Dyspareunia Associated with VVA

Change in baseline to week 12

Superficial Cells

Parabasal Cells

P< 0.0001 versus placebo for all


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Ospemifene and Dyspareunia Associated with VVA

Change in baseline to week 12

P < 0.0001 versus placebo

57% change from baseline score of 2.7

Ospemifene Effects on Genitourinary Health Assessed by Prospective Vulvar-Vestibular Photography and Vulvovaginal Health Indices

a P < 0.0001;
b P = 0.0002; c P = 0.0154 versus placebo

n’ s are indicated in the bars.


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Safety: Cardiovascular-Related AEs: Ospemifene Phase 2/3 Placebo-Controlled Trials

FDA label warns of potential DVT/CVA risk
DVT 1.45 vs. 1.0 per thousand vs. PBP CVA 2.27 vs. 1.0 per thousand vs. PBO

Portman D 61st Annual Clinical Meeting of ACOG in New Orleans, LA on May 7, 2013.

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

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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?