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SERMs: Managing the Most Bothersome Symptoms of Menopause

Announcer:
Welcome to CME on ReachMD. This activity, entitled “SERMs: Managing the Most Bothersome Symptoms of Menopause” is provided by Omnia Education and is supported by an independent educational grant from Duchesnay.

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Dr. Shulman:
The genitourinary syndrome of menopause, or GSM, is a constellation of signs and symptoms associated with decreased estrogen and other sex steroids. GSM can involve changes to the labia majora and minora, vestibule and introitus, clitoris, vagina, urethra and bladder, and manifest with bothersome or distressing symptoms that may include vaginal dryness, dyspareunia, bladder and urethral symptoms, and recurrent urinary tract infections. An estimated 50-70% of the more than 64 million postmenopausal women in the United States will be affected by GSM symptoms. Dyspareunia and vaginal dryness are the most bothersome symptoms reported.

This is CME on Reach MD, and I’m Dr. Lee Shulman. Joining me to discuss selective estrogen receptor modulators, or SERMs, and their role in managing dyspareunia and vaginal dryness associated with vulvovaginal atrophy is Dr. David Portman, Founder and Director Emeritus at the Columbus Center for Women’s Research, Adjunct Faculty with The Ohio State University, and Founder and CEO of Sermonix Pharmaceuticals in Columbus, Ohio.

Dr. Portman, welcome to the program.

Dr. Portman:
Thank you, Dr. Shulman. It’s a pleasure to be here.

Dr. Shulman:
David, as I mentioned in the introduction, dyspareunia and vaginal dryness are the two most bothersome symptoms of vulvovaginal atrophy. Can you talk to the pathophysiology that underlies these two conditions?

Dr. Portman:
Sure, in contrast to vasomotor symptoms, VVA’s a chronic condition with symptoms that worsen over time and do not improve without treatment. Although treatment of the symptomatic VVA may improve all of the components of genitourinary syndrome of menopause, 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. Consequently, poor understanding and communication between patients and providers may results in underdiagnosis, under treatment, or delays in seeking treatment. Further GMS, and particularly vaginal dryness, irritation, and dyspareunia, can significantly interfere with sexual function, spontaneity, intimacy, and enjoyment.

Dr. Shulman:
What is the pathophysiology that underlies dyspareunia and vaginal dryness of VVA?

Dr. Portman:

The reduction of estrogen associated with menopause leads to anatomic and physiologic changes in the vulvovaginal region. The premenopausal vagina is well estrogenized, has surface squamous epithelium filled with glycogen on the surface, which serves as a substrate for lactobacilli and gives the vagina an acidic pH, protecting against pathogens. In contrast, the postmenopausal vagina is atrophic with a marked thinning of the epithelium and loss of glycogen, leading to an increased pH and greater vulnerability to pathogens. Tissue become friable, easily injured, stenotic and fibrotic without intervention. Estrogen, whether systemic or topical, can reverse these changes; however, not all women are willing or able to use estrogen. Another treatment option, of course, is intervaginal DHEA.

Dr. Shulman:
Well, David, let's talk a little bit about SERMs, or selective estrogen receptor modulators. What's their mechanism of action?

Dr. Portman:
Another way to modulate the estrogen responsiveness in tissues is by delivering an agent systemically that binds estrogen receptors. The vagina has both estrogen receptor alpha and beta. Selective estrogen receptor modulators, also referred to as estrogen agonists/antagonists, include a structurally diverse group of compounds that bind to the estrogen receptor, despite lacking estrogen steroid moiety. Well-known SERMs include clomiphene, tamoxifen, bazedoxifene, raloxifene, and ospemifene.

Dr. Shulman:
So, how do they work?

Dr. Portman:
Well, SERMs confer mixed functional ER agonist or antagonist activity, depending on the target tissue. This is mediated by expression of the ER-alpha and ER-beta and coregulators in different tissues and different levels. ER conformation after binding of the ER ligand and then expression and binding of that ER ligand complex to coregulators, of which there are hundreds, either activators or repressors, lead to different transcriptional activity. Whereas, estrogen largely turns receptors on, activity of SERMs in a particular tissue appears to be influenced by the relative expression level of the estrogen receptor subtypes and coregulators. In contrast to estrogen, SERMs are not steroids. Both ER subtypes are expressed in bone cells, for instance; where, as ER alpha is expressed predominantly in uterine tissue. SERMs may be agonists or antagonists, or even neutral for specific tissues, and many SERMs fall somewhere in between. In general, SERMs are agonists at bone and antagonist or beneficial for breast tissue.

Dr. Shulman:
So, David, tissue selectivity is clearly a key component of SERMs. Can you discuss this and how the various SERMs differ from each other regarding this?

Dr. Portman:
Yeah, each available SERM has variable effects on different tissues, as I've been referring to as tissue selectivity. For example, tamoxifen has both estrogen agonist and antagonist effect on the vaginal epithelium, causes estrogenic changes in the vaginal epithelium, increases vaginal discharge but 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 women treated with tamoxifen for other indications. Raloxifene has a neutral effect on the vaginal mucosa. It cannot be administered with oral estrogens, although studies have demonstrated its use, it does not diminish the effect of vaginal estrogen cream on subjective signs of vaginal atrophy. It does not have negative sexual effects, but it also does not protect the endometrium. Bazedoxifene, in contrast, does protect the endometrium and is antagonistic by itself on the vagina, but has modest effects when combined with estrogen in a combination of BZA and CE. BZA/CE is indicated for the treatment of vasomotor symptoms as well as 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, and is not indicated for the treatment of VVA.

Dr. Shulman:
David, given the varying effects of SERMs on various tissues, which SERMs have demonstrated efficacy on the dyspareunia and vaginal dryness associated with vulvovaginal atrophy?

Dr. Portman:
Two SERMs have demonstrated beneficial activity on vaginal atrophy, and those are ospemifene and lasofoxifene – the latter an investigational drug. These two agents largely act like estrogen on the vagina, are relatively neutral on the endometrium, and like other SERMs, have beneficial effects on breast and bone in preclinical models. Although data have demonstrated that very low doses of lasofoxifene have improved symptoms of dyspareunia and vaginal dryness, it was never approved for that indication or other GSM symptoms, and its investigational use currently is focused specifically on patients with advanced breast cancer driven by mutations. Ospemifene is a once daily, oral, non-hormonal treatment initially investigated for 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 seen with a SERM. Consequently, it was approved for treatment of moderate to severe dyspareunia due to VVA and was recently indicated for the treatment of moderate-to-severe vaginal dryness due to VVA. The second indication's 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, and this being an orally given treatment, it is absorbed better when taken with food. A recent study that used controlled photography with a rigorous vulvoscopic exam, demonstrated highly significant improvement in the actual architecture of the vulva and the vagina with the use of ospemifene versus placebo. In comparison with topical treatments which address surface level changes, oral administration of ospemifene enables the binding to the estrogen receptor with resulting significant improvements in both vaginal health indices and vulvar indices, in addition to these vulvoscopic exams.

Dr. Shulman:
David, can you compare and contrast the SERM ospemifene versus topical therapies, specifically with regard to safety considerations?

Dr. Portman:
Sure. Topical therapy is while estrogen and vaginal DHEA products are available and highly effective, it may not be right for every patient. Some may not want vaginal administration, or the messiness involved with those types of medication. It is imperative to identify which parents are appropriate candidates for SERMs as well as to match the patient needs with the appropriate SERM. 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's important for patients to appreciate the benefits compared with the absolute risk. For example, while the relative risk of blood clots with SERMs is doubled, the absolute risk remains small.

There are some warnings about potential stimulation of the endometrium with ospemifene, although it is relatively neutral on the endometrium, doesn't require the concomitant use of a progestin, and bleeding rates were similar to placebo in clinical trials. No case of complex hyperplasia or cancer were seen and only one case of simple hyperplasia was identified. These results are comparable to those demonstrated with estrogen/bazedoxifene combination.

Dr. Shulman:
Thanks, David. Any closing thoughts on our discussion?

Dr. Portman:
So, what I'd like to summarize is that, you know, SERMs are one of the great advancements in endocrine and medical therapy. Notably, tamoxifen has revolutionized the treatment of breast cancer and is probably responsible for saving more lives than almost any cancer drug yet developed. However, it's also become apparent the benefits of SERMs are highly tissue specific. What might be good for one tissue is not necessarily good for another. So, in this context, tamoxifen would not be an appropriate treatment for osteoporosis in a healthy patient population, owing to its endometrial effects. However, ospemifene, in comparison, has demonstrated substantial vulvovaginal benefits, leading to its approval for both the management of dyspareunia and vaginal dryness due to vulvovaginal atrophy.

Dr. Shulman:
David, that's a great way to round out our discussion on this topic today. I want to thank Dr. David Portman for helping us better understand the role of selective estrogen receptor modulators in managing both dyspareunia and vaginal dryness associated with vulvovaginal atrophy. David, it was great speaking with you today.

Announcer:
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