Women's Health Annual Visit 15th Anniversary

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

David J. Portman, MD
Founder and Director Emeritus, Columbus Center for Women's Health Research
Adjunct Faculty, The Ohio State University
Department of Obstetrics and Gynecology
Founder and CEO, Sermonix Pharmaceuticals
Columbus, OH

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Disclosures

Grant/Research Support: Boehringer Ingelheim, Endoceutics, Palatin Technologies, QuatRx Pharmaceuticals, Shionogi Pharmaceuticals, TherapeuticsMD

Consultant/Advisory Board: AMAG Pharmaceuticals, Agile Therapeutics, Duchesnay Pharmaceuticals, ITF Pharma

Commercial Interest Speakers Bureau: AMAG Pharmaceuticals

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

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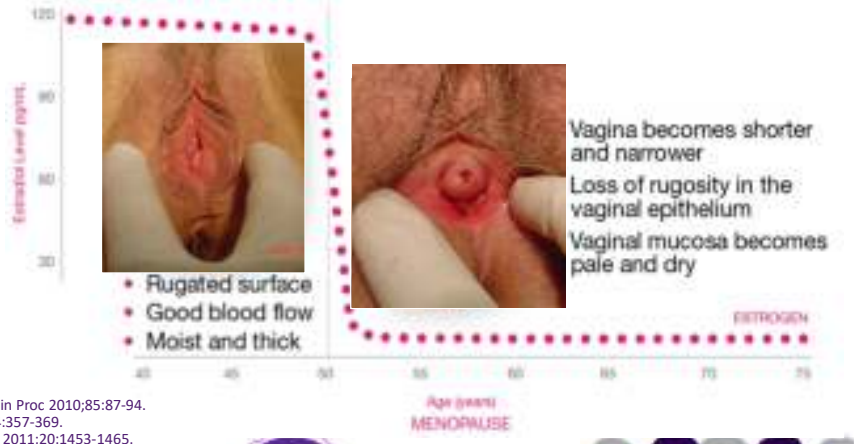
Anatomic Correlates to Estrogen Deficiency



MacBride MB et al Mayo Clin Proc 2010;85:87-94.
NAMS Menopause 2007;14:357-369.
Simon JA J Womens Health 2011;20:1453-1465.
Photos courtesy Dr Murray Freedman

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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

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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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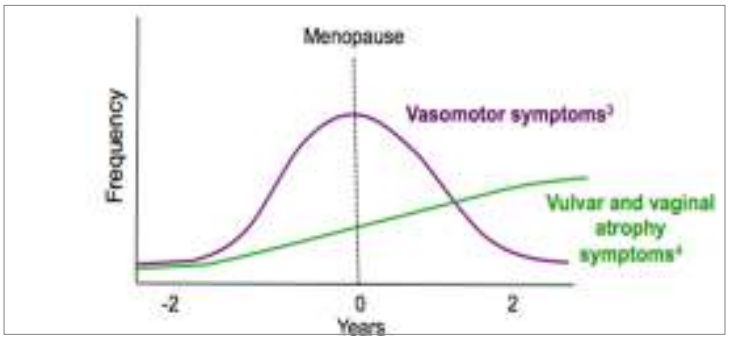
Onset of Vasomotor Symptoms vs. Vulvovaginal Symptoms



1. Nelson HD. Lancet. 2008;371(9614):760-770.
2. Bachmann GA, Nevadunsky NS. Am Fam Physician. 2000;61(10):3090-3096.
3. Kronenberg F. Ann N Y Acad Sci. 1990;592:52-86.
4. Dennerstein L et al. Obstet Gynecol. 2000;96(3):351-358.

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VVA/GSM Incidence and Unmet Need

- VVA, a component of genitourinary syndrome of menopause (GSM)[1], is prevalent and bothersome in postmenopausal women
- GSM symptoms will affect 50-70% of the >64 million US postmenopausal women at some point[2]
  - 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[3,4]
- Communication challenges result in underdiagnosis, undertreatment or delays in seeking treatment

1.Portman DJ, Gass ML. Menopause. 2014;21:1063-1068. 2. Kingsberg SA et al. J Sex Med. 2013;10:1790-1799. 3. Krychman M, Graham S, Bernick B, Mirkin S, Kingsberg SA. J Sex Med. 2017. 4. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. J Sex Med. 2013

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Unmet Need (con't)

- Although quite common and bothersome, most women fail to get treatment (~93%)[1] due to:
  - Embarrassment[2]
  - Lack of knowledge about VVA[1]
  - Lack of knowledge of approved treatment options[1]
  - Negative attitudes regarding hormone therapy[3]
- Women who do seek treatment are often dissatisfied with the safety, convenience, and efficacy of current approved products[1]

1. Kingsberg SA et al. J Sex Med. 2013;10:1790-1799.
2. Nappi et al. Maturitas. 2010;67:233-238.
3. Simon et al. Menopause. 2013;20:1043-1048.

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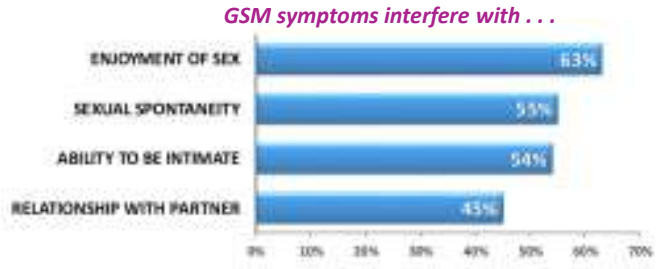
Impact of GSM Symptoms on Sexual Function (REVIVE)

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



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

Kingsberg S, et al. J Sex Med. 2013;10:1790-1799.

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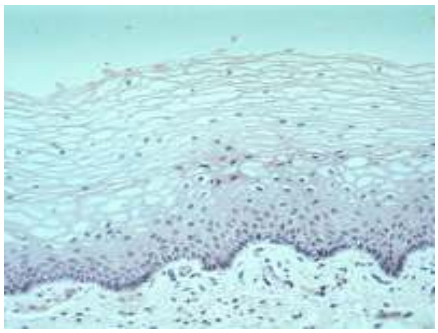
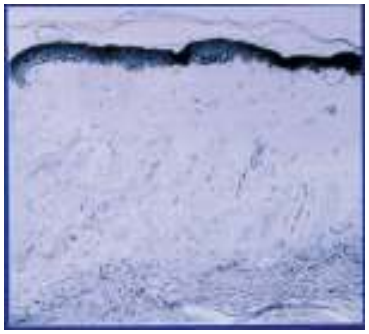
Vaginal Histology



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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Effect of Estrogens on VVA

- Changes in Vaginal Maturation Index (VMI) noted by six cycles of treatment with low-dose oral estrogens
- Improvements in VMI have reported as early as 2 to 4 weeks after initiation of vaginal CEE cream or estradiol vaginal tablets
- Vaginal pH falls to lowest levels by 3rd week of vaginal estrogen treatment (number of superficial cells in the vagina has already increased by that time)
- Superficial cells continue to increase during 12-weeks of therapy

Santen RJ, Pinkerton JV, Conaway M, et al Menopause 2002;9: 179-187.

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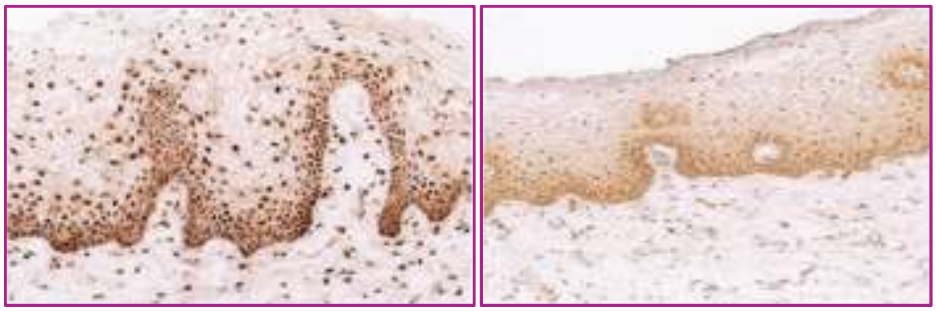
ER Distribution in Human Vagina



ER α **ER β**

Gebhart JB, Rickard DJ, Barrett TJ et al. Am J Obstet Gynecol 2001; 185:1325-31.

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SELECTIVE ESTROGEN RECEPTOR MODULATORS: SERMS

WHAT THEY ARE

HOW THEY WORK

WHICH DOES WHAT and WHERE

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SERMS:

WHAT THEY ARE

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SERMs and Mechanisms of Actions

- Selective estrogen receptor modulator (SERM): a structurally diverse group of compounds that bind to estrogen receptor (ER) despite lacking estrogen steroid moiety
- Confer mixed functional ER agonist or antagonist activity depending on the target tissue, mediated by:
  - Expression of the ER-α and ER-β and coregulators and coactivators in different tissue
  - ER conformation after binding of the ER ligand
  - Expression and binding of the ER ligand complex to coregulator (coactivator and corepressor) proteins

Hadji P Climacteric 2012;15:513–523.
Riggs BL, Hartmann LC N Engl J Med 2003;348:618-629.
Taylor H Menopause 2009; 16:1-6.

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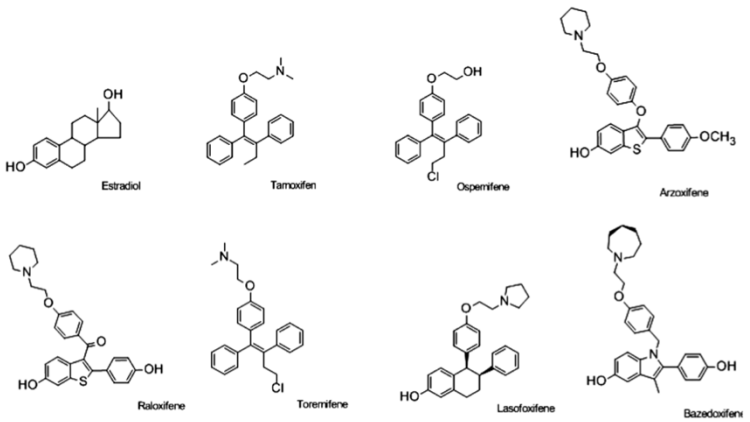
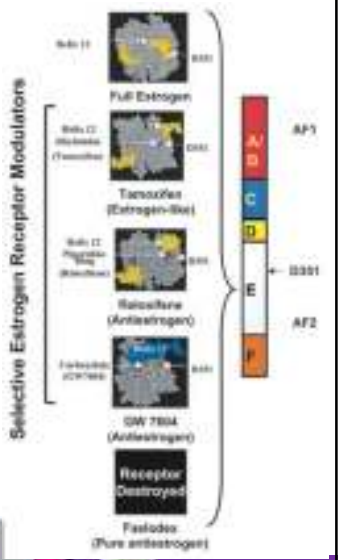
Chemical Structure of Estradiol and SERMs





Maximox PY, Lee TM, Jordan VC. Current Clinical Pharmacology 2013;8:135-155.

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SERMS:

HOW THEY WORK

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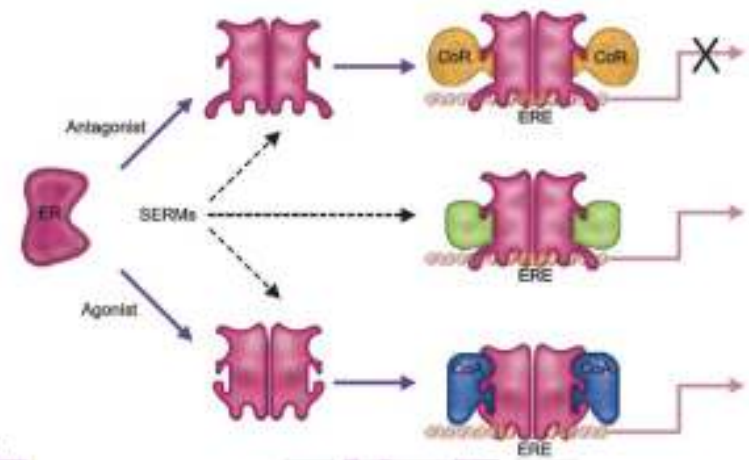
Estrogen Receptors and SERMs

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.



Nelson E, Wardell S, McDonnell D. *Bone*. 2013 March ; 53(1): 42–55 doi:10.1016/j.bone.2012.11.011.

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SERMS:

WHICH DOES WHAT and WHERE

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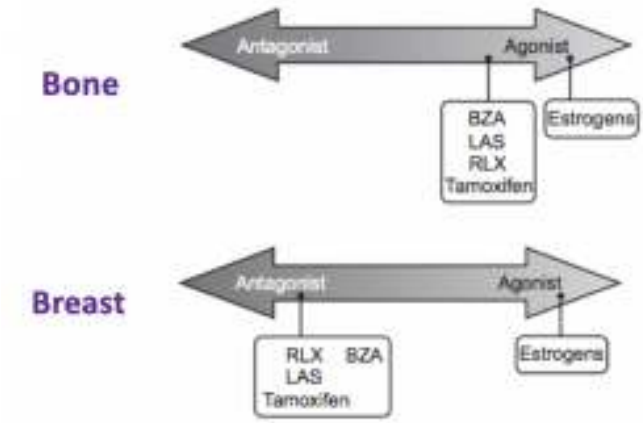
SERMs and Selectivity: Agonist on Bone, Antagonist on Breast



Hadji P Climacteric 2012;15:513–523.

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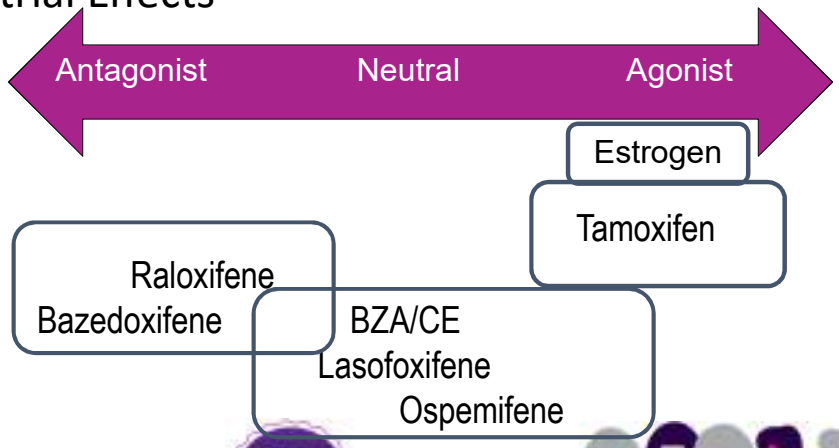
Selective Estrogen Receptor Modulators: Endometrial Effects



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Unopposed Estrogen and Endometrial Stimulation: 12 Months

	E2 1 mg	E2 1 mg + NETA 0.1 mg
No. of patients randomized	296	294
No. of available biopsies	247	249
No. normal (%)	189 (76.5)	246 (98.8)
No. with disordered proliferative phase (%)	21 (8.5)	1 (0.4)
No. with endometrial hyperplasia (%)	36 (14.6)	2 (0.8)
Simple without atypia (%)	30 (12.2)	1 (0.4)
Complex without atypia (%)	4 (1.6)	0 (0.0)
Simple with atypia (%)	0 (0.0)	0 (0.0)
Complex with atypia (%)	2 (0.8)	1 (0.4)
No. with carcinoma (%)	0 (0.0)	0 (0.0)
No. with other conditions (%)	1 (0.4)*	0 (0.0)

E2 = 17β-estradiol; NETA = norethindrone acetate.
* Scant endometrium with ciliated and eosinophilic metaplasia.

Kurman RJ, Felix JC, Archer DF et al Obstet Gynecol 2000; 96:373-379.

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Bazedoxifene: Effects on Endometrium in Postmenopausal Women with Osteoporosis

AE, n (%)	Overall safety population (years 0–7)	
	BZA-treated (n = 3758)	PBO (n = 1885)
Endometrial carcinoma	3 (0.1)[a]	7 (0.4)
Endometrial hyperplasia	2 (0.1)	1 (0.1)
Endometrial neoplasia (polyps)	34 (0.9)	15 (0.8)
Ovarian carcinoma	4 (0.1)	0
Ovarian cyst	35 (0.9)	17 (0.9)
Uterine hemorrhage	10 (0.3)	5 (0.3)
Vaginal hemorrhage	45 (1.2)	28 (1.5)
Vaginitis	229 (6.1)[b]	143 (7.6)

AE, adverse event; BZA, bazedoxifene; PBO, placebo.
[a] $P = 0.020$ vs. PBO (Fisher exact test).
[b] $P = 0.035$ vs. PBO (Fisher exact test).

Palacios S et al Maturitas 2013;76:81-87.

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

Parameter	*BZA 20mg CE 0.45 n=314*	*BZA 20 CE 0.625 n=336*	*Placebo n=313*
Endometrial hyperplasia, n (%)	0	1 (0.32)	0
Endometrial thickness in mm change from baseline adjusted mean (standard error)	0.50 (0.20)	0.62 (0.21)	0.37 (0.21)
Endometrial thickness >5mm, n (%)	7 (5.5)	4 (3.4)	4 (3.5)
Proliferative endometrium, n (%)	10 (3.4)*	14 (5.2)**	2 (0.8)

Selective estrogen Menopause And Response to Therapy trial

*$p \leq 0.05$ **$p < 0.001$ vs. placebo

Pinkerton JV, Komm BS, Mirkin S Climacteric 2013;16:1-11.

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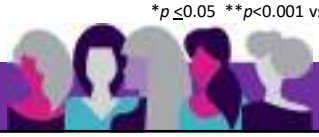

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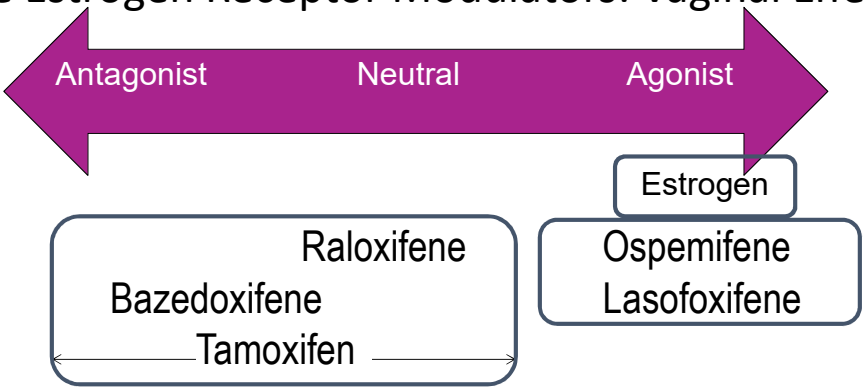
Selective Estrogen Receptor Modulators: Vaginal Effects



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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

1. Love R, Kuurtycz D, Dumesic D et al J Womens Health Gend Based Med 2000;9:559-563. 2. Day R, Ganz PA, Costantino JP et al J Clin Oncol 1999;17:2659– 69. 3. Mortimer JE, Boucher L, Baty J, Knapp DL, Ryan E, Rowland JH J Clin Oncol 1999;17:1488–92. 4. Day R. Qua Ann NY Acad Sci 2001;949:143– 50 Plouffe L J Soc Gynecol Invest 2000;7(Suppl):S38– 46. 5. Kessel B Nactigall L Plouffe L et al Climacte 6:248-256. 6. Carneiro A Dardes R Haidar M Menopause 2012;19: 8

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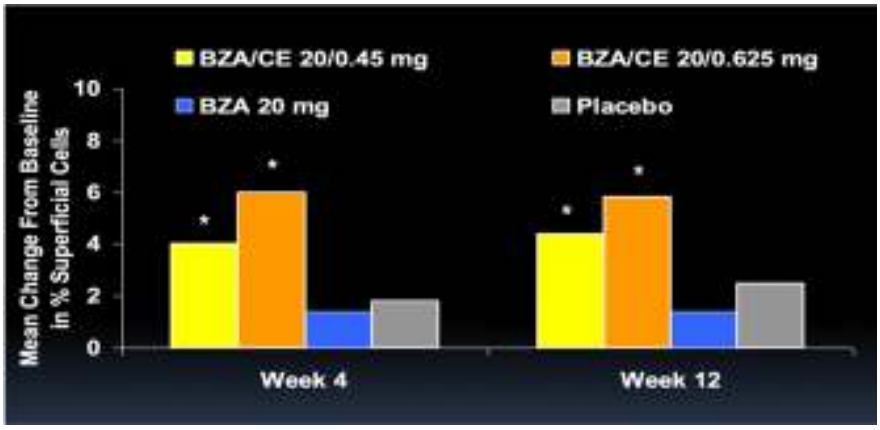
Bazedoxifene (BZA)

Vaginal Superficial Cells



*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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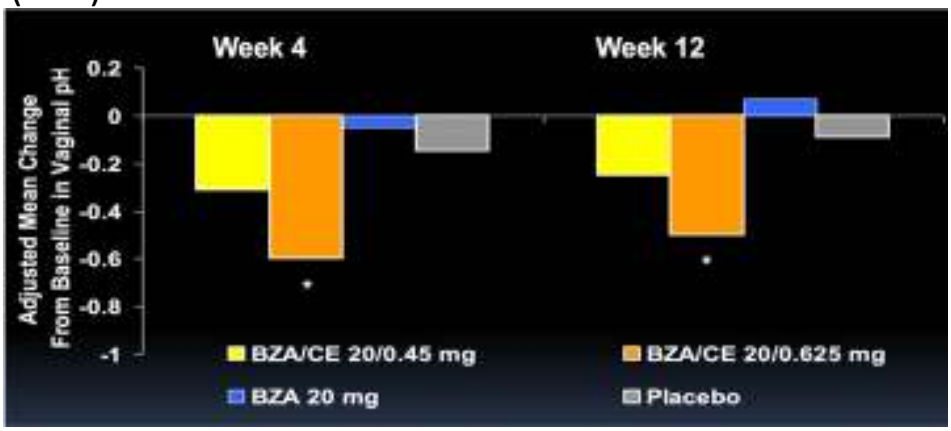
Bazedoxifene (BZA)

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

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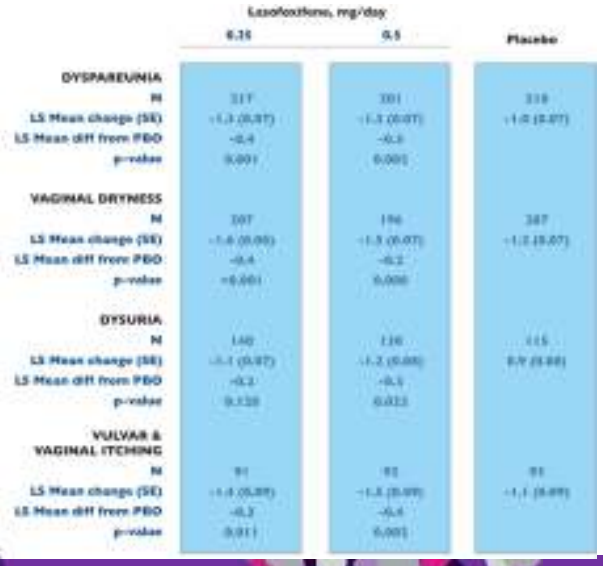
Lasofoxifene

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

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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

Burich R, Mehta N, Wurz, G et al Menopause 2012;19:19-26 Qu Q, Zheng H, Dahllund J et al Endocrinology 2000;141:809-820.
Taras TL, Wurz GT, DeGregorio MW. J Steroid Biochem Mol Biol 2001;77:271-279.

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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

Portman DJ, Bachman GA, Simon JA Menopause 2013; 20(6):1-8.

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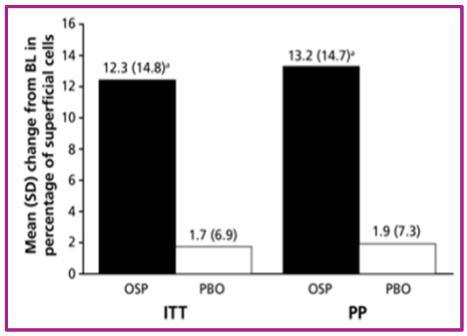
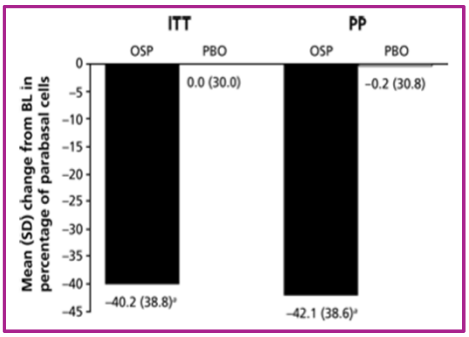
Ospemifene and Dyspareunia Associated with VVA

Change in baseline to week 12





P< 0.0001 versus placebo for all

Superficial Cells

Parabasal Cells

Portman DJ, Bachman GA, Simon JA Menopause 2013; 20(6):1-8.

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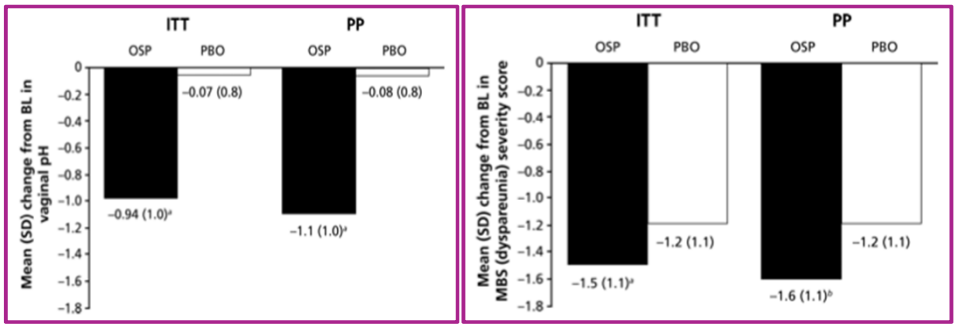
Ospemifene and Dyspareunia Associated with VVA

Change in baseline to week 12



pH

P <0.0001 versus placebo

MBS Dyspareunia

P =0.0001 versus placebo

57% change from baseline score of 2.7

Portman DJ, Bachman GA, Simon JA Menopause 2013; 20(6):1-8.

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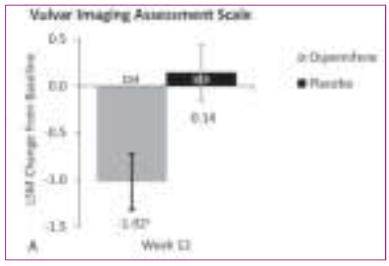
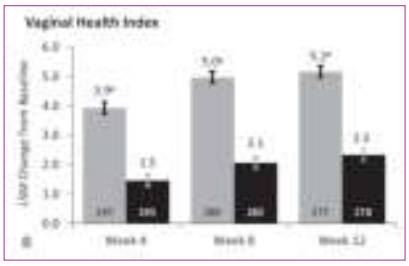
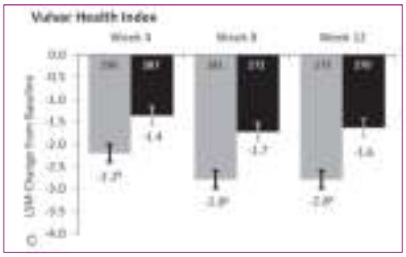
Ospemifene Effects on Genitourinary Health Assessed by Prospective Vulvar-Vestibular Photography and Vulvovaginal Health Indices







a P<0.0001;
b P=0.0002; c P=0.0154 versus placebo n's are indicated in the bars.

Goldstein I, et al. Menopause 2019;26(9):1-8.

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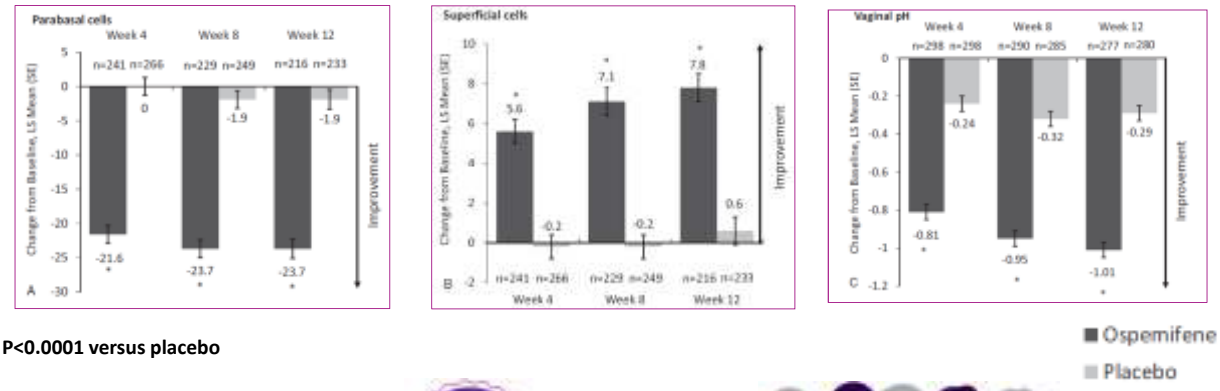
Ospemifene Efficacy in Postmenopausal Women with Moderate-to-Severe Vaginal Dryness



P<0.0001 versus placebo

Archer DF, et al. Menopause 2019;26(6):1-11.

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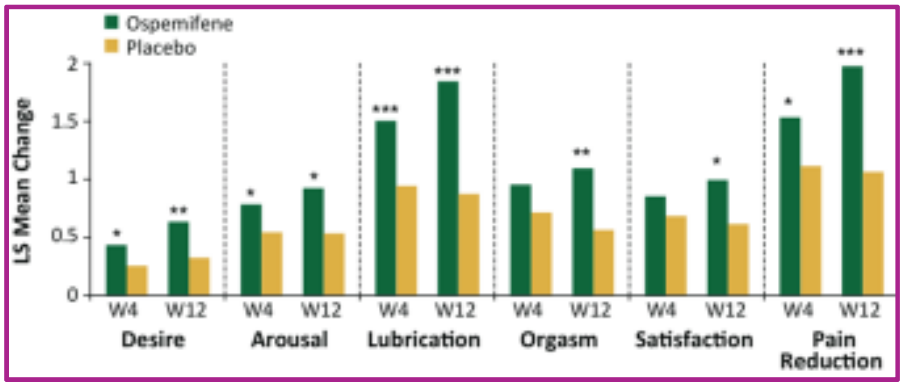
Ospemifene and Female Sexual Function Index (FSFI)

Change from Baseline to Weeks 4 and 12 (LOCF) in FSFI Domain Scores Dyspareunia Strata



*P<0.05 compared with placebo
**P<0.001 compared with placebo
***P<0.0001 compared with placebo

Constantine GD et al The Endocrine Society 95th Annual Meeting
June 15-18, 2013 San Francisco, CA

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

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

	Number (%) of Subjects		
Preferred Term	Placebo (n=958)	Ospemifene 30 mg (n=352)	Ospemifene 60 mg (n=1242)
Any CV-related TEAE	2 (0.2)	1 (0.3)	4 (0.3)
Cerebrovascular Accident	1 (0.1)	1 (0.3)	1 (0.1)
Deep Vein Thrombosis	1 (0.1)	0	2 (0.2)
Cerebral Haemorrhage	0	0	1 (0.1)

Note: Subjects given ospemifene ≤15 mg (n=62) and 90 mg (n=40) had no cardiovascular events.
If a subject had more than 1 TEAE that coded to the same preferred term, the subject was counted only once for that preferred term.
Preferred terms are sorted in descending frequency in all the ospemifene group.
CV – cardiovascular; TEAE – treatment-emergent adverse event

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.

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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

Simon J, Lin V, Radovich C et al Menopause 2013;20:418-427.

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Ospemifene 12-month Endometrial Histologic Biopsy Characteristics

Variable n (%)	*Ospemifene* 60mg/d (n=364)		*Placebo* (n=62)	
Histologic Characteristics	**Baseline**	**Week 52**	**Baseline**	**Week 52**
Tissue insufficient for dx	59 (16.2)	27 (8.7)	8 (12.9)	11 (19.6)
Atrophic	300 (82.4)	267 (86.1)	52 (83.9)	45 (80.4)
Inactive	1(0.3)	1 (0.3)	1 (1.6)	0 (0)
Weakly proliferative	1 (0.3)	7 (2.3)	0 (0)	0 (0)
Active proliferative	0 (0)	3 (1.0)	0 (0)	0 (0)
Hyperplasia	0 (0)	1 (0.3)	0 (0)	0 (0)

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

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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

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

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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?

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