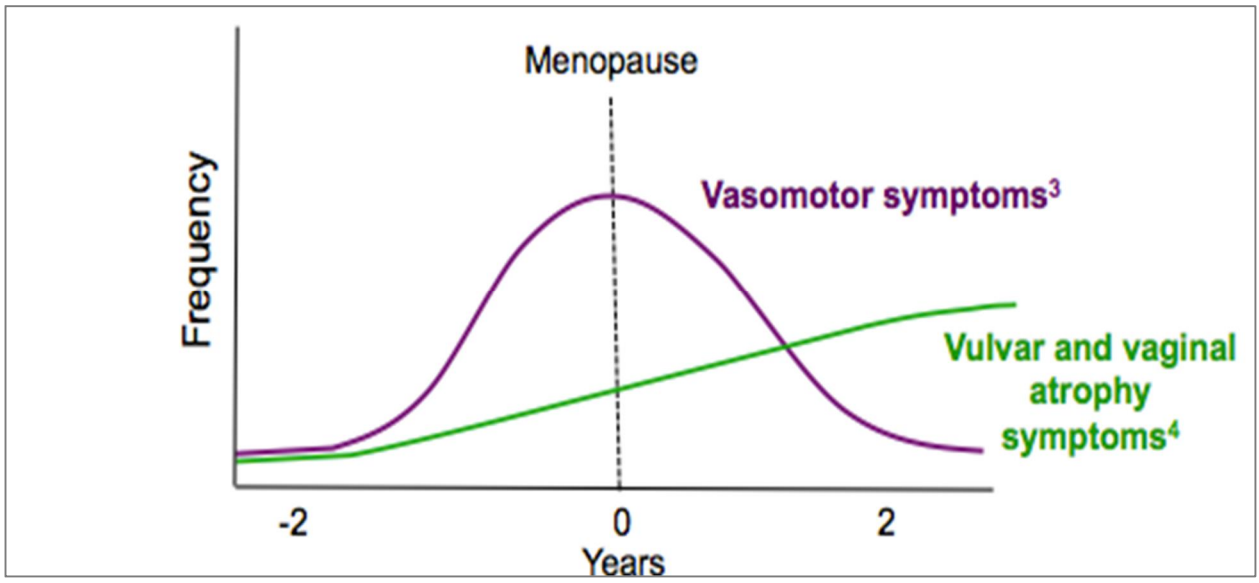
The Role of SERMs in Managing the Most Bothersome Symptoms of Vulvovaginal Atrophy: Dyspareunia and Dryness

Introduction

The genitourinary syndrome of menopause (GSM) is a constellation of signs and symptoms associated with decreased estrogen and other sex steroids.[1] GSM can involve changes to the labia majora/minora, vestibule/introitus, clitoris, vagina, urethra, and bladder and manifests with bothersome or distressing symptoms that may include vaginal dryness, dyspareunia, bladder and urethral symptoms, recurrent urinary tract infections, and burning/itching/irritation. An estimated 50 to 70% of the more than 64 million postmenopausal women in the US will be affected by GSM symptoms.[2] Dyspareunia and vaginal dryness are the most common bothersome symptoms.

In contrast to vasomotor symptoms (VMS), vulvovaginal atrophy (VVA) is a chronic condition with symptoms that worsen over time and do not improve without treatment (**Figure 1**). Although treatment of symptomatic VVA may improve all of the components of GSM, many women remain unaware that vulvar and vaginal changes may be a direct result of the menopausal transition, as they frequently become bothersome well after menopause.[2,3] Consequently, poor understanding and communication between patients and providers may result in underdiagnosis, undertreatment, or delays in seeking treatment. Furthermore, GSM, and particularly vaginal dryness, irritation, and dyspareunia, can significantly interfere with sexual function, spontaneity, intimacy, and enjoyment.[2]

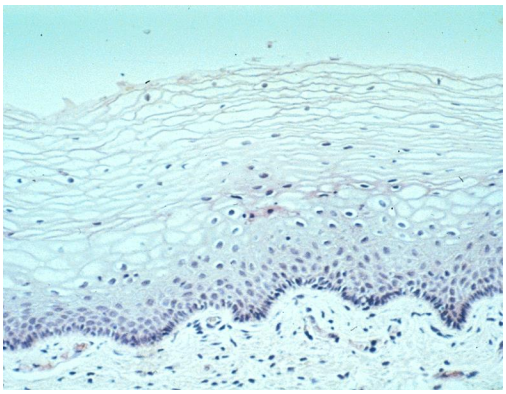
Figure 1: Onset of Vasomotor versus Vulvovaginal Symptoms[4-7]



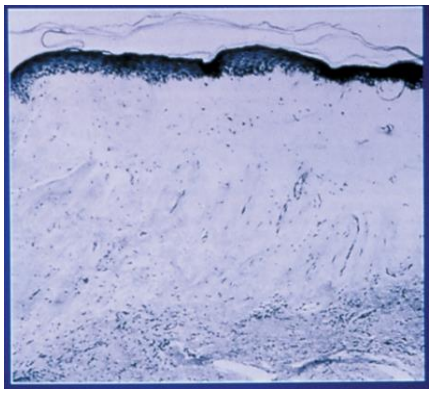
Pathophysiology Underlying Dyspareunia and Vaginal Dryness of VVA

The reduction of estrogen associated with menopause leads to anatomic and physiologic changes in the vulvovaginal region. As seen in **Figure 2a**, the premenopausal vagina is well estrogenized, and the squamous epithelium is filled with superficial cells filled with glycogen on the surface, which serves as a substrate for lactobacilli to give the vagina an acidic pH that protects against pathogens. In contrast, the postmenopausal vagina demonstrated in **Figure 2b** is atrophic with a marked thinning of the epithelium and loss of glycogen, leading to an increased pH and greater vulnerability to pathogens. Tissues become friable, easily injured, stenotic, and fibrotic without intervention. Estrogen, whether systemic or topical, can reverse these changes; however, not all women are able or willing to use estrogen.

Figure 2: Pre- versus Postmenopausal Vaginal Histology



2a. PREMENOPAUSE: Epithelium well-estrogenized, multi-layered with good blood supply, superficial cells rich in glycogen



2b. POSTMENOPAUSE: Estrogen-deficiency atrophy with marked thinning of epithelium, reduced blood supply, and loss of glycogen

Selective Estrogen Receptor Modulators (SERMs)

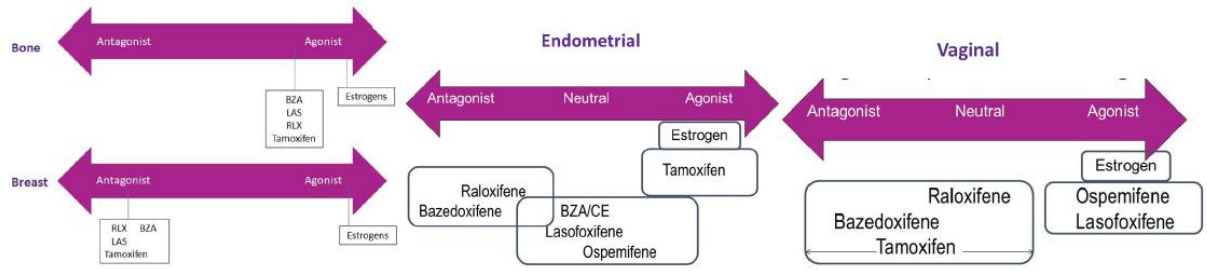
Another means to modulate the estrogen responsiveness in these tissues is by delivering an agent systemically that binds to estrogen receptors. The vagina has both estrogen receptors (ER) α and β.[8] Selective estrogen receptor modulators (SERMs) include a structurally diverse group of compounds that bind to ERs despite lacking estrogen steroid moiety. Well-known SERMs include clomiphene, tamoxifen, bazedoxifene, raloxifene, lasofoxifene, and ospemifene.

Mechanisms of Action of SERMS

SERMS confer mixed functional ER agonist or antagonist activity depending on the target tissue (**Figure 3**). This is 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, and expression and binding of the ER ligand complex to coregulator (coactivator and corepressor) proteins.[9-11] Whereas estrogen largely turns most receptors 'on', activity of SERMs in a particular tissue appear to be influenced by the relative expression levels of the ER subtypes.[12] In contrast to estrogens, SERMs are not steroids. Both ER subtypes are expressed in bone cells, whereas ER alpha is expressed predominantly in uterine tissue. SERMs may be

agonists, antagonists, or neutral for specific tissues; some SERMs may be intermediates – they can activate and inactive in different tissues simultaneously. In general, SERMs are good for bone and antagonists for breast tissue.

Figure 3: SERM Effects on Bone, Breast, Endometrium, and Vagina



Indications and Usage of SERMS

As demonstrated in Figures 3a-c, each available SERM has variable effects on different tissue (i.e., "tissue selectivity"). For example, tamoxifen has both estrogen agonist and antagonist effects on the vaginal epithelium.[13-16] It causes estrogenic changes in the vaginal epithelium, increases vaginal discharge, and has been associated with pain, burning, or discomfort with intercourse. Despite its mechanism of action, vaginal dryness and dyspareunia have been reported in both pre- and postmenopausal patients treated with tamoxifen.

Raloxifene has a neutral effect on vaginal mucosa.[17,18] It should not be administered with oral estrogen, although studies have demonstrated its use does not diminish the effect of vaginal CEE cream on subjective signs of vaginal atrophy. It does not have negative sexual effects but also is not protective of the endometrium.

Bazedoxifene (BZA) protects the endometrium and is antagonistic by itself on the vagina but has modest effects when combined with estrogen (BZACE) (**Figure 4**).[19,20] BZACE is indicated for the treatment of vasomotor symptoms as well as the prevention of osteoporosis. However, BZA alone is antagonistic towards the vagina. In currently approved doses, BZA does not improve pH and does not sufficiently improve GSM symptoms; therefore, it is not indicated for the treatment of VVA.

The two SERMs with demonstrated beneficial activity on vaginal atrophy are ospemifene and lasofoxifene. These two agents largely act like estrogen on the vagina, are neutral on the endometrium, and are comparable to other SERMs on the breast and bone. Although data have demonstrated that very low doses of lasofoxifene improved dyspareunia and vaginal dryness, among other GSM symptoms, its use is focused specifically on patients with advanced breast cancer driven by particular mutations.

Ospemifene is a once-daily, oral, non-hormonal treatment initially studied for the prevention of osteoporosis; however, evidence from the preclinical trials demonstrated substantial mucification and beneficial shifts in the vaginal maturation indices, along with the typical bone and breast profile.

Consequently, it was approved for the treatment of moderate to severe dyspareunia due to VVA and was indicated in early 2019 for the treatment of moderate to severe vaginal dryness due to VVA (**Figure 5**). This second indication is unique in that no other studies have focused on patients who are either sexually inactive or who are complaining of vaginal dryness as their most bothersome symptom (**Figure 6**).

A recent study that used controlled photography with a rigorous vulvoscopic exam demonstrated highly significant improvements in the actual architecture of the vulva and vagina with the use of ospemifene versus placebo.[21] In comparison with topical treatments, which address surface-level changes, oral administration of ospemifene enables binding to the estrogen receptor with resulting significant improvements (decreases) to the vaginal health index (VHI).

Figure 4: Bazedoxifene (BZA)

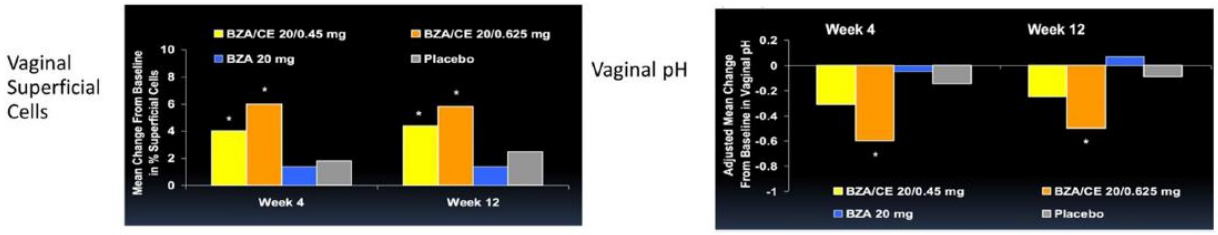


Figure 5: Ospemifene and Dyspareunia Associated with VVA

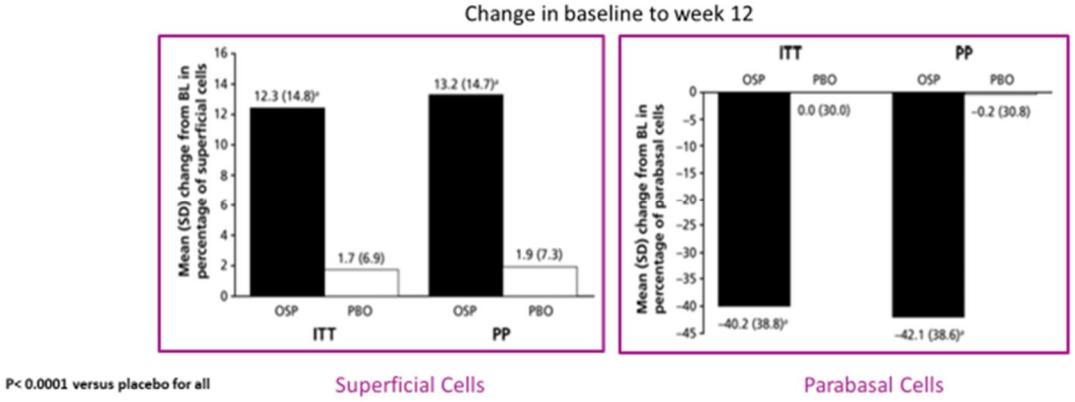
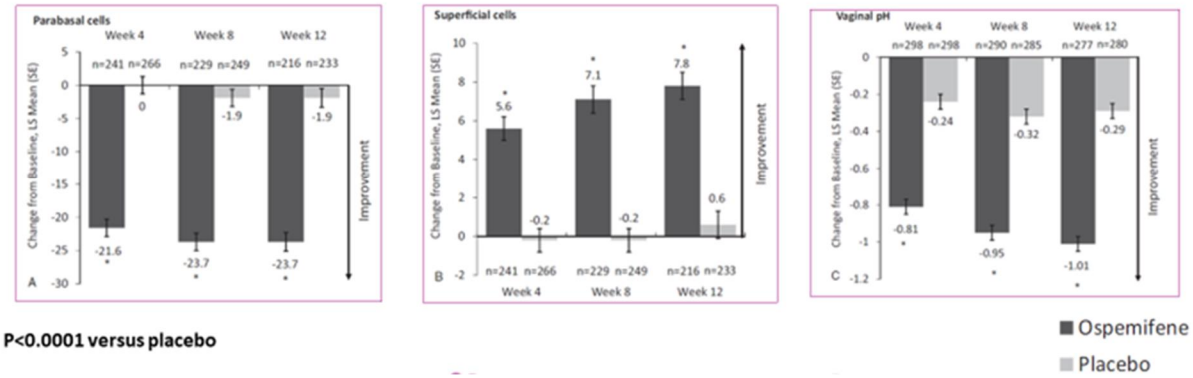


Figure 6: Ospemifene Efficacy in Postmenopausal Women with Moderate-to-Severe Vaginal Dryness



Oral versus Topical Therapy for the Management of Dyspareunia and Dryness of VVA

It is imperative to identify which patients are appropriate candidates for SERMs, as well as to match patient needs with the appropriate SERM. As discussed above, available SERMs have distinct indications and are not interchangeable owing to their tissue selectivity. All SERMs have a labeled warning for venous thrombosis; however, it is important for patients to appreciate the benefits compared with the absolute risk. For example, while the risk of blood clots with SERMs is doubled, the absolute risk remains miniscule.

There are some warnings about the potential stimulation of the endometrium with ospemifene, although it is relatively neutral on the endometrium, and bleeding rates were similar to placebo in clinical trials. No cases of complex hyperplasia or cancer and only one case of simple hyperplasia have been identified; these results are comparable to those demonstrated with local vaginal estrogens or other SERMS.[22,23]

Conclusions

Dr. David Portman has noted that “SERMs are one of the great advancements in endocrine and medical therapy.” Notably, tamoxifen has revolutionized the treatment of breast cancer. However, it has also become apparent that the benefits of SERMs are tissue specific in that what might be good for one tissue is not necessarily good for another; in this context, tamoxifen would not be an appropriate treatment for osteoporosis in a healthy patient population owing to its endometrial effects. Ospemifene, in comparison, has demonstrated substantial vulvovaginal benefits leading to its approvals for both the management of dyspareunia and vaginal dryness owing to vulvovaginal atrophy.

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