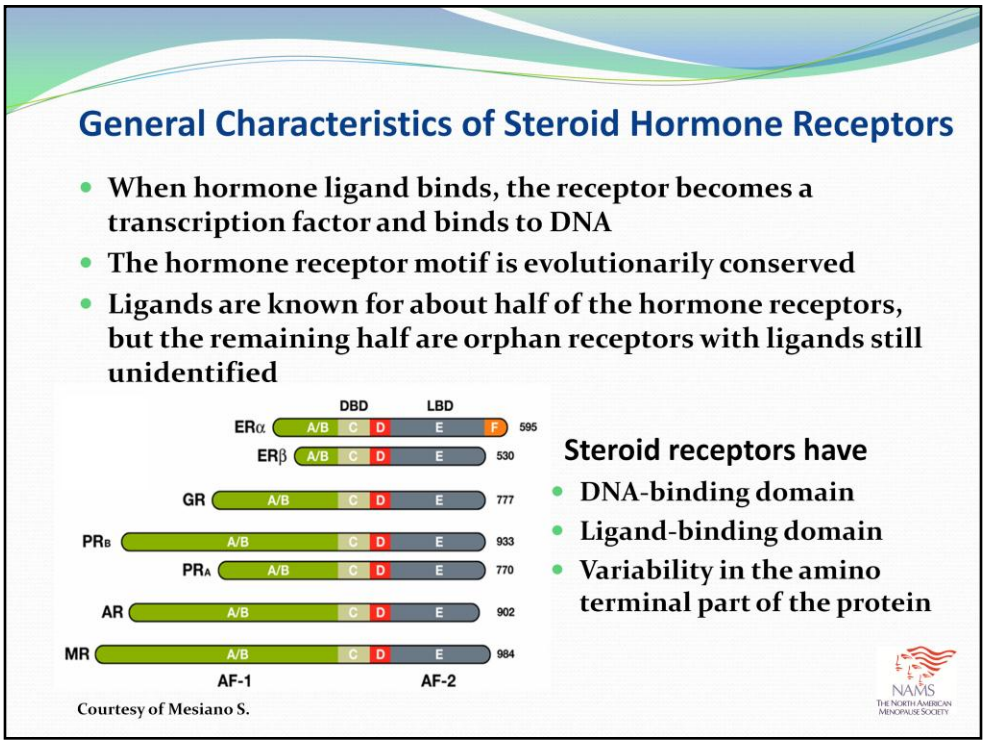
Selective Estrogen Receptor Modulators (SERMs)

Also known as Estrogen Receptor Agonists/Antagonists (ERAAs)

Background and Mechanisms

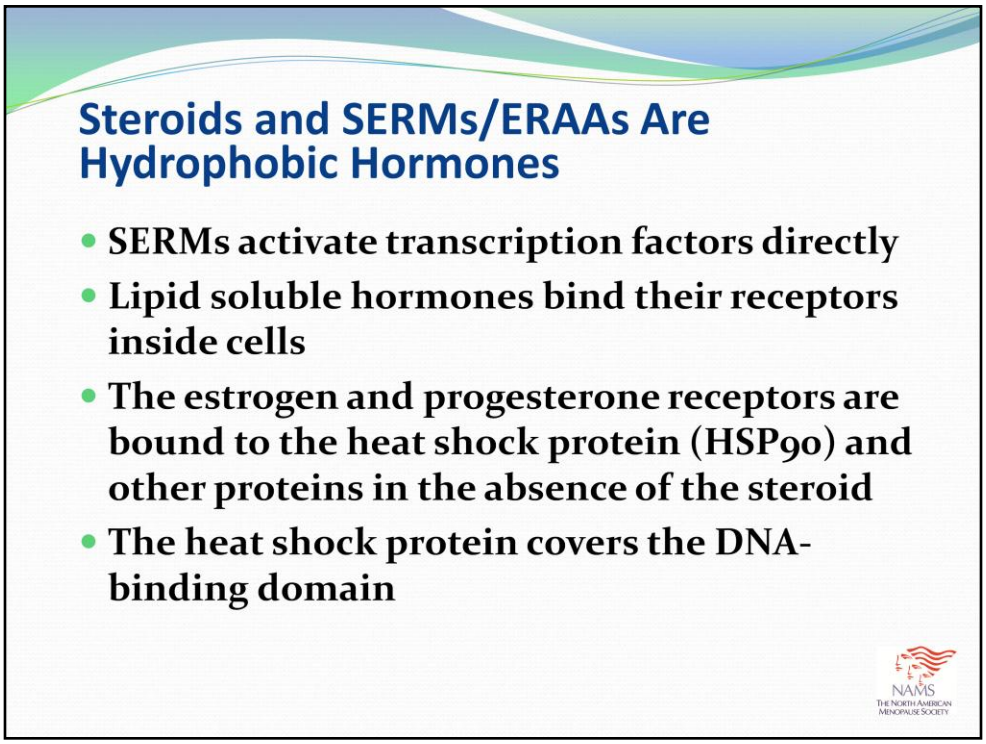


KEY CONCEPTS

- Selective estrogen receptor modulators (SERMs), also known as estrogen agonists/antagonists (ERAAs), need to interact with estrogen receptors alpha and beta (ER-α and ER-β)
- The hormone-like ligand binds to the receptor through a ligand-binding domain (LBD)

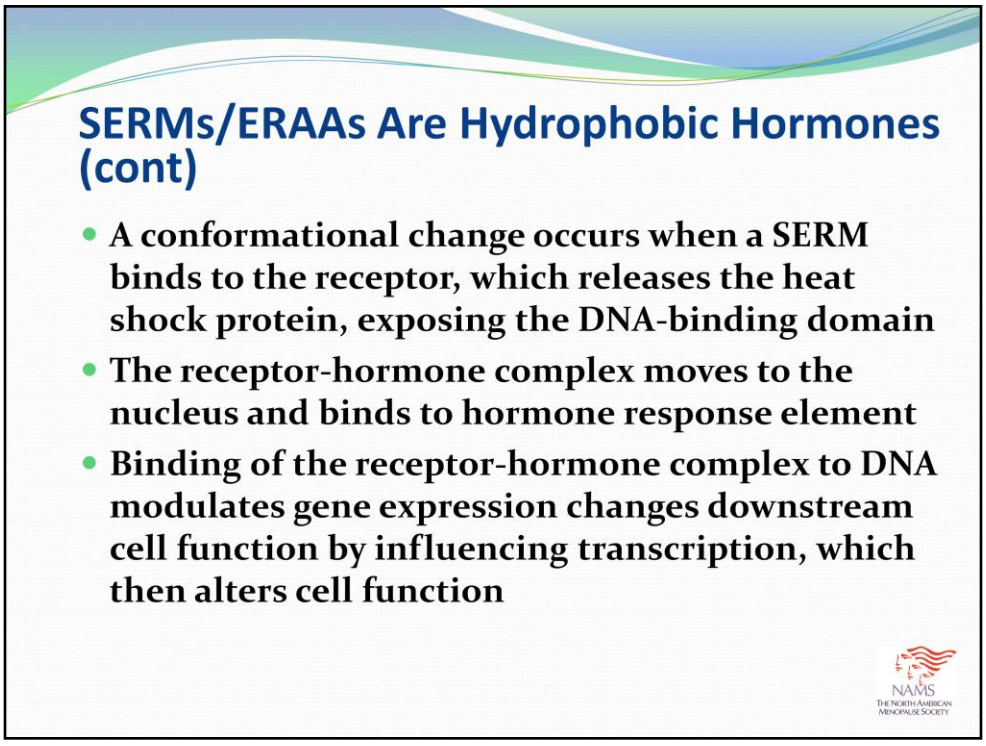
DIVE DEEPER

- Drugs that have been designed to have hormone-mimicry properties need to interact with hormone receptors.
- In the case of SERMs, ER-α and ER- β are potential targets. The general template for this interaction is that the hormone-like ligand binds to the receptor through an LBD.
- This entire complex in its new molecular conformation then binds to DNA via a specific DNA-binding site (DBD) and becomes a transcription factor for RNA transcription.
- The common structural components of the various steroid receptors are shown in the slide for the estrogen receptor (ER), glucocorticoid receptor (GR), progesterone receptors A and B (PRa and PRb), androgen receptor (AR), and the mineralcorticoid receptor (MR).
- The hormone receptor motif is evolutionarily conserved; more than 70 members of this receptor superfamily have been described in species ranging from fruit flies to humans.



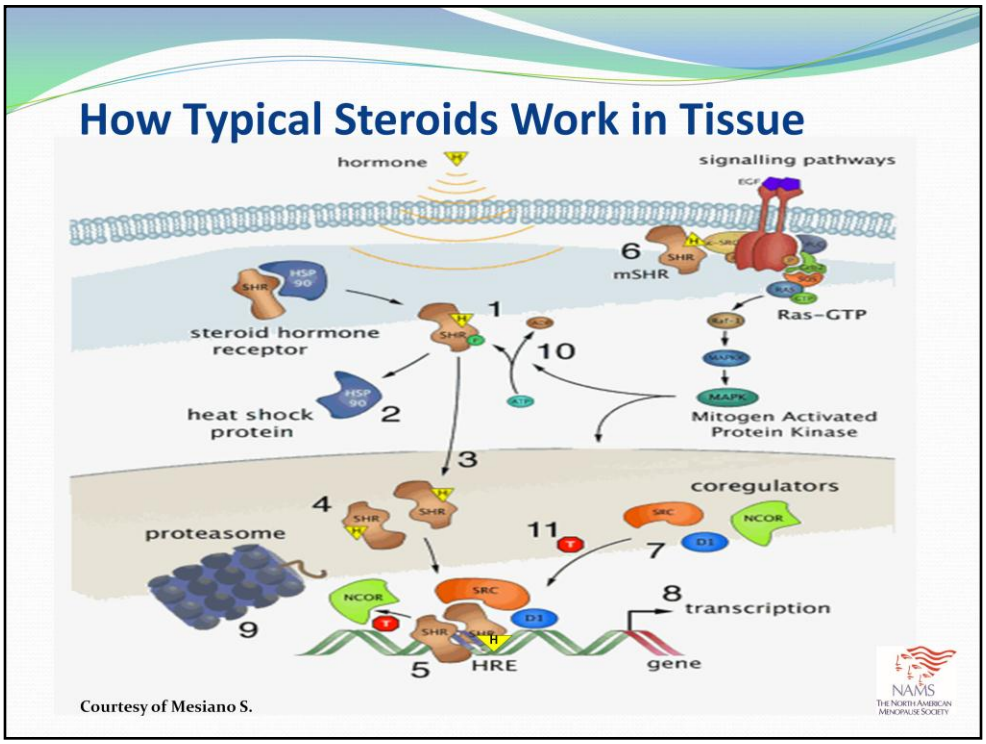
KEY CONCEPTS

- How steroid hormones act
  - SERMs (ERAAs) are hydrophobic and lipid soluble and thus can pass through the cell membrane into cytoplasm
  - In the cytoplasm, the steroid receptor is bound to heat shock protein (HSP 90) and other proteins in the absence of the steroid
  - The heat shock protein covers the DNA-binding domain



KEY CONCEPTS

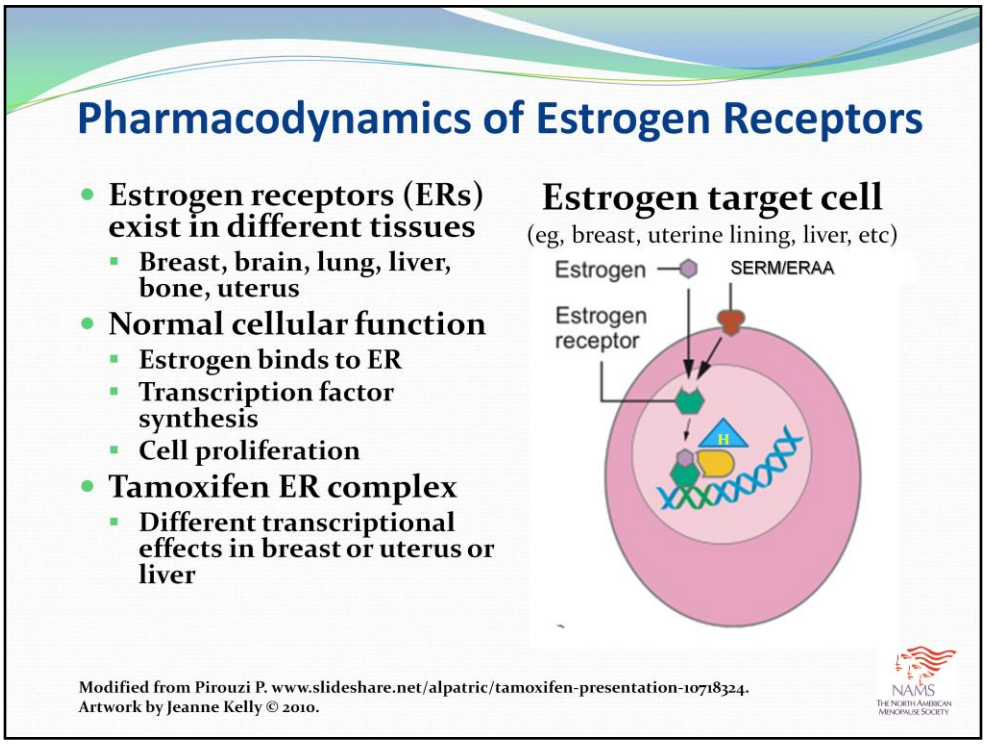
- Changes that occur to modulate downstream cell function
  - A conformational change occurs when the steroid or SERM binds to the receptor
  - This hormone receptor complex then binds to a specific DNA conformation
  - Gene expression then takes place through RNA transcription
  - Downstream cell function can be altered



KEY CONCEPTS

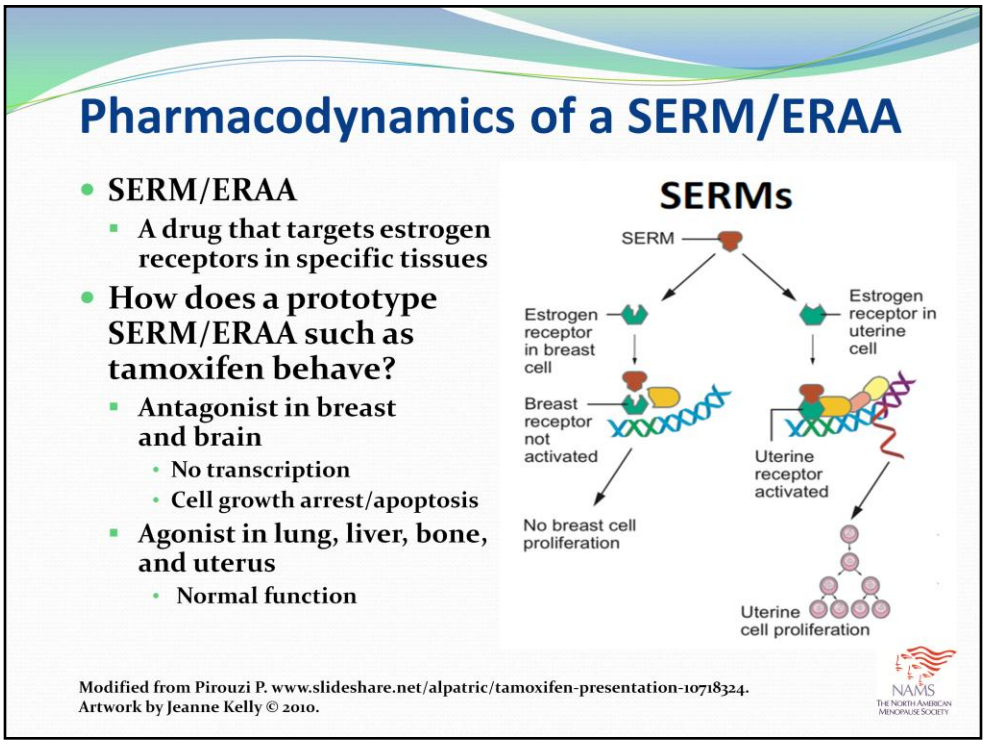
- During transcription, the binding of the hormone-receptor complex to the hormone response element can be modified by tissue-specific factors
  - These tissue specific factors include steroid hormone coactivators and nuclear hormone receptor corepressors
  - SERMs and estrogen differ in their ability to bind coactivators and corepressors (step 5 in illustration)
  - The differences in binding leads to different downstream cell effects

Abbreviations: EGF, epidermal growth factor; HRE, hormone-responsive element; NCOR, nuclear hormone receptor corepressor; SHR, steroid hormone receptor; SRC, steroid hormone coactivator.



KEY CONCEPTS

- Estrogen receptors (ERs) exist in many tissues, including the breast, brain, lung, liver, bone, and uterus
- Target tissues that respond to estrogen all contain ERs; however, the target tissues may contain different coactivators and corepressors that alter the transcriptional efficiency of the hormone-receptor complex
- Normally, estrogen binds to the ER and is involved in transcription and leads to cell proliferation
- SERMs/ERAAs such as tamoxifen compete with native estrogen for binding with the ER
- The newly formed tamoxifen ER complex has different transcriptional efficiencies (works differently through the ER) than estrogen and works differently in breast tissue versus uterine lining versus liver
- Part of the reason for the different downstream effects of the tamoxifen ER complex is the different coactivators and corepressors found in these tissues

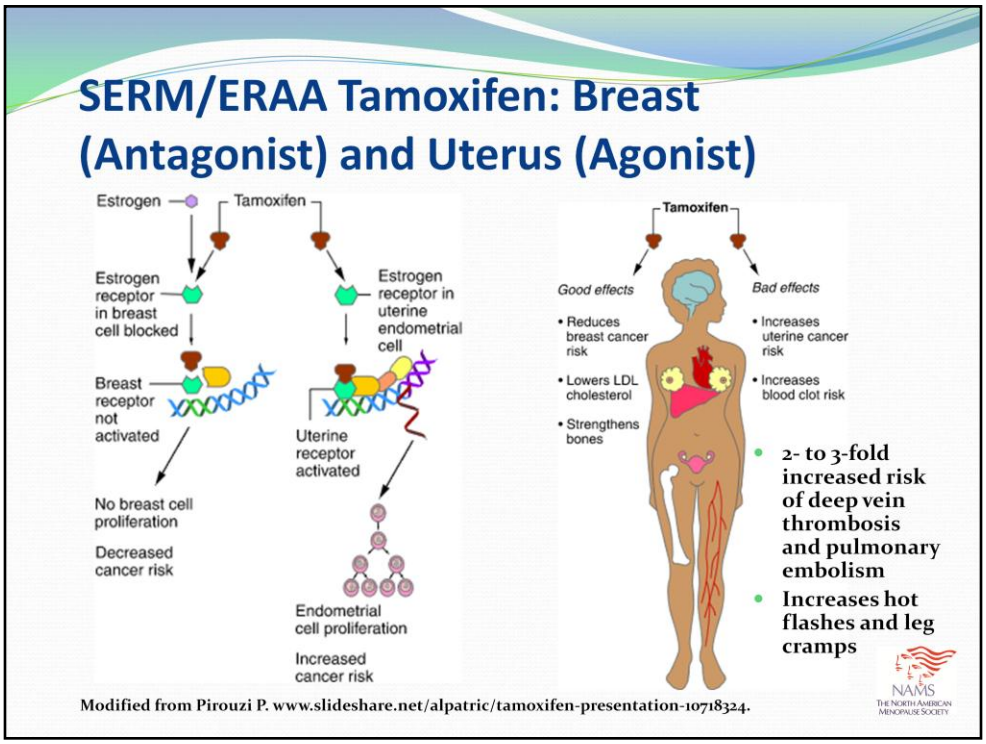


KEY CONCEPTS

- Tamoxifen is an estrogen antagonist in both breast and brain—the bound SERM (ERAA)-receptor complex results in no transcription in the breast and the brain
- Tamoxifen is an estrogen agonist in lung, liver, bone, and uterus, thus the bound complex activates the receptors in these tissues

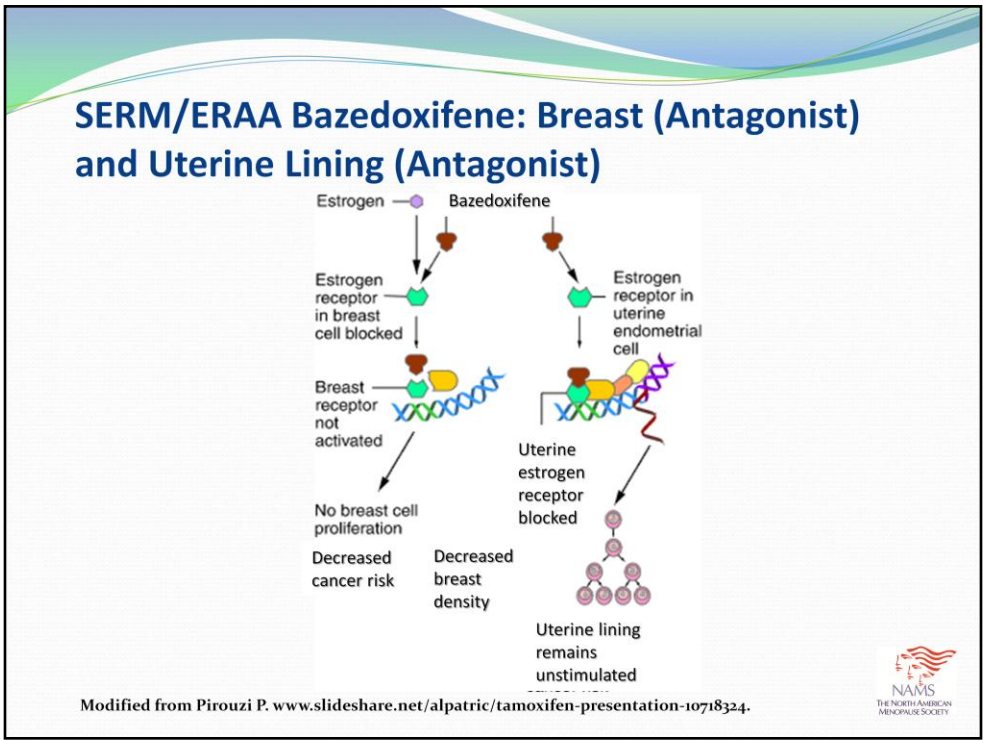
DIVE DEEPER

- In the breast and brain, in which the tamoxifen bound ER complex is an antagonist, tamoxifen competes against the formation of the normal interaction between estrogen and its receptor complex. Thus, cell growth in those two tissues are inhibited, or apoptosis occurs.
- In contrast, the tamoxifen-receptor complex in the liver, bone, and uterus behaves more like estrogen, and normal function is retained in those tissues because tamoxifen behaves as an estrogen agonist.



KEY CONCEPTS

- Different SERMs have different effects on different tissue cells
- On the basis of its tissue-specific behaviors, tamoxifen is an estrogen agonist in uterus, bone, and liver and an estrogen antagonist in the breast
- Specific effects of tamoxifen
  - Estrogen antagonist in the breast; reduces breast cancer risk
  - Estrogen agonist in the liver—lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol
  - Estrogen agonist in the bone; inhibits bone resorption with reduced bone mineral turnover and reduced bone loss
  - Estrogen agonist in the uterus, with increased risk of uterine cancer similar to estrogen
  - SERM and estrogen-like effect in increasing risk of blood clots and pulmonary embolism
  - Increases hot flashes and leg cramps



KEY CONCEPTS

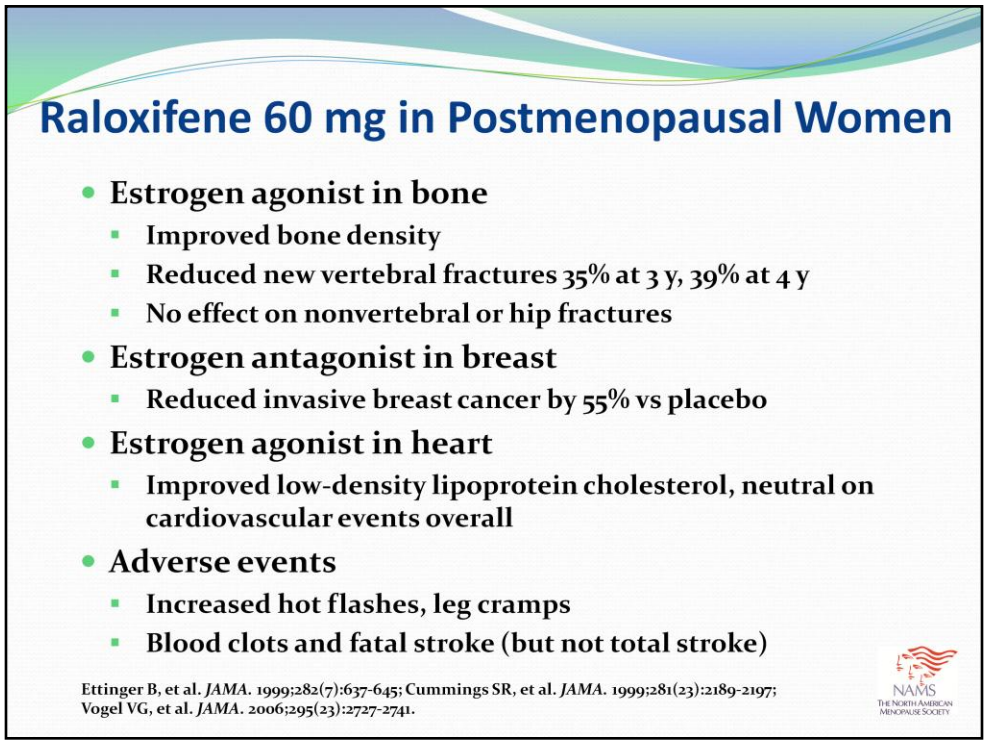
- Different SERMs have different tissue effects
- The SERM/ERAA bazedoxifene exhibits different tissue-selective properties than tamoxifen
- In breast tissue, bazedoxifene is an estrogen antagonist and will inhibit breast cell proliferation
- In uterine endometrial tissue, bazedoxifene is an estrogen antagonist and prevents stimulation of the uterine lining by estrogen

DIVE DEEPER

- SERMs have different affinities for estrogen receptors
- Some may be more strongly estrogen agonistic effect in uterus (ie, tamoxifen more estrogenic in uterus than ospemifene)
- Some may have stronger estrogen antagonistic effects in uterus (ie, bazedoxifene more antagonistic in uterus than raloxifene)
- This makes understanding the unique estrogen agonist and antagonist effects more important

Selective Estrogen Receptor Modulators (SERMs)

Clinical Data: FDA-approved SERM/ERAA Raloxifene

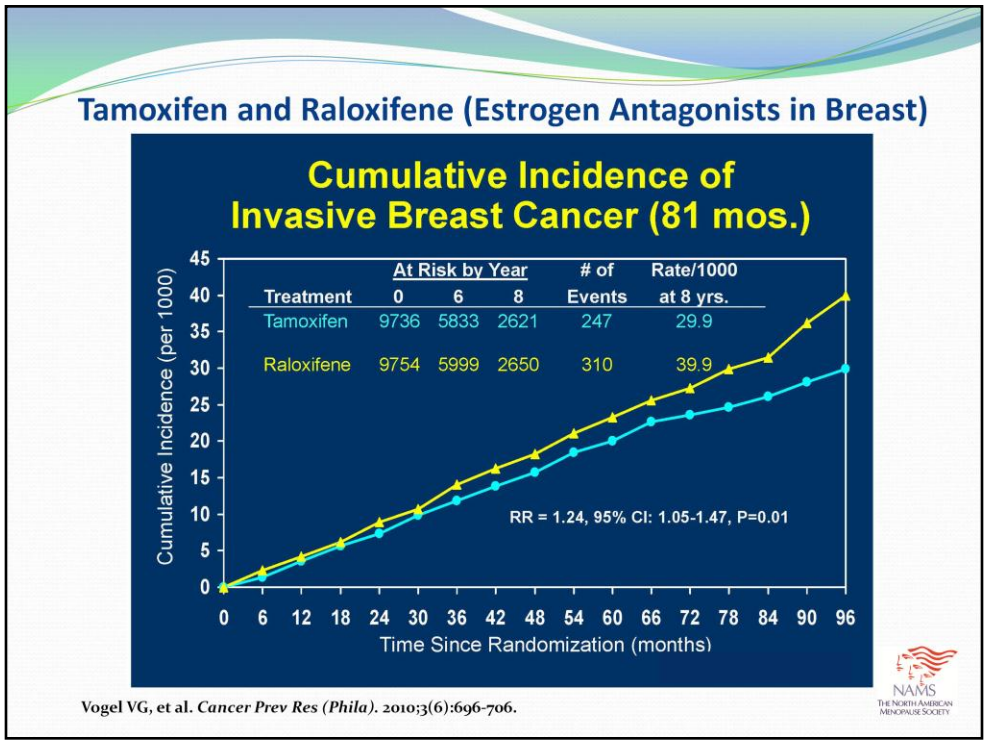


KEY CONCEPTS

- Raloxifene is a SERM (estrogen agonist/antagonist) used in postmenopausal women at 60 mg/d
- Estrogen agonist in bone—improves bone density and reduces new vertebral fractures by 35% at 3 y, 39% in 24 y; no effect on nonvertebral fractures or hip fractures
- Estrogen antagonist in breast—reduced invasive breast cancer by 55% compared with placebo
- Estrogen agonist in heart—improved low-density lipoprotein cholesterol, neutral on cardiovascular (CV) events overall
- Similar to estrogen; increased hot flashes, leg cramps, blood clots, and fatal stroke (but not total stroke)

DIVE DEEPER

- The Multiple Outcomes of Raloxifene Evaluation (MORE) trial
  - Large double-blind, placebo-controlled trial of postmenopausal women with osteoporosis, enrolling 7,705 women (average age, 67 y) at 180 sites in 25 countries. Trial consisted of a 3-y core treatment phase with a 1-y extension phase.
  - Raloxifene increased the risk of venous thromboembolism (VTE) 2- to 3-fold over placebo in postmenopausal women with osteoporosis
  - CV events over 4 y in subset of women with higher CV risk
- MORE trial results supported by Study of Tamoxifen and Raloxifene (STAR) trial
  - Both tamoxifen and raloxifene lowered risk of invasive breast cancer by ~50% in postmenopausal women at higher risk of disease
  - Women who took raloxifene (vs tamoxifen) daily for 4 y had 36% fewer uterine cancer; 29% fewer blood clots



KEY CONCEPTS

- Tamoxifen (20 mg/d) and raloxifene (60 mg/d) are estrogen antagonists in the breast
- Both are good preventive choices for postmenopausal women with elevated risk for breast cancer
- Graph shows mean 81-mo median follow-up data from the extended Study of Tamoxifen and Raloxifene (STAR) trial of women on either tamoxifen or raloxifene for 5 y
  - Long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to tamoxifen in preventing noninvasive disease with far less toxicity (highly significantly less endometrial cancer)
  - Raloxifene would be expected to reduce the risk of invasive breast cancer by about 38% versus the 50% reduction seen with tamoxifen

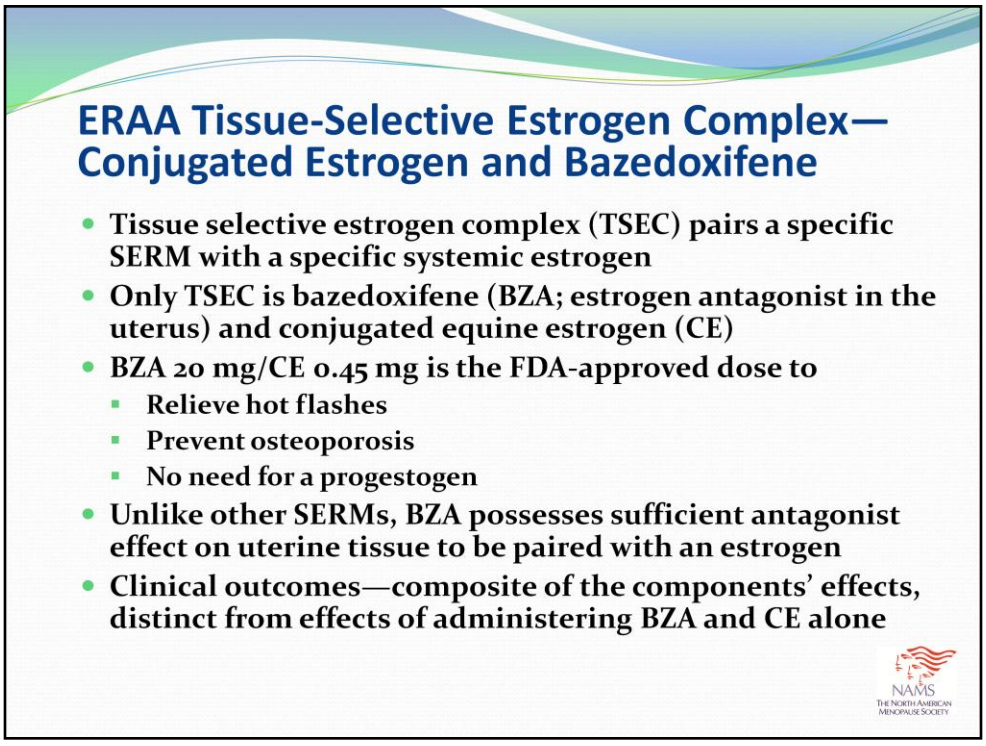
DIVE DEEPER

- Compared with initial results, relative risk (RR) ratios widened for invasive and noninvasive breast cancer
  - Toxicity RRs were 0.55 for endometrial cancer (not significant in the initial results), 0.19 for uterine hyperplasia, and 0.75 for thromboembolic events
  - No significant mortality differences
  - Invasive breast cancer RR ratio of raloxifene:tamoxifen was 1.24, indicating that the rate in the raloxifene group was about 24% higher than the rate in the tamoxifen group
- In the Breast Cancer Prevention Trial (Fisher B, et al. *J Natl Cancer Inst*. 1998;90[18]:1371-1388), compared with placebo, tamoxifen reduced the risk of invasive breast cancer by about 50%

Selective Estrogen Receptor Modulators (SERMs)

Clinical Data: Tissue-selective Estrogen Compounds (TSECs)

The SMART (Selective estrogen, Menopause, and Response to Therapy) trials

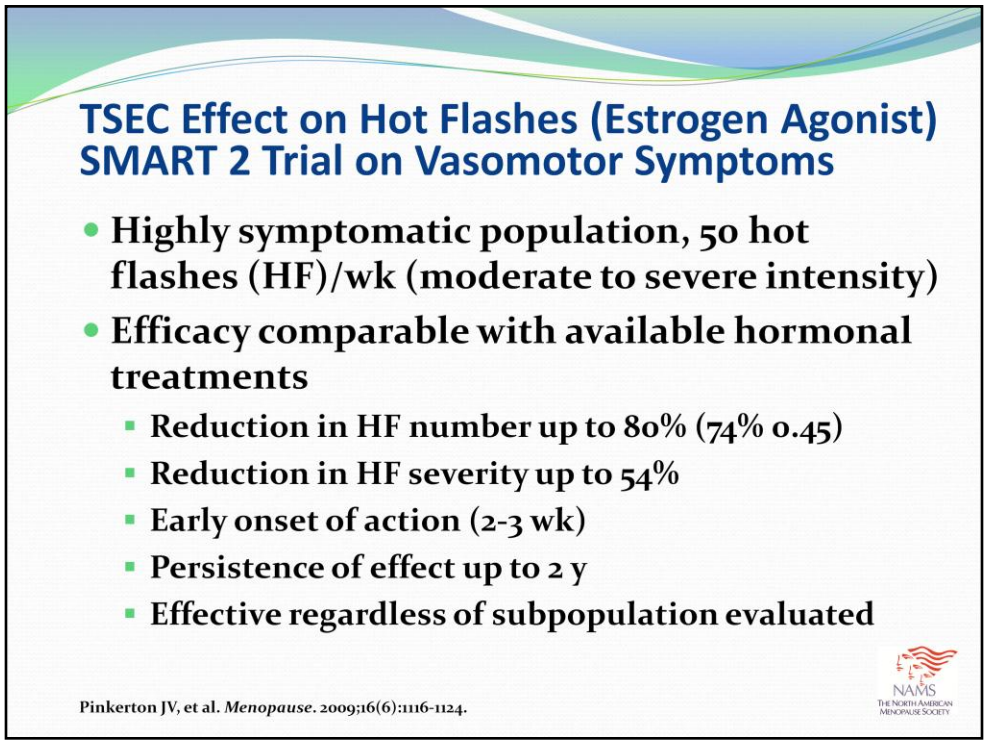


KEY CONCEPTS

- A tissue-selective estrogen complex (TSEC) pairs a specific SERM (ERAA) with a specific systemic estrogen
- The only FDA-approved TSEC consists 20 mg of bazedoxifene (BZA) paired with 0.45 mg conjugated equine estrogen (CE) to relieve hot flashes and prevent bone loss
- SERMs have varying antagonist effects on the uterus
- Bazedoxefine has sufficient antagonist effect on the uterus that it can be safely paired with a specific estrogen, CE, without endometrial stimulation

DIVE DEEPER

- The SERM must have sufficient estrogen antagonist effect to protect against the systemic estrogen's effect on the uterus
- The TSEC BZA/CE has a clinical outcome that depends on combining these two compounds into one product
- Clinical efficacy and safety are dependent on the specific SERM, specific estrogen, and specific dosing of each
- Future TSECs need to be evaluated in rigorous clinical trials to identify clinical effects on hot flashes, bone, breast, and endometrium, as well as thrombotic risk

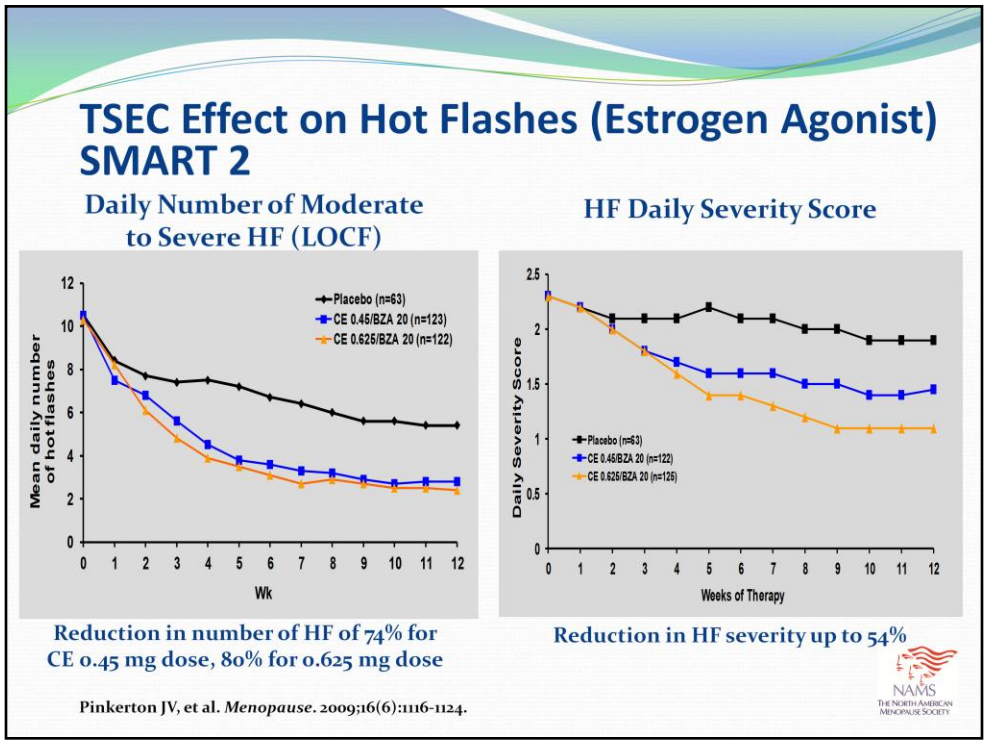


KEY CONCEPTS

- The SMART 2 trial evaluated highly symptomatic postmenopausal women with a uterus
- Showed effective, persistent hot flash improvement of up to 80% in frequency and 54% in severity

DIVE DEEPER

- The SMART trials 1, 2, 3, 4, and 5 were randomized, placebo-controlled trials that included generally healthy postmenopausal women with an intact uterus and who had endometrial biopsies that could be evaluated (Lobo RA, et al. *Fertil Steril*. 2009;92[3]:1025-1038)
- Across trials, participants were primarily white; average body mass index was 26; and included women <5 y and >5 y from menopause (average age, 53-57 y)
- Key exclusion criteria
  - Abnormal pap smear or breast findings
  - Nonmeasurable thickness or unacceptable endometrial thickness (>4 mm)
  - Insufficient tissue or unacceptable endometrial biopsy confirmed by two pathologists

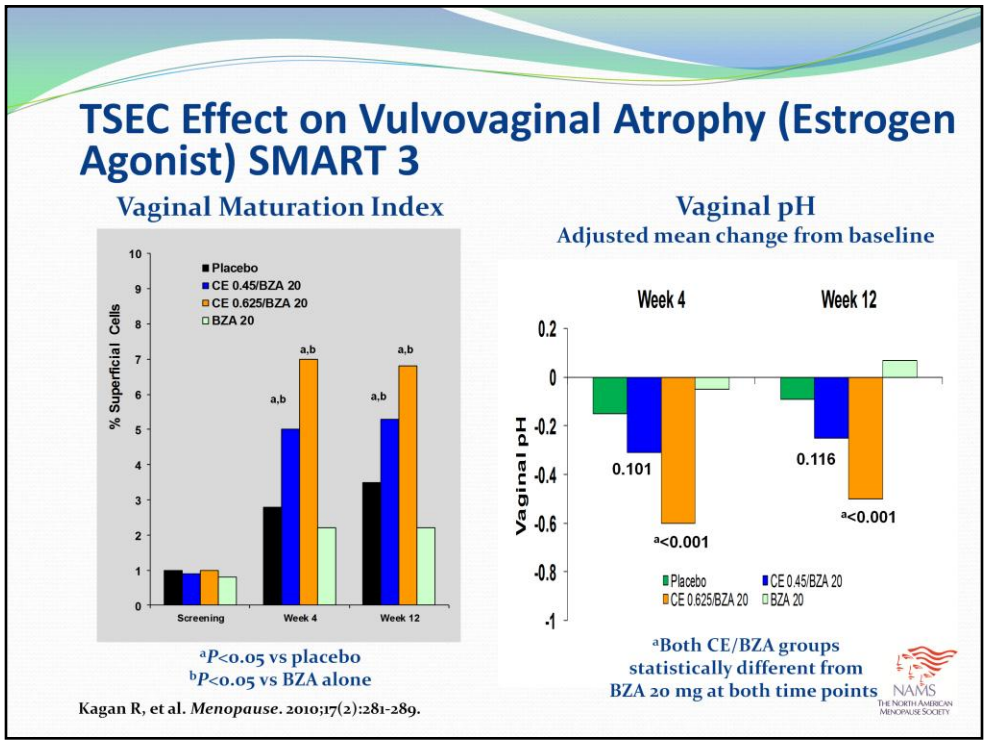


KEY CONCEPTS

- In SMART 2, hot flash frequency and severity were decreased
- Although both doses (BZA 20 mg with CE 0.45 mg or 0.625 mg) reduced number and severity of hot flashes more than placebo, the higher dose had more reduction in severity

DIVE DEEPER

- SMART 2 was a multicenter, double-blind, randomized, placebo-controlled, phase 3 study conducted in the United States
- Healthy postmenopausal women (N = 332, aged 40-65 y) with moderate to severe hot flashes (≥7/d or 50/wk) were randomized to BZA 20 mg/CE 0.45 mg; BZA 20 mg/CE 0.625 mg; or placebo once daily for 12 wk
- Changes from baseline in the average daily number of moderate and severe hot flashes and daily severity scores were assessed at wk 4 and 12; adverse events were recorded
- BZA/CE significantly reduced the number and severity of hot flashes at wk 4 and 12 ($P < .001$)
- At wk 12, BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg reduced hot flashes from baseline by 74% (10.3 hot flashes [baseline] vs 2.8 [wk 12]) and 80% (10.4 [baseline] vs 2.4 [wk 12]), respectively, compared with 51% (10.5 [baseline] vs 5.4 [wk 12]) for placebo
- More participants at wk 12 had at least a 75% decrease in hot flashes with BZA 20 mg/CE 0.45 mg (61%) and BZA 20 mg/CE 0.625 mg (73%) vs placebo (27%; $P < .001$)
- Safety profile was similar between BZA/CE and placebo, with no unexpected safety findings

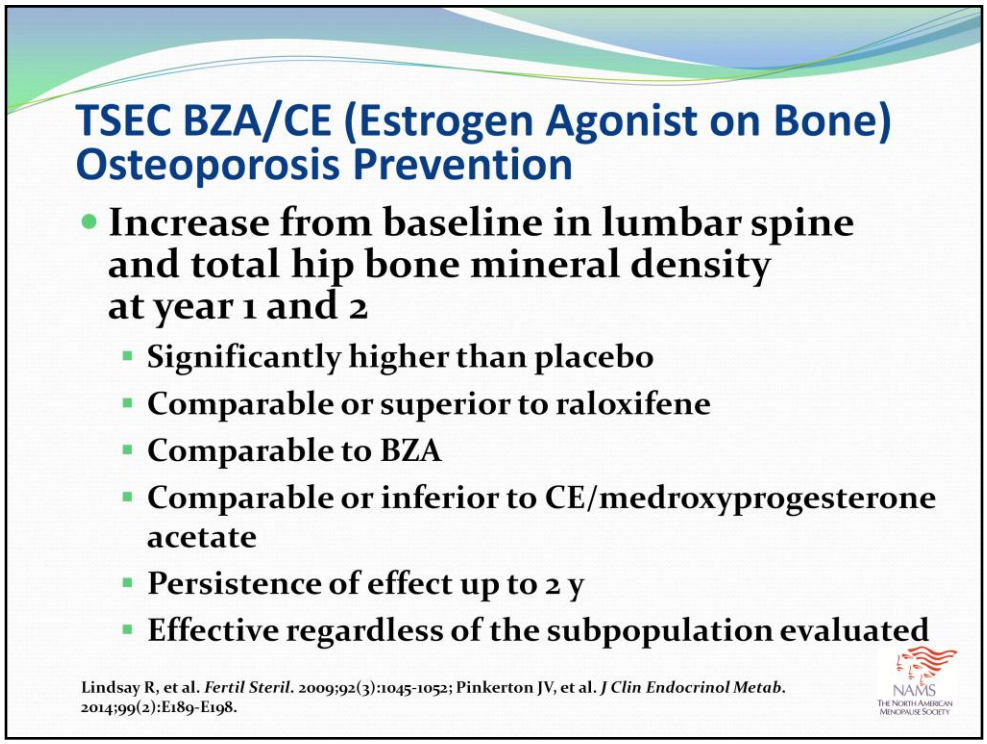


KEY CONCEPTS

- In the SMART 3 trial in postmenopausal women with moderate to severe vulvovaginal atrophy (VVA), BZA 20 mg alone was similar to placebo for vaginal maturation index (VMI) and vaginal pH
- BZA combined with CE showed improvement in VMI and vaginal pH
- Greater improvements ($P < .001$) were seen with the higher CE 0.625-mg dose compared with 0.45 mg; however, both doses were statistically different compared with BZA 20 mg alone at 4 and 12 wk

DIVE DEEPER

- SMART 3 was a phase 3, multicenter, double-blind, randomized, placebo-controlled, active comparator-controlled study
  - Healthy postmenopausal women (N = 664 aged 40-65 y) with moderate to severe VVA were randomized to BZA 20 mg; BZA 20 mg/CE 0.45 mg; BZA 20 mg/CE 0.625 mg; or placebo once daily for 12 wk
  - Changes in VMI, vaginal pH, and severity of the most bothersome symptom of VVA from baseline were assessed at screening and at wk 4 and 12
  - Adverse events were recorded throughout the study
- Efficacy for BZA 20 mg/CE 0.625 mg demonstrated in 4 coprimary endpoints; showed persistence of efficacy up to 2 y (VMI)
  - Proportion of vaginal superficial cells
  - Proportion of parabasal cells
  - Vaginal pH statistical difference
  - Severity of the most bothersome vulvar/vaginal symptom improved by 56%
- In addition, vaginal pH improved with BZA 20 mg/CE 0.45 mg compared with BZA alone or placebo

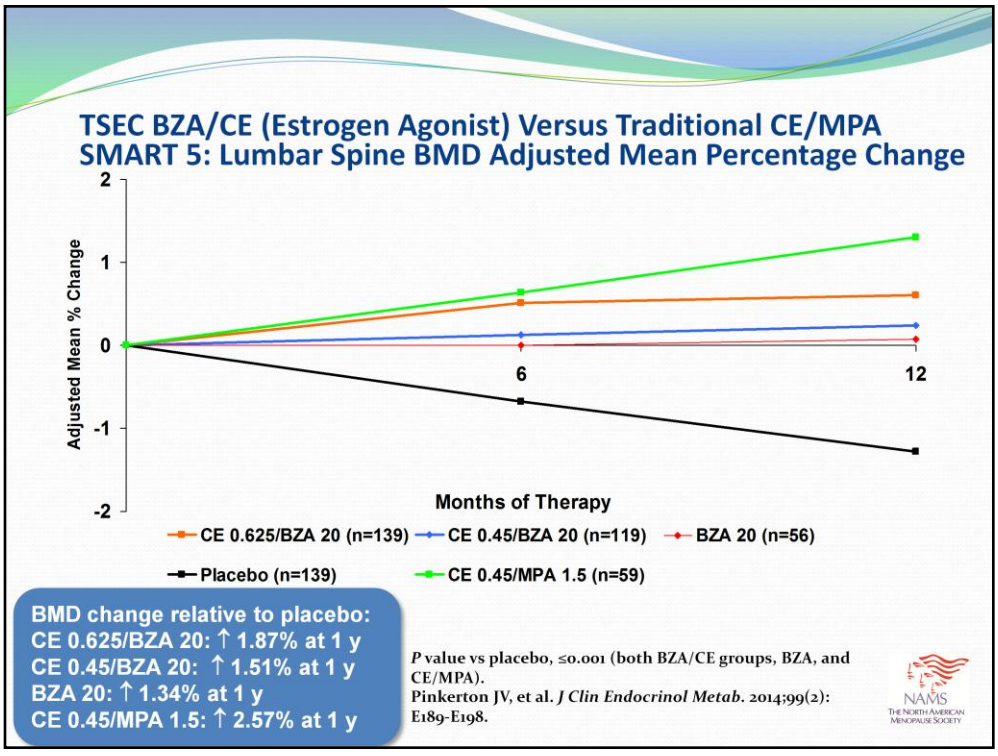


KEY CONCEPTS

- BZA 20 mg/CE 0.45 mg is FDA approved for prevention of bone loss (tested in SMART 1 and SMART 4)
- Both doses BZA 20 mg/CE 0.45 mg or CE 0.625 mg were significantly better than placebo at increasing bone density
- TSEC effect on bone was comparable to BZA alone, raloxifene, and traditional CE 0.45 mg/medroxyprogesterone acetate (MPA) 1.5 mg
- Persistence of bone increase seen to 2 y in SMART 1
- No fracture data available for BZA 20 mg/CE 0.45 mg

DIVE DEEPER

- SMART 1—at 2 years, BZA 20 mg/CE 0.45 mg increased bone mineral density (BMD) at the spine 3.61% relative to placebo; BZA 20 mg/CE 0.625 mg increased BMD at the spine 3.72% relative to placebo
- BZA alone is also an estrogen agonist on bone and showed reduction in vertebral fractures
- In 6,847 women in the modified intent-to-treat population, new vertebral fractures at 3 y (Kaplan-Meier estimates) were significantly lower with BZA 20 mg (2.3%), BZA 40 mg (2.5%), and raloxifene 60 mg (2.3%) compared with placebo (4.1%; $P < .05$; Silverman SL, et al. *Bone Miner Res*. 2008;23[12]:1923-1934)

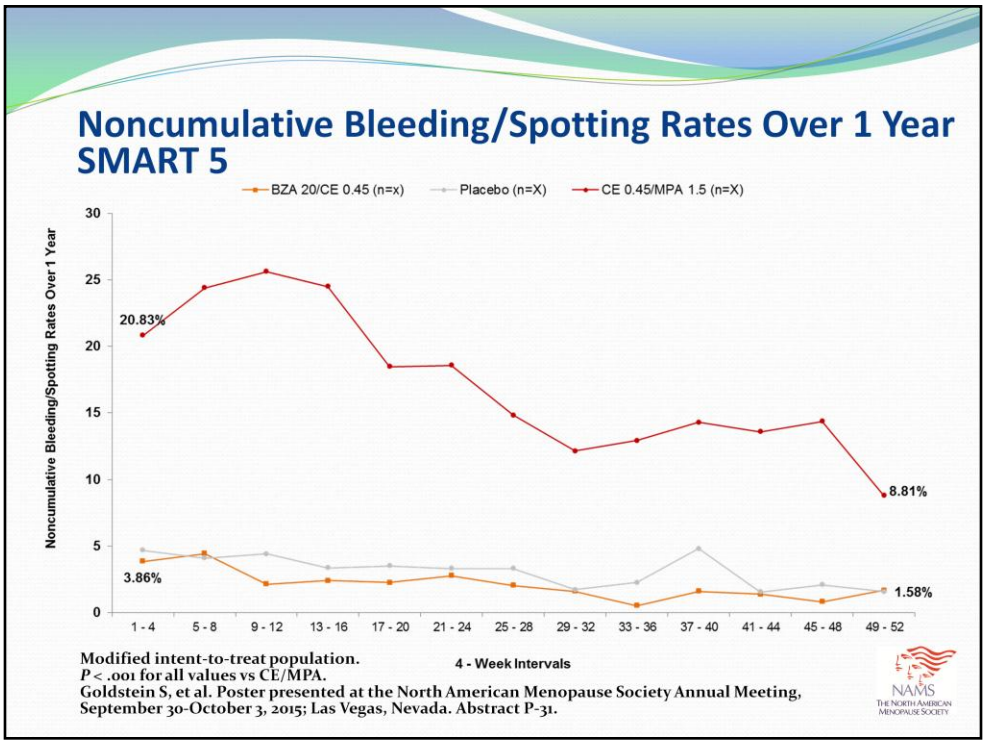


KEY CONCEPT

- SMART 5 1-y trial revealed that BZA 20 mg/CE 0.45 mg and 0.625 mg; BZA 20-mg alone; and active comparator CE 0.45 mg/MPA 1.5 mg all improved bone density compared with placebo

DIVE DEEPER

- SMART 5 data includes CE 0. 0.45 mg and 0.625 mg; BZA 20 mg alone; and active comparator CE 0.45 mg/1.5 mg MPA
- The 20-mg combinations are significantly better than raloxifene at all time points studied
- The BZA/CE group showed significantly greater increases in lumbar spine and total hip bone mineral density (BMD) vs decreases with placebo ($P < .001$); the CE/MPA group had increased lumbar spine BMD compared with that in the BZA/CE group

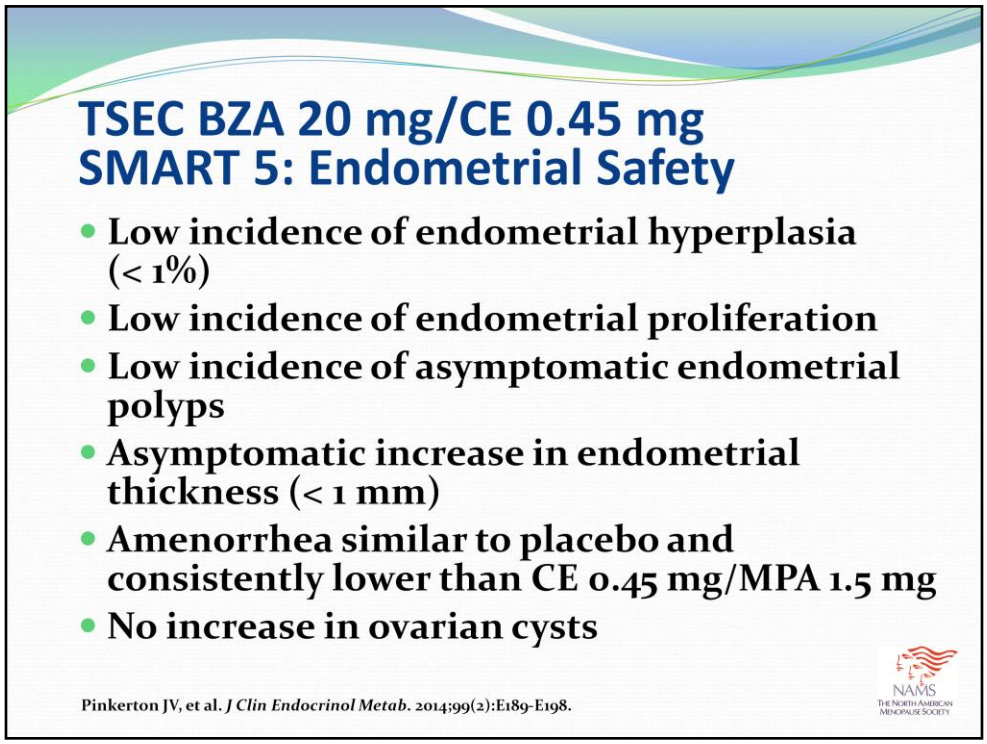


KEY CONCEPTS

- Compared with the TSEC BZA/CE at both doses, CE 0.45 mg/MPA 1.5 mg showed much more significant bleeding/spotting compared with FDA-approved dose BZA 20 mg/CE 0.45 mg
- There is a clear superiority over CE/MPA at any time interval

DIVE DEEPER

- Unscheduled bleeding is the main reason for discontinuation of hormone therapy, especially during the first months of treatment
- SMART 5 included CE/MPA as an active comparator
- Percentage of patients with cumulative amenorrhea, defined as no bleeding or spotting, for each 4-wk interval was based on a daily diary
- Both BZA/CE combinations have a similar bleeding profile to placebo at 1 y
- At month 3, 55% of CE/MPA users had some days of bleeding/spotting
- At month 3, only 10% of BZA/CE users had some bleeding

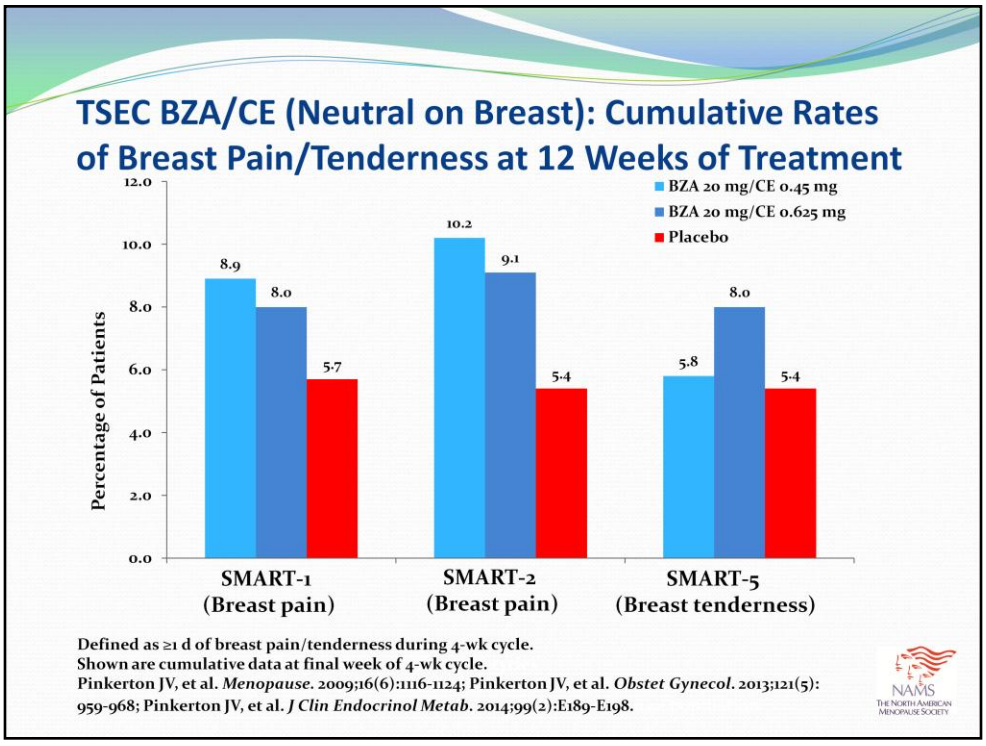


KEY CONCEPTS

- SMART 5 showed endometrial safety of combining BZA 20 mg with CE 0.45 mg and 0.625 mg
- Low incidence of endometrial hyperplasia or proliferation, few polyps
- No significant increase in endometrial lining
- No increase in ovarian cysts
- Bleeding pattern similar to placebo and lower than CE 0.45/MPA 1.5 mg

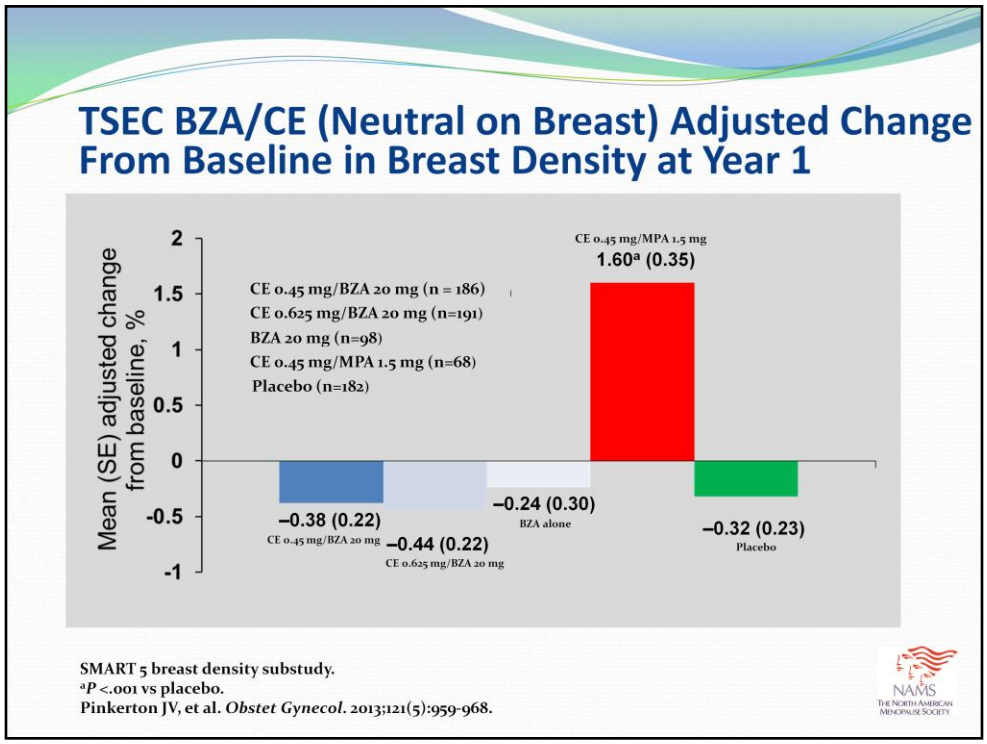
DIVE DEEPER

- The SMART 5 trial was a multicenter, randomized, double-blind, placebo- and active-controlled study in postmenopausal women with intact uteruses (N = 1,843 aged 40-65 y) seeking treatment for menopause symptoms
- Patients received daily oral BZA 20 mg/CE 0.45 or CE 0.625 mg; BZA 20 mg; CE 0.45 mg/ MPA 1.5 mg; or placebo
- Primary endpoints were incidence of endometrial hyperplasia and percent change in lumbar spine bone mineral density (BMD) at 12 mo
- At 12 mo, endometrial hyperplasia incidence was low (<1%) and similar among groups
- The BZA 20 mg/CE 0.45 mg and CE 0.625 mg groups had cumulative amenorrhea rates similar to placebo and BZA and significantly higher than those with CE 0.45 mg/ MPA 1.5 mg ($P < .001$). The incidence of breast tenderness with BZA/CE was similar to that of placebo and BZA and significantly lower than that of CE/MPA ($P < .01$)
- Adverse event (AE) rates were similar among the groups, but incidence of serious AEs overall and AE-related discontinuation rates were higher with CE/MPA than with BZA/CE, BZA, or placebo
- BZA/CE showed low rates of endometrial hyperplasia and improved lumbar spine and total hip BMD and was generally safe and well tolerated



KEY CONCEPTS

- In SMART 1, 2, and 5, the TSEC BZA/CE was similar to placebo for breast pain, whereas traditional CE/MPA had significantly higher rates of breast tenderness
- In SMART 5, CE/MPA had significantly higher rates of breast tenderness than CE/BZA



KEY CONCEPTS

- The TSEC BZA/CE appears neutral on the breast with regard to breast tenderness and breast density
- In SMART 5, in the breast density substudy, breast density rates were similar to placebo for BZA 20 mg/CE 0.45 mg and CE 0.625 mg at year 1
- Traditional CE 0.45 mg/MPA 1.5 mg had significant increase in breast density at year 1

DIVE DEEPER

- SMART 5 included all women enrolled in the breast density substudy who took at least one dose of study drug, had a baseline breast density evaluation, and had at least one postbaseline evaluation
- CE 0.45 mg/MPA 1.5 mg had significant increase in breast density at year 1

More About Breast Density

- Breast density is an independent risk factor for breast cancer
- Concern exists that increase in hormone-stimulated breast density may be associated with higher risk of breast cancer but not proven in randomized, controlled trials
- New onset of tenderness with estrogen-progestogen therapy linked to increase in mammographic density

TSEC CE/BZA (Neutral on Breast) Cumulative Incidence of Breast Cancer Across SMART 1, 2, 3, 4, and 5 (Up to 2 Y)

	BZA 20 mg/ CE 0.45 mg (n = 1,585)	BZA 20 mg/ CE 0.625 mg (n = 1,583)	Placebo (n = 1,241)
Events	4	0	2
Incidence rate per 1,000 women-years (95% CI)	1.0 (0.0-3.2)	0.0 (0.0-1.5)	1.4 (0.0-4.2)
Relative risk (95% CI)	1.1 (0.3-3.8)	0.4 (0.1-2.0)	

Includes cumulative data (up to 2 y) from SMART-1, SMART-2, SMART-3, SMART-4, and SMART-5.
Pinkerton JV, et al. *J Clin Endocrinol Metab*. 2014;99(2):E189-E198.

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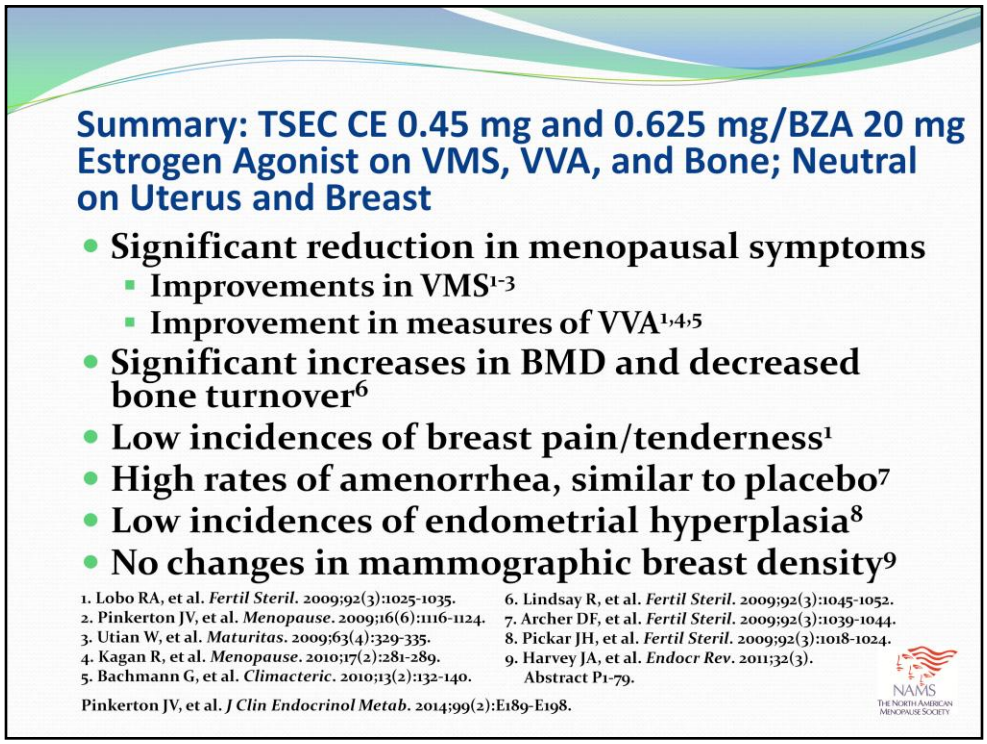
KEY CONCEPTS

- The TSEC BZA/CE appears neutral on breast cancer cases
- The cumulative data from SMART 1, 2, 3, 4, and 5 up to 2 y show no significant difference in breast cancer incidence rates between BZA 20 mg/CE 0.45 mg or CE 0.625 mg compared with placebo



KEY CONCEPTS

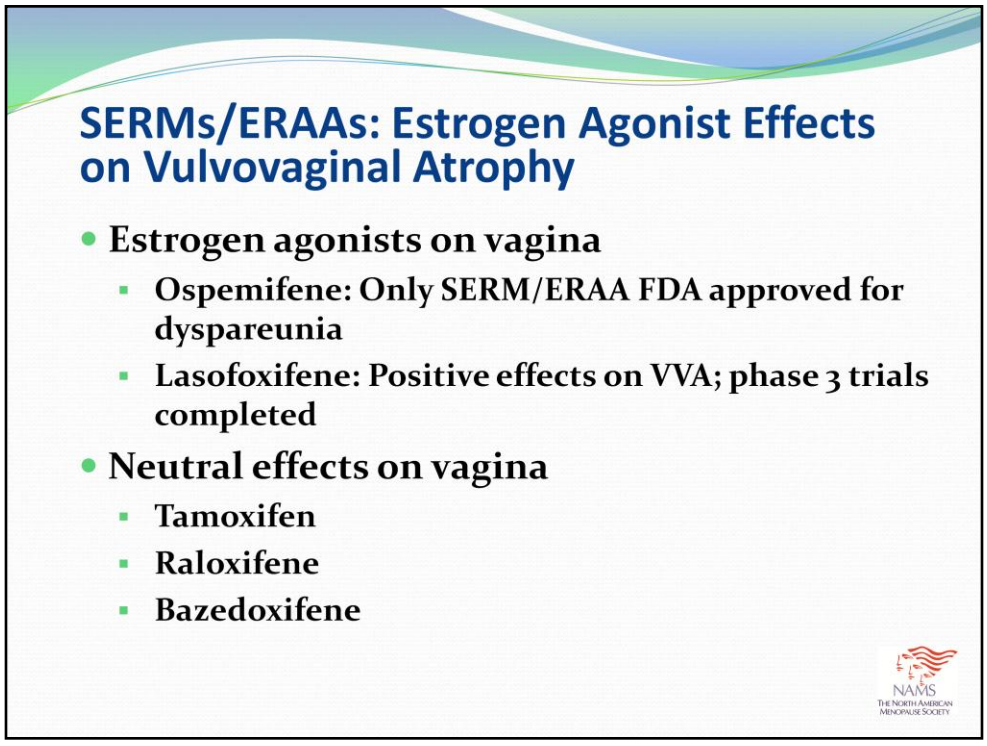
- The TSEC BZA 20 mg/CE 0.45 mg is an FDA-approved estrogen agonist for treatment of hot flashes and prevention of bone loss
- Randomized, controlled trials show relief of hot flashes, vaginal atrophy, and prevention of bone loss, comparable with traditional estrogen-progestogen therapy, without the need for a progestogen
- Because of the estrogen antagonist properties of BZA, the BZA/CE combination appears neutral on the uterus and the breast

DIVE DEEPER

- Both doses CE 0.45 mg and 0.625 mg showed reduction in hot flashes, improvement in VVA, prevention of bone loss (no fracture data available), and low incidence of breast pain and tenderness similar to placebo
- High rates of amenorrhea, similar to placebo and significantly better (less bleeding) than active comparator CE 0.45/MPA 1.5 in SMART 5
- No evidence of uterine stimulation—no endometrial hyperplasia or cancer
- Breast density at 1 y similar to placebo and significantly different from increases in breast density seen with active comparator in SMART 5
- Limited data shows BZA 20 mg/CE 0.45 mg works across populations and other ethnic groups, but small numbers tested

Selective Estrogen Receptor Modulators (SERMs)

Genitourinary syndrome of menopause (vulvovaginal atrophy)

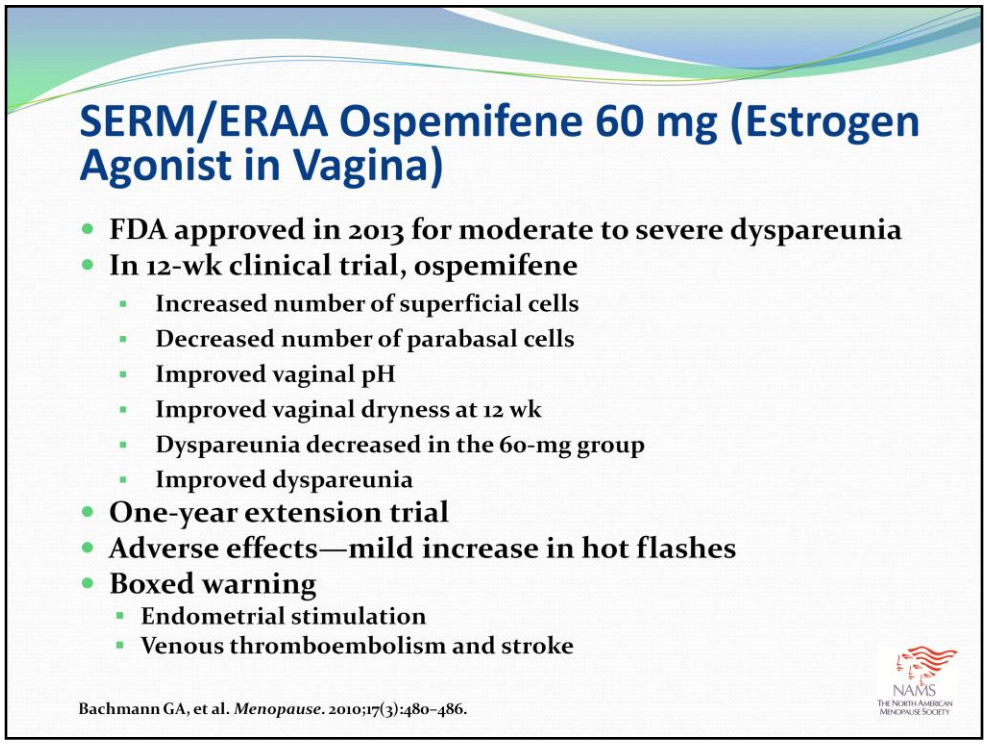


KEY CONCEPTS

- Ospemifene is the only SERM/ERAA with estrogen agonist effects on the vagina
- Ospemifene is FDA approved for moderate to severe dyspareunia of menopause
- Lasofoxifene, a SERM in development, has estrogen agonist effects on vulvovaginal atrophy (VVA)
- SERMs with neutral effects on the vagina include tamoxifen (mixed effects), raloxifene, and bazedoxifene

DIVE DEEPER

- Studies of tamoxifen report small but significant increases in vaginal symptoms and difficulty in sexual functioning
- Some studies has shown beneficial shift in vaginal maturation index (VMI)
- Vaginal tamoxifen is in early development
- Studies of raloxifene treatment demonstrate neutral effect on vaginal mucosa
- Raloxifene did not diminish beneficial effect of vaginal CE cream on subjective signs of VVA and had no negative sexual effects

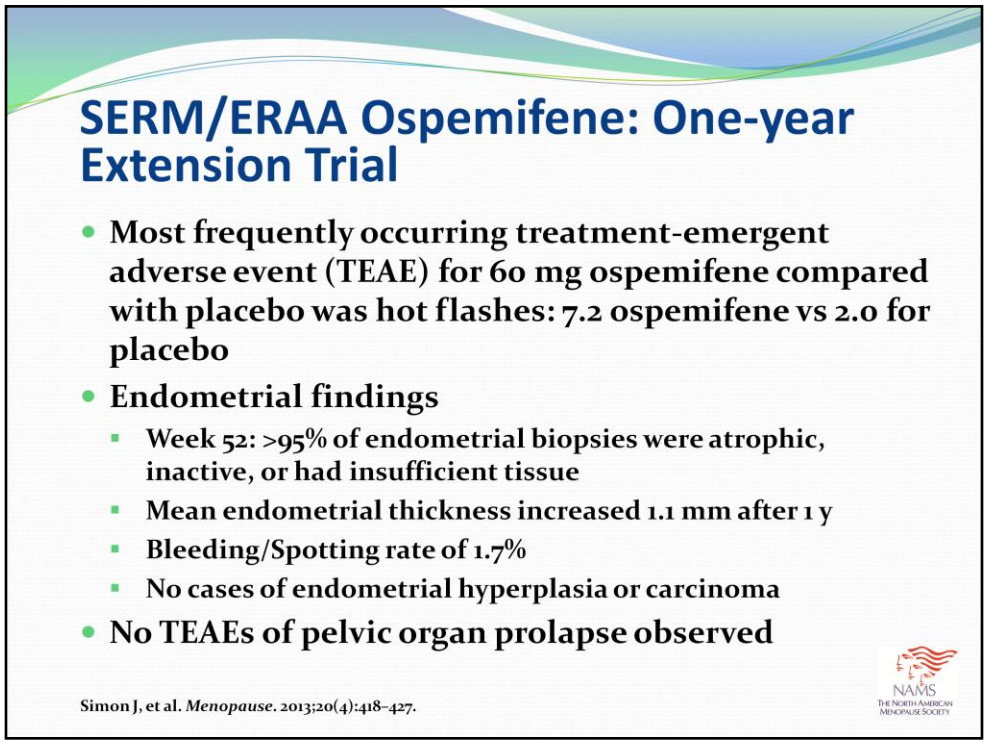


KEY CONCEPTS

- Ospemifene is an estrogen agonist in the vagina
- Preclinical work suggests agonist effect on bone and antagonist effect on breast, but phase 3 randomized, controlled trials are lacking
- FDA approved to treat moderate to severe dyspareunia of menopause
- A boxed warning was placed regarding potential for endometrial stimulation and concern about the class effect of risk of venous thromboembolism and stroke

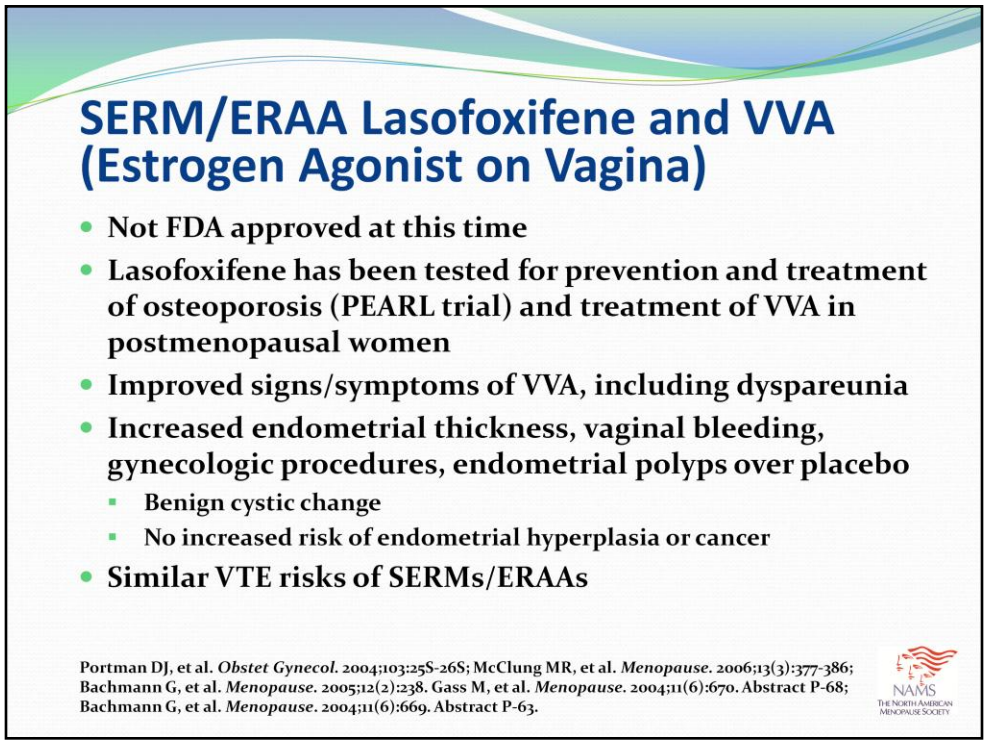
DIVE DEEPER

- Twelve-wk study of 826 postmenopausal women aged 40 to 80 y with moderate to severe vulvovaginal atrophy
- Increased superficial cells and decreased parabasal cells at 4 and 12 wk
- Vaginal pH decreased at 4 and 12 wk relative to placebo
- Vaginal dryness decreased in both 30-mg and 60-mg groups at 12 wk
- Dyspareunia decreased in the 60-mg group
- Hot flashes increased: Placebo, 3.4%; ospemifene 30 mg, 9.6%, 60 mg, 8.3%



KEY CONCEPTS

- Ospemifene vs placebo was evaluated in a 1-y extension of a 2010 12-wk trial in 180 women with a uterus
- The most common adverse event during the 1-y extension trial was hot flashes
- No significant endometrial stimulation was seen in endometrial biopsies, rate of bleeding, or endometrial thickness at 1 y
- More than 95% of endometrial biopsies were atrophic, and no uterine hyperplasia or cancers were seen
- Unlike earlier SERMs that did not proceed to clinical use, there were no reports of pelvic organ prolapse

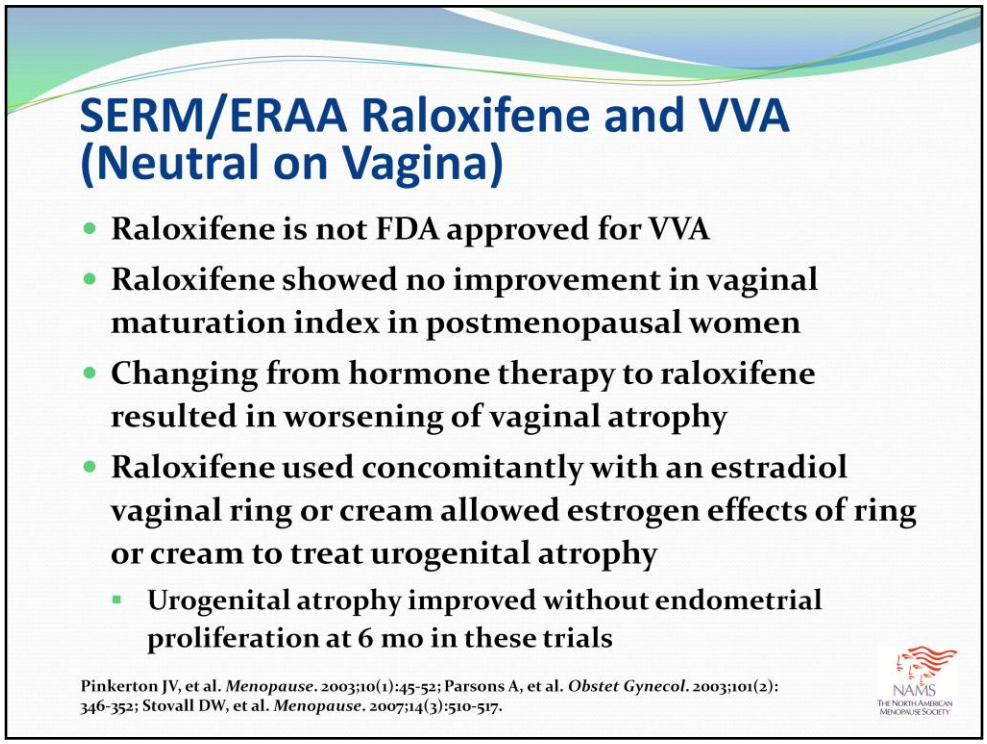


KEY CONCEPTS

- Lasofoxifene is an estrogen agonist on the vagina and the bone and a mild agonist on the uterus
- Lasofoxifene improved dyspareunia and objective measures of vulvovaginal atrophy (VVA)
- Increased endometrial thickness (benign cystic change similar to tamoxifen) and polyps were seen but no uterine hyperplasia or cancer
- Risks of venous thromboembolism similar to other SERMs

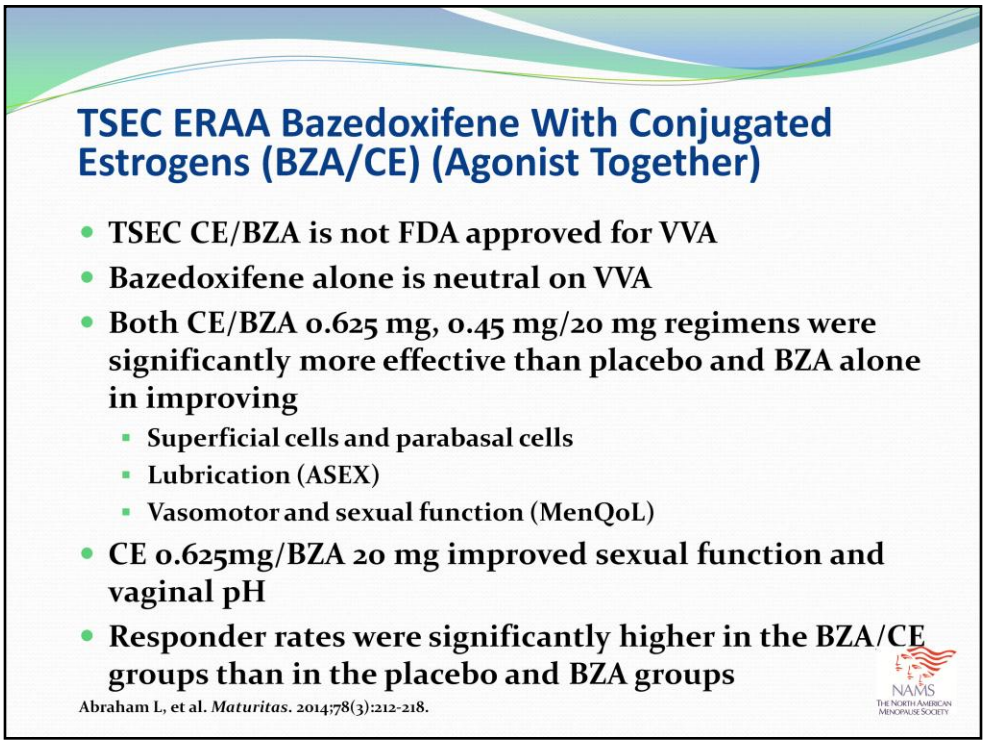
DIVE DEEPER

- Randomized, controlled trial data of 387 postmenopausal women after 12 wk of treatment
- 52% on lasofoxifene (0.025, 0.25, or 0.5 mg/d) reported improved discomfort during sexual intercourse compared with 21% on placebo
- Lasofoxifene exerts significant estrogenic and antiestrogenic activity in vitro and in vivo, targeting any tissues that possess ERs, such as bone, uterus, breast, blood vessels, and liver
- Vaginal bleeding was low but twice as frequent in lasofoxifene-treated women than in placebo-treated women—significantly more women treated with lasofoxifene underwent one or more diagnostic uterine procedures
- In the small PEARL substudy, endometrial effect was associated with cystic echotexture on ultrasound consistent with benign cystic atrophy on biopsy and, extrapolating these findings during the entire study, was not associated with endometrial hyperplasia



KEY CONCEPTS

- Raloxifene is not approved for VVA (neutral on vagina)
- Raloxifene has no effects on vaginal maturation index when used alone
- Urogenital atrophy improved when raloxifene was combined with either the 7.5-µg estradiol ring or conjugated estrogen cream
- No evidence of endometrial stimulation at 6 mo
- Raloxifene has not been shown to provide adequate uterine safety when combined with systemic estrogen



KEY CONCEPTS

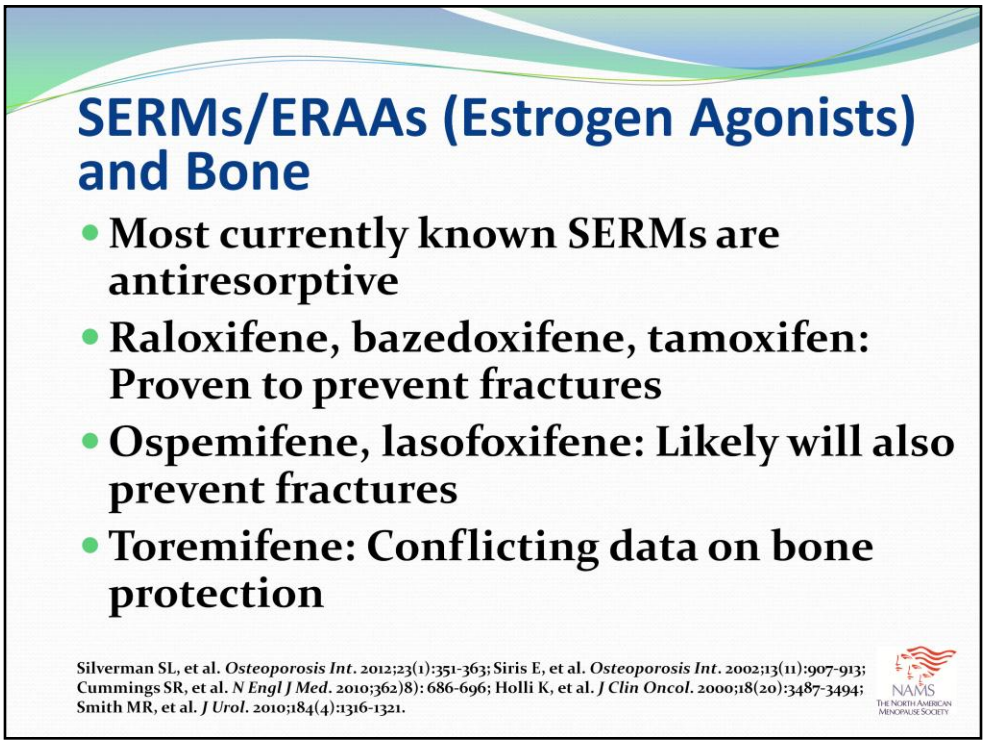
- BZA 20 mg used alone has no effect on vulvovaginal atrophy (VVA)
- The TSEC BZA 20 mg/CE 0.45 mg is not FDA approved for VVA
- In randomized, controlled trials, the TSEC BZA/CE combination (BZA 20 mg/ CE 0.45 mg and 0.625 mg) improved vaginal maturation index and lubrication
- The higher dose (not FDA approved) BZA 20 mg/CE 0.625 mg improved sexual function

DIVE DEEPER

- The higher dose CE 0.625 mg/BZA 20 mg was significantly more effective than placebo and BZA alone in improving
  - Vaginal pH
  - Most bothersome symptom
  - Physical function (MenQoL)
- No differences were observed among treatment groups at either dose in
  - Incidence of treatment-emergent adverse events
  - Discontinuation rates

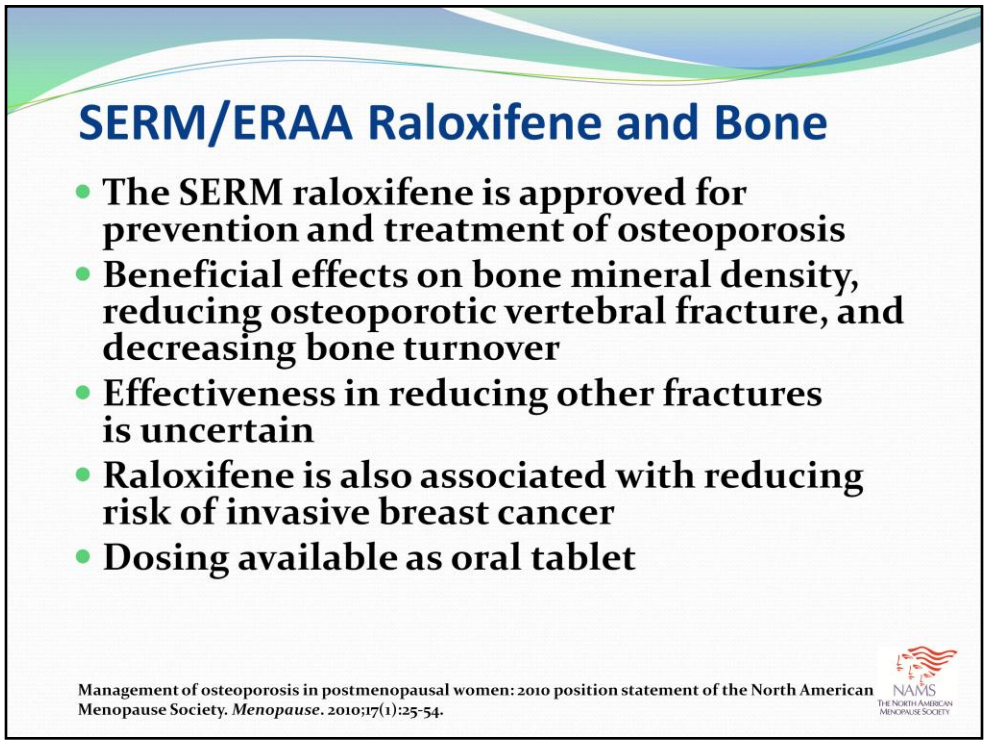
Selective Estrogen Receptor Modulators (SERMs)

Clinical Scenarios and Prevention



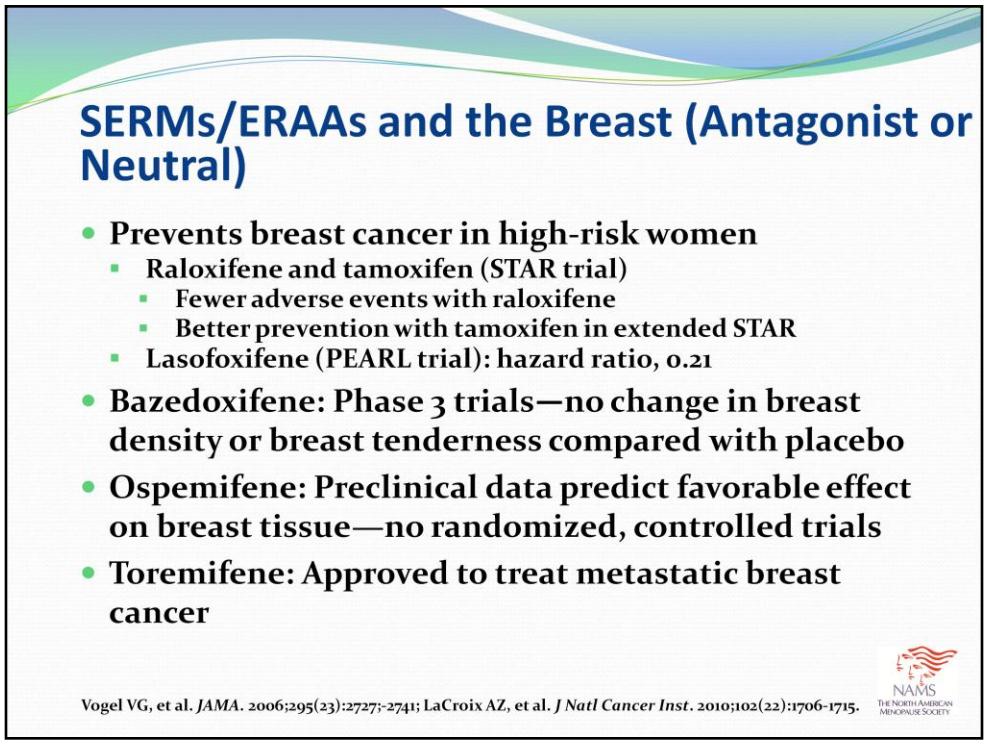
KEY CONCEPTS

- Based on their molecular mechanism of action, most SERMs are predicted to be bone sparing, which has been shown in clinical trials to be the case
- Vertebral fracture prevention has been shown with raloxifene, bazedoxifene, and tamoxifen



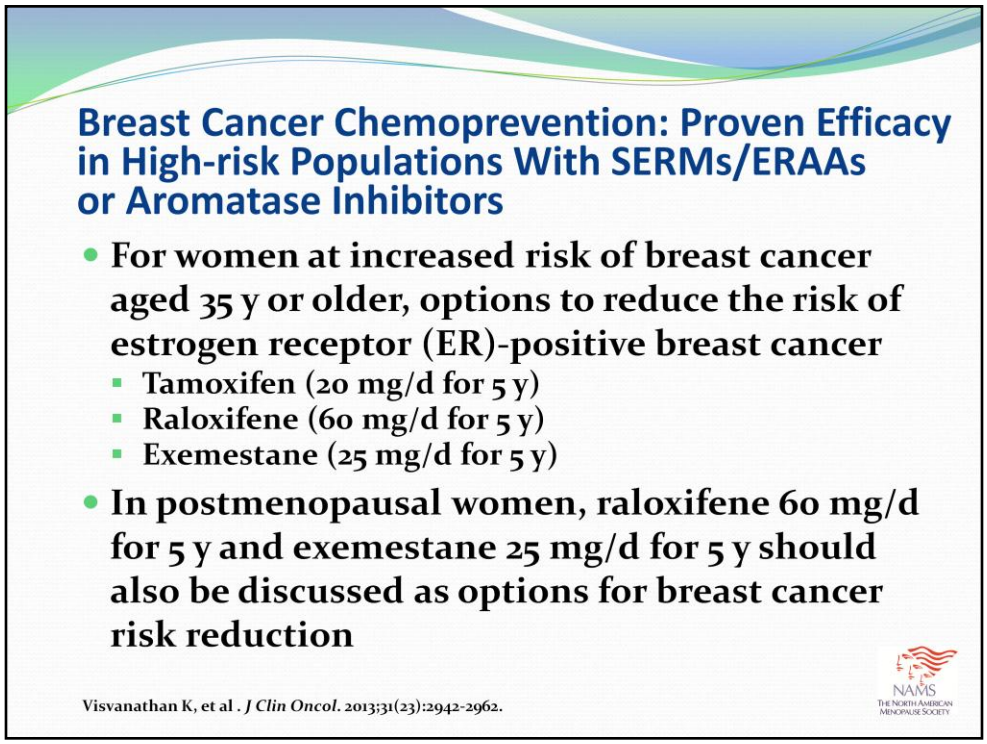
KEY CONCEPTS

- Raloxifene is approved for prevention and treatment of osteoporosis
- Beneficial effects seen on bone density, reducing osteoporotic vertebral fracture, and decreasing bone turnover
- Raloxifene reduces the risk of invasive breast cancer
- Adverse events include hot flashes, leg cramps, and small risk of venous thromboembolism



KEY CONCEPTS

- Most known SERMs/ERAAs are either neutral or estrogen antagonists in the breast
- They do not promote breast cancer, and most appear to oppose sex steroid-induced breast proliferation
- Clinical trial evidence and degree of antagonism of estrogen in the breast varies for each SERM

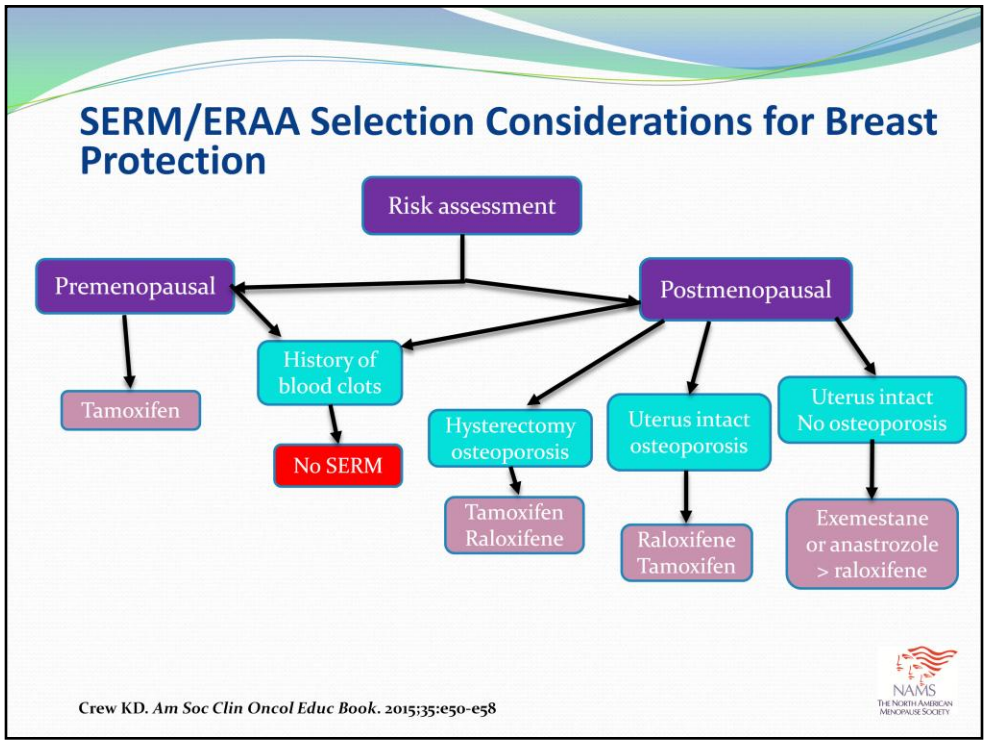


KEY CONCEPTS

- Most known SERMs do not promote breast cancer, and most appear to oppose sex steroid-induced breast proliferation
- Breast cancer reduction clinical evidence varies for each SERM
- For women who are at an increased risk of breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or exemestane

DIVE DEEPER

- Tamoxifen (20 mg/d), taken for 5 y, may reduce the risk of developing estrogen receptor (ER) positive invasive breast cancer for up to 10 y. In a 2003 meta-analysis of these trials, the risk of ER-positive breast cancer was decreased by 48%
- The greatest clinical benefit with fewest adverse effects seen with tamoxifen use by younger (premenopausal) women aged 35 to 50 y who have less risk of thromboembolism or uterine cancer, women without a uterus, and women at high risk of breast cancer
- Raloxifene (60 mg/d) has been approved to reduce the risk of ER-positive invasive breast cancer for women who are postmenopausal and at increased risk of breast cancer and for women who are postmenopausal with osteoporosis in whom breast cancer risk reduction is a secondary benefit
- Those at increased breast cancer risk are defined as women with a 5-y projected absolute risk of breast cancer of at least 1.66% (based on the National Cancer Institute Breast Cancer Risk Assessment Tool or an equivalent measure) or women diagnosed with lobular carcinoma in situ

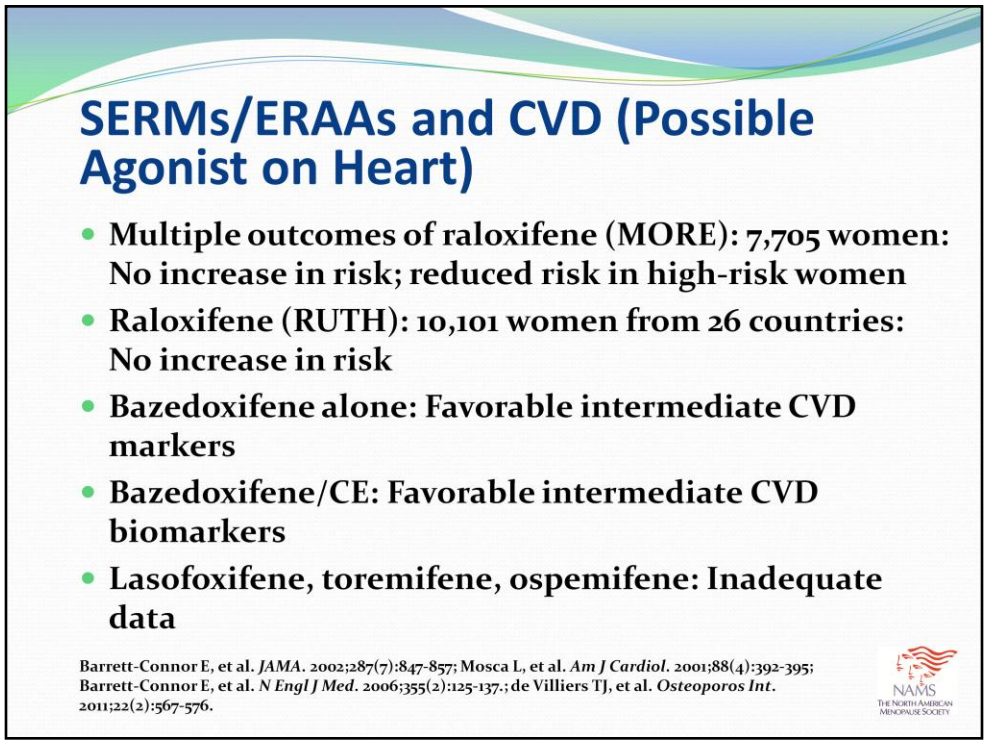


KEY CONCEPTS

- This flow diagram demonstrates an approach to chemoprevention of breast cancer using tamoxifen or raloxifene

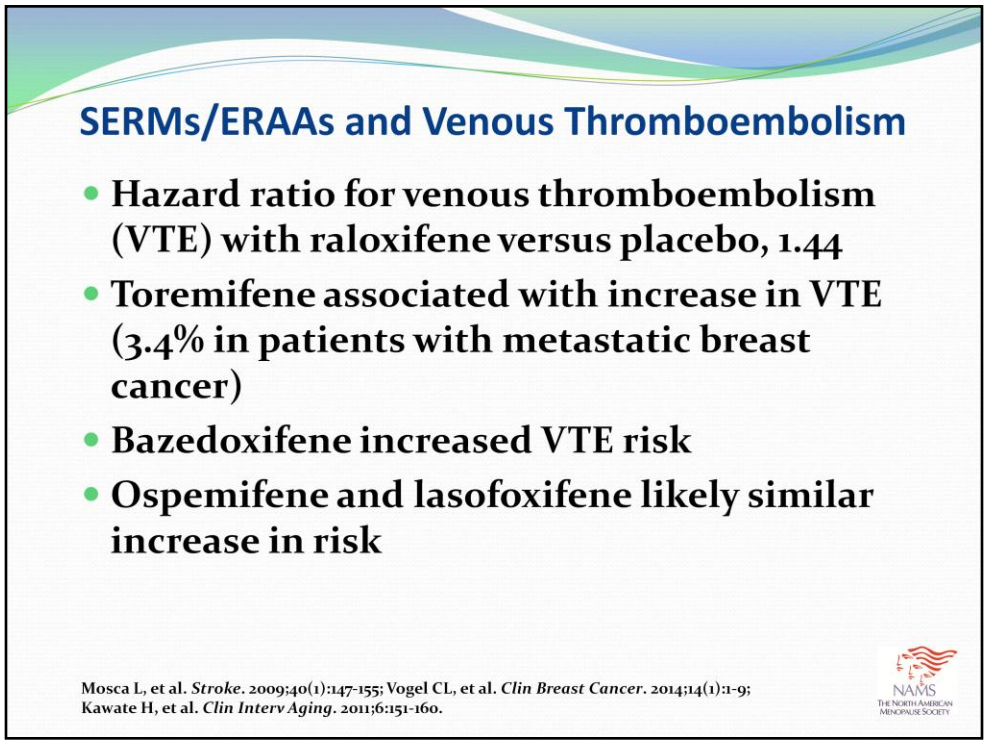
DIVE DEEPER

- Adverse events to keep in mind when deciding which SERM best serves an individual women, with both having the class effect of SERMs of increased risk of blood clots (Vogel VG, et al. *JAMA*. 2006;295[23]:2727-2741; Vogel VG, et al. *Cancer Prev Res [Phila]*. 2010;3[6]:696-706)
- Tamoxifen
  - Increase in uterine cancer, cataracts
  - Hot flashes
  - Vaginal symptoms (discharge, dryness)
  - Leg cramps
  - Bladder control problems
- Raloxifene
  - Hot flashes
  - Leg cramps
  - Musculoskeletal problems
  - Weight gain
- Compared to tamoxifen, raloxifene has lower rate of (Vogel VG, et al. *Cancer Prev Res [Phila]*. 2010;3[6]:696-706)
  - Endometrial hyperplasia, 0.19 (95% CI, 0.12-0.29)
  - Uterine cancer, 0.55 (95% CI, 0.36-0.83; *P*=.003)
  - Hysterectomy, 0.45 (95% CI, 0.37-0.51)



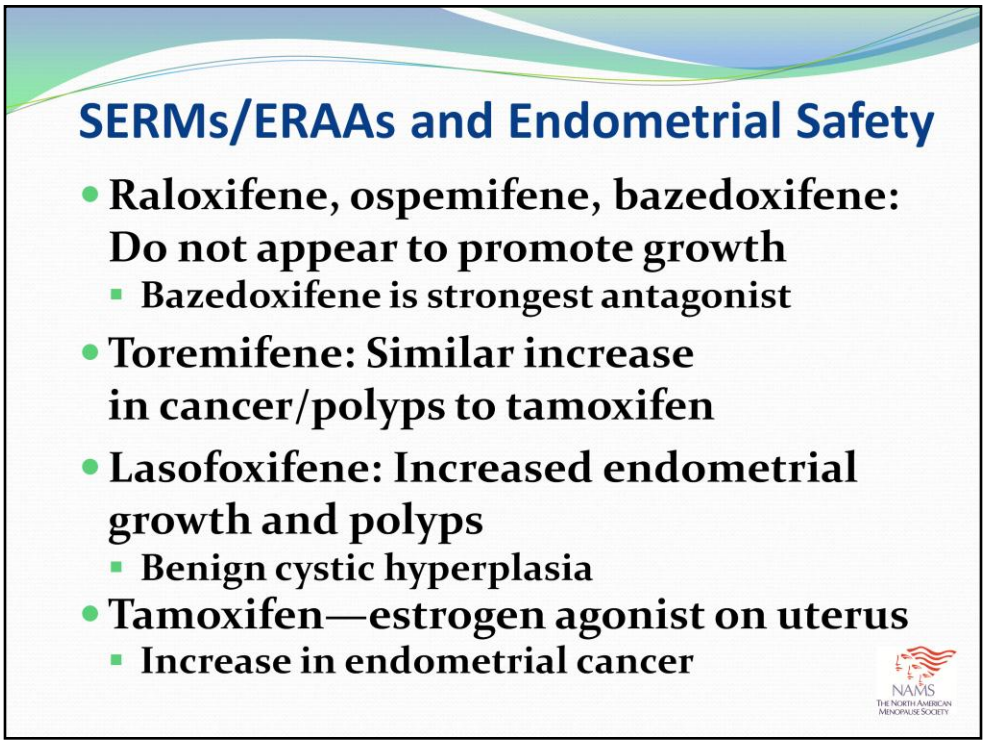
KEY CONCEPTS

- With respect to cardiovascular disease, raloxifene is the most widely tested SERM/ERAA and does not appear to increase cardiovascular disease risk
- BZA has demonstrated a beneficial profile using intermediate markers of disease
- The remaining SERMs have not been well studied enough to make conclusions or predictions



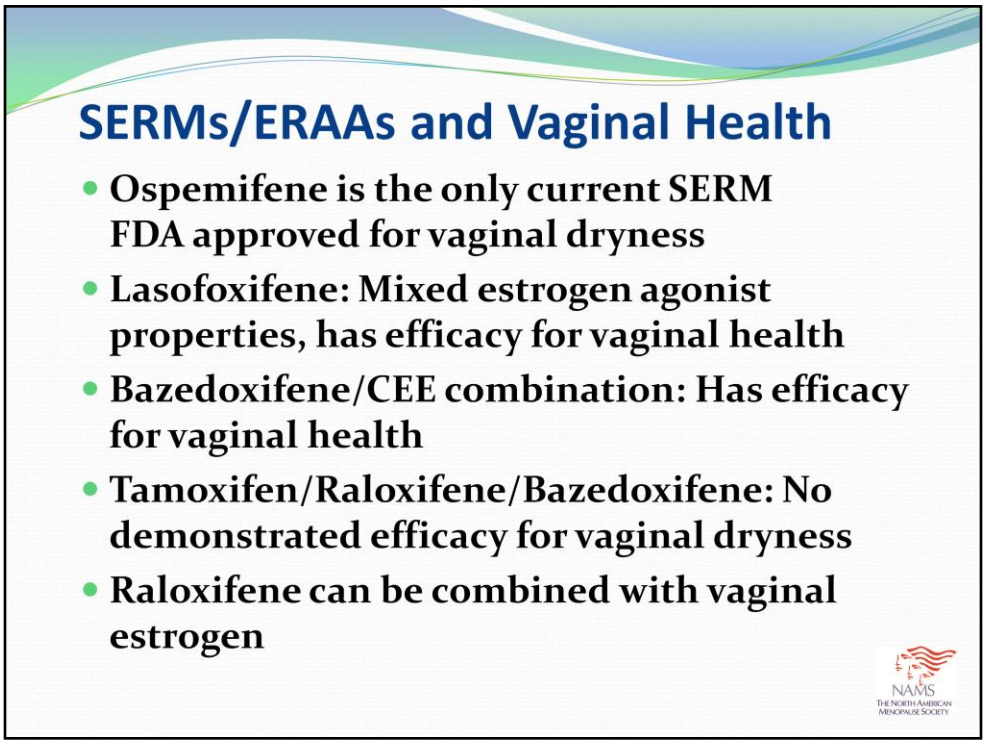
KEY CONCEPT

- Venous thromboembolism risk is considered a class effect with SERMs and appears intermediate between placebo and oral estrogen



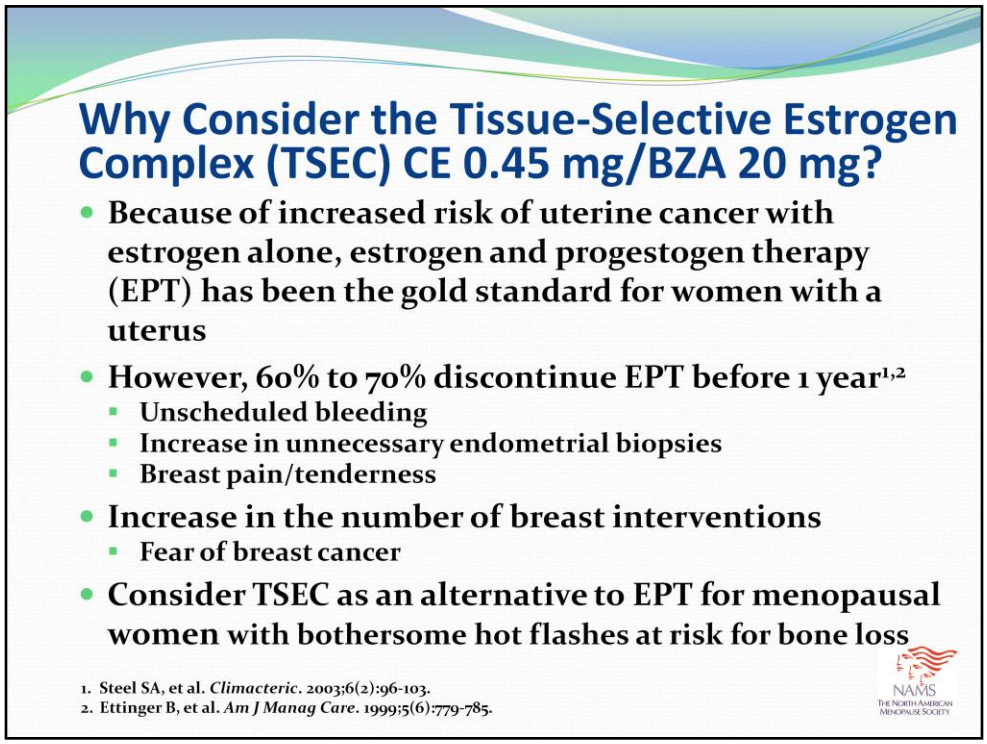
KEY CONCEPTS

- Different SERMs have differential effects on endometrial proliferation along a continuum from estrogen agonist to antagonist
- Bazedoxefine is the strongest antagonist for endometrium, allowing it to be combined with systemic estrogen
- Tamoxifen is an agonist on uterus, with increased endometrial cancer rates



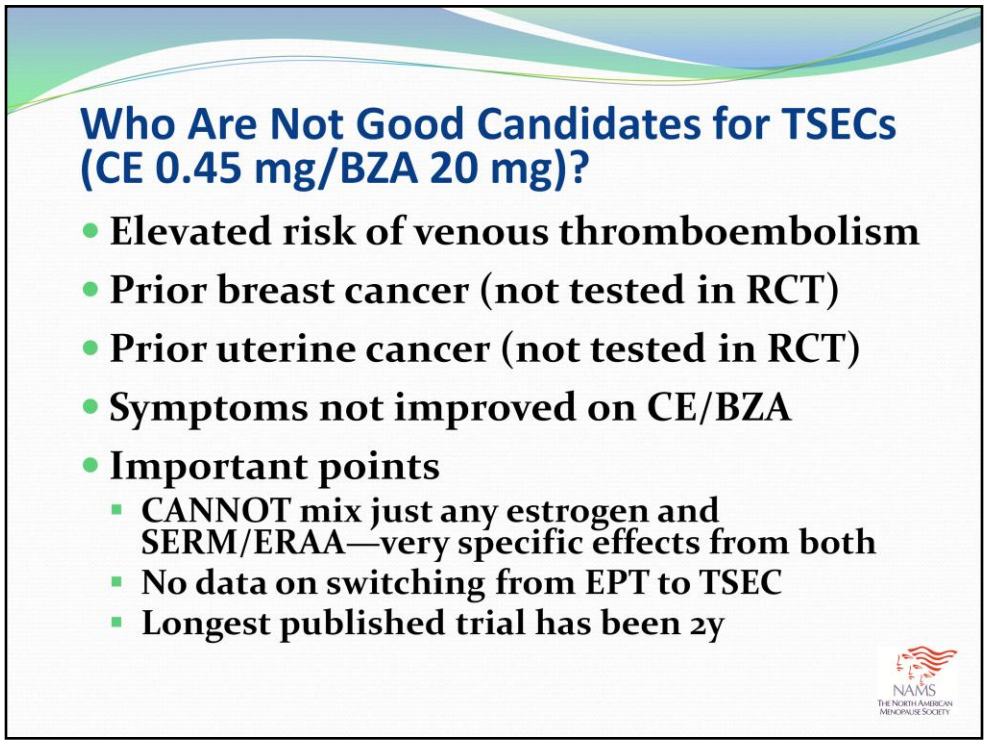
KEY CONCEPT

- Similar to their behavior in the endometrium, different SERMs affect the vaginal lining differently, with some such as ospemifene and lasofoxifene improving genitourinary atrophy (GSM), whereas others are ineffective



KEY CONCEPTS

- Unopposed estrogen use in postmenopausal women with a uterus leads to uterine hyperplasia or cancer
- For women with a uterus, traditional hormone therapy includes estrogen combined with a progestogen (EPT) to protect the uterus against unopposed estrogen stimulation
- Adverse effects of EPT include unscheduled (breakthrough) bleeding, leading to more endometrial biopsies, breast pain and tenderness, more mammograms, and more breast interventions
- In the Women's Health Initiative, a small increase in breast cancer was seen in women taking CE 0.625 mg/MPA 2.5 mg
- An alternative to traditional EPT has been needed for symptomatic menopausal women with a uterus
- Consider TSEC BZA 20 mg/CE 0.45 mg as an alternative to EPT for symptomatic menopausal women with bothersome hot flashes at risk for bone loss

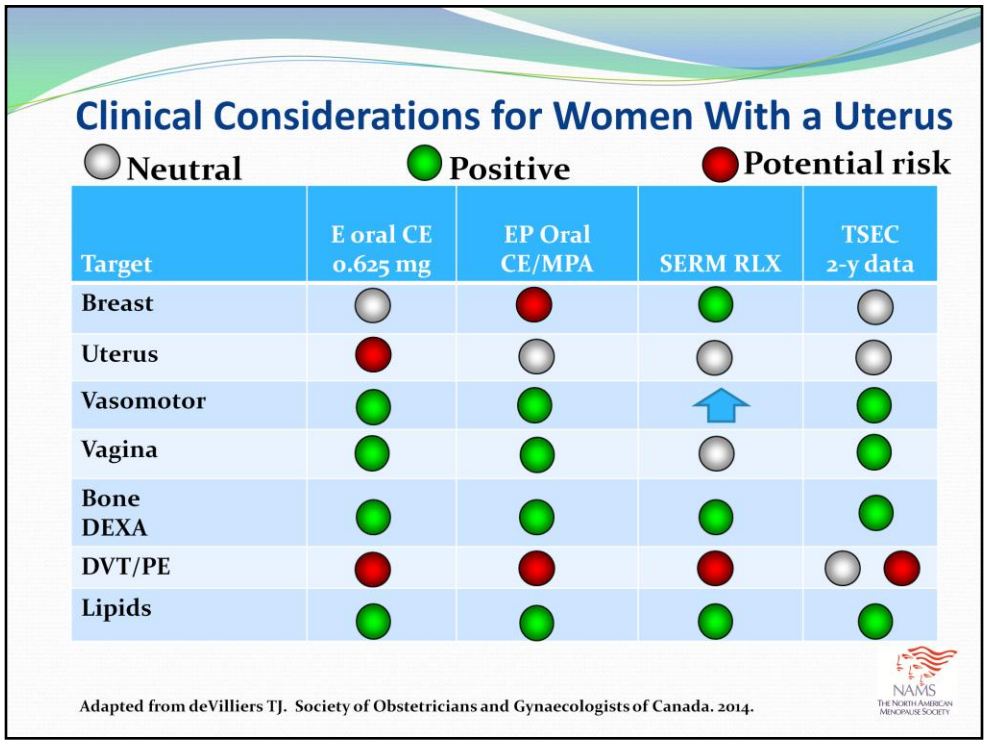


KEY CONCEPTS

- Women who would not be good candidates for the TSEC BZA 20 mg/CE 0.45 mg include
  - Those with increased risk of blood clots
  - Those with prior breast or uterine cancer (not tested in those populations)
  - Those in whom a trial of the TSEC does not relieve vasomotor symptoms or vaginal changes
- The FDA-approved TSEC BZA/CE has been tested in prospective, randomized, double-blind, placebo-controlled trials of up to 2 y
- There is no data about safety or efficacy in women on traditional EPT switched to TSEC

DIVE DEEPER

- BZA 20 mg/CE 0.45 mg was tested in healthy postmenopausal women
- No randomized, controlled trials on women at risk for venous thromboembolism or who had prior estrogen-sensitive cancers (breast, endometrium)
- Cannot combine other SERMs/systemic estrogen because of potential increased risk of uterine cancer
- BZA is sufficiently antagonistic to endometrium that it can be combined with systemic estrogen

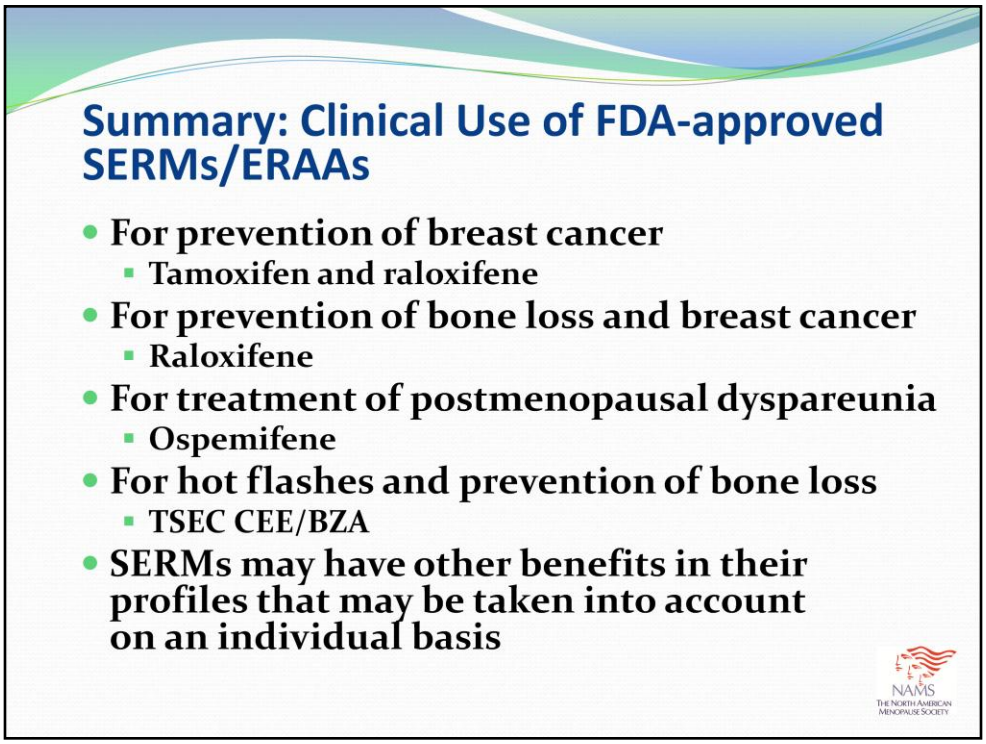


KEY CONCEPTS

- This table provides visual comparisons of potential differences among TSEC, estrogen alone (oral), and EPT (oral) compared with raloxifene
- Transdermal estrogen alone and transdermal estrogen with progestin are FDA approved and would have less venous thromboembolism (VTE) risk but are not included

DIVE DEEPER

- Estrogen alone increases risk of endometrial cancer, but paired with progesterone or BZA, the endometrium is protected
- Raloxifene has no increased risk of endometrial cancer
- Breast cancer was decreased with oral estrogen
- There are no good randomized, controlled trials for risk of breast cancer with transdermal estradiol alone
- Increased risk was found in Women's Health Initiative (WHI) with CE 0.625 mg/ MPA 2.5 mg
- No trial data on combined transdermal EPT
- Raloxifene is protective on breast, and at 2 y, BZA/CE appeared neutral
- All are protective against bone loss
- All improved VVA except raloxifene used alone
- Concern exists about VTE risk with oral estrogen alone, EPT, raloxifene, and probably CE/BZA
- All have beneficial effects on cholesterol; oral CE increases triglycerides
- Breast protection data was seen in WHI with CE 0.625 mg alone; it is not known whether transdermal estradiol has same benefit on breast or increases risk of breast cancer



KEY CONCEPTS

- Because of differential effects at target tissues, SERMs have differing clinical effects
- BZA/CE is approved to treat hot flashes and prevent bone loss
- Tamoxifen and raloxifene are approved to prevent breast cancer
- Raloxifene is approved to prevent bone loss and breast cancer
- Ospemifene is approved for treatment of postmenopausal dyspareunia