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Released: 11/01/2017
Valid until: 11/01/2018
Time needed to complete: 30 minutes

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Postmenopausal Dyspareunia: Innovations in Therapy and Patient Management

ANNOUNCER INTRODUCTION

Welcome to the Omnia Education CME activity, entitled *Postmenopausal Dyspareunia: Innovations in Therapy and Patient Management* presented by Dr. David Portman, recorded live at the Women's Health Annual Visit in Philadelphia, Pennsylvania.

This activity is supported by an independent medical educational grant from AMAG Pharmaceuticals.

Dr. Portman

We are going to talk about a common condition and hopefully put it into the context of patient counseling, barriers to having that conversation, some new nomenclature around this disorder, genitourinary syndrome of menopause, vulvovaginal atrophy, might not capture exactly what is going on with these patients, and then look at the therapeutic options.

What we are going to do is try to define our terms. First, it's important to identify and understand what we are treating and diagnosing, and talk a little bit about the barriers to making the diagnosis. This is a very underdiagnosed and undertreated disorder, and review some of the clinical trial data from recent pivotal studies on innovative therapies, and talk also about some tried and true therapies, local vaginal estrogen, and then discuss the benefits and risks and how to counsel and put that into the context of a treatment selection.

So, I think it's first important to recognize that lifelong sexuality is something that we often dismiss. I think in a hyper-sexualized culture which values youth, that mature women and men often get dismissed as being sexual beings, and I think that everybody understands that it is a lifelong drive and desire, and it doesn't just simply end with aging or menopause, and there is actual data to support this. This is from a large cross-sectional study of over 2,000 women. They identified 61% of those who are sexually active and stratified due to age, and if you look towards the bottom of the slide that sexual activity, women who are sexually active and had a high sexual satisfaction, is not age-related, so it is not as though something just shuts off at a certain time point, although there are some physiologic changes that may impact the quality of that sexual life, but one of the most important things about sexual activity in mature and post-midlife women is the availability of a functional and available partner, so oftentimes the male partner or the same-sex partner may have a sexual disorder, they may have some age-related health issues, there may be divorce, so the one thing that really is a strong correlate is good communication with a cohabiting partner. So, if your patient is in a relationship and if she is 60, 70, 80, you need to talk about sex. It is not something that you should just simply assume is not going on. Frequency does go down, and that may be due to physical capabilities. It also may be due to vulvovaginal atrophy or GSM. So, we are going to look at some of those physiologic changes which take place, which may impact the ability to function sexually.

As I mentioned, while there is lifelong sexuality, there is also a very strong overlap between vulvovaginal atrophy and sexual dysfunction. This is another cross-sectional study, the MEPI study, looking at 1400 women, 40-65, so it's in the mid to earlier menopause years. The prevalence of VVA was 57%, so there might be a hint to some of the answers to your questions there, and they identified a very strong correlation, a fourfold increase, of FSD seen with women who have VVA. So, if you examine your patient, you identify changes consistent with hypoestrogenism, menopause in the vulva, there may be some reason to discuss their sexual function

and certainly not to avoid the conversation. So, I think that the nomenclature is a little bit confusing, and is this a physiologic or a biologic condition, is it a sexual disorder? ACOG has helped put this a little bit into context and says that dyspareunia is really characterized as a pain disorder, and we will identify why some of the changes that we see with GSM would elicit that kind of pain, and then that pain subsequently interferes with sexual function.

So, what's the impact? We saw from the MIDUS study that older women want to be sexually active. They engage in sexual activity. What happens when they have VVA and they lose that capability? You see here – this is a survey, the CLOSER survey which was published by Dr. Jim Simon, in menopause, again a large sample. They also interviewed male partners of postmenopausal women with symptoms of VVA, and you see that this really is a dyadic problem. It is not just the single partner that is experiencing difficulty, but the partners also don't want to hurt their spouses or their partners. It impacts the partner's sense of intimacy as well, and this can cascade into quality of life issues, self-esteem issues, so I think it's certainly important to have on your radar screen and ask about it.

Ok, so let's define our terms. This is actually fairly new nomenclature. I'm not sure. How many of you in the room have heard about genitourinary syndrome of menopause? So, we've got a smattering of hands, so I guess we have our work cut out for us. It's always hard to change terminology. This came out of a consensus conference that I co-chaired with about a dozen leaders in the field – endocrinologists, urologists, sex therapists, pelvic floor surgeons. We were trying to figure out exactly what is going on based on all the literature and all the things that we understand about this common condition which was being neglected. Even though there were available treatments, there seemed to be a disconnect between awareness and discussion with patients. So, after all was said and done, we realized that it really isn't an isolated problem or one solitary symptom. If you look at some of these labels for these therapies, it says it treats atrophic vaginitis. Well, this problem doesn't just affect the vaginal epithelium. It's not an inflammatory condition. It affects genital, sexual, and lower urinary tract symptoms. So, when you take a review of systems and you take a history, it's really important to ask these questions about, you know, are they having any dryness, burning, or irritation, even outside of the context of sexual activity. Some of these women complained about their clothes not feeling right. They can't exercise. They can't be on their bicycle because of the external genital dryness or burning. They burn after intercourse, not just feeling pain or tearing during sexual activity, loss of lubrication, and then the lower urinary tract can be affected with symptoms of urgency and dysuria and recurrent urinary tract infections. Our urology colleagues see a lot of menopausal women who all of a sudden come in and are getting all these recurrent urinary tract infections, have cycle after cycle of antibiotic when, in fact, treating the underlying condition could do a lot to alleviate that comorbidity. VVA is a component of GSM. We're not getting rid of that term, especially since that's part of the regulatory process to get a drug approved for treatments of this condition and its symptoms, but we're trying to put it into context of a syndrome, which is a constellation of signs and symptoms. And of 500 women who have symptoms of VVA, 85% in this one particular survey identified dryness as being their bothersome symptom and half pain with intercourse, likely associated with whether or not they were in a paired relationship.

So, do we have any data to support this idea that we came up with as a group of doctors in a room trying to figure out, you know, how to name a condition? Well, there is a very large big data claims database that does support this. When they looked at over 50 million covered lives, 4 million Medicare recipients, they looked at ICD-9 codes for vulvar and vaginal atrophy or atrophic vaginitis to see whether or not there was an overlap with other conditions. And here are just a few of the categories, and this may be partly due to the challenges of coding. I'm sure that that could be a whole day symposium in and of itself in how to categorize the complex patients you see into a code, but what you see is anywhere from a twofold to a six-fold association with other symptoms or conditions. You know, and I point to, largely to the menopausal disorders, the overlap with this with menopause which some women fail to recognize. They think that menopause was hot flashes. Their hot flashes are gone. Their periods are over. "I'm done with menopause. So why are you telling me now I have a menopause-related condition?" And then the urinary tract symptoms, which we talked about infections, a twofold increase associated with urogenital atrophy.

Ok, so why is there this disconnect between a prevalent and common condition and identification and treatment? Well, as I mentioned, it is a component of a broader syndrome or a complex of symptoms. It affects between 50-70% of the 64 million women in the US. So, it is incredibly prevalent, probably far more common in the ongoing dealing with the consequences of menopause than hot flashes. Your most common sufferers of vasomotor symptoms are women in the early menopausal transition. It looks to be fluctuation of hormones that are associated with the vasomotor instability, and once the body adapts to that, patients often have resolution of their symptoms in a relatively brief period of time, although you do have women who suffer for decades with hot flashes, but unfortunately, GSM or VVA is the gift that keeps on giving. It worsens over time and doesn't improve without treatment. So, you really do need to ask and evaluate it each visit because this may be a chronic and progressive condition, and they are unaware that it is associated with menopausal state simply because it is happening remote from that sentinel event of their last period.

So, it's vital that you raise the issue with your patients because although it's quite common, most women fail to get treatment. About 93% fail, so we're really missing the boat, and if these numbers look startling to you, then it means you're maybe doing something right

or that we often convince ourselves that we're giving comprehensive care, but in that time that you have for the well-woman visit you've got to cover a lot of ground, and there are some things that the patient might think are more important, their mammography, a history of a breast biopsy, whether or not they are having any abnormal bleeding, incontinence. So you have a lot of ground to cover, and this may be something that just simply gets lost. It might be embarrassing to talk about sexual function. We don't really get much training in taking a sexual history. A lack of knowledge, lack of awareness of approved treatments or concerns about the risks and labels of therapies that are out there. Women who do seek treatment are often dissatisfied with safety, convenience, and efficacy, and we're going to get into that very soon.

So, it is, women report that only 19% of their health care providers address their sexual life, which I think is unfortunate when we think about how important, again looking back to the MIDUS survey. This is an important issue for women and men lifelong, and we shouldn't neglect it, and they come to a health care provider for good evidence-based and balanced information. So, if we're not the ones they're talking to, they're getting their information from not the most reliable sources. Only 13% of the clinicians raise the issue at the time of the check-up. Women think it might be a consequence of aging. This is just, you know, "Sorry, you know, I had a good run, and now this is, you know, what happens." And they again don't associate it with menopause. There are some surveys to support this. The dash bars are patients who bring up the symptoms of VVA, and the pink bars are the ones of, you know, the clinicians. There's really only one outlier, the international VIVA survey, which showed that half of those clinicians, whether or not that's due to cultural differences, some of the Scandinavian countries or European countries are a little bit more open with sexuality, but even in the EU and across the US, very small numbers of us are bringing this up with our patients, and I think it's tragic.

So, let's talk about diagnosis. Just ask. Every woman who is transitioning into the menopause may start having some of these symptoms. So when they come in, you know, say, "Are you having any changes in your sexual function? Are you having any dryness? Are you having any pain with intercourse? Is it something different than it was before?" Also, you can look at during the time of exam, the introitus is just not a space to introduce your speculum, to grab your Pap and get it over with, although certainly patients do want that exam to be quick and as uneventful as possible, but you need to examine the vulva before you go ahead and quickly insert a speculum because that is where you're going to see the majority of these changes. The vaginal changes may be a little bit later, and they present variably. Everybody does present variably, but there are some morphologic changes that are very consistent with this syndrome, which we're going to show you some of those. So what's going on physiologically, and why is it so sensitive to hormones? If you look on the right of the slide, a cross-section shows an area where the most dense area of estrogen and androgen receptors in the female body derive from the urogenital sinus, and that covers the vulva, the clitoris, the lower bladder, the urethra, the vestibule, so these are incredibly receptor-rich tissues, and as soon as there's fluctuations in these sex steroids, you have marked changes in the tissue. You have a lush, superficial cellular layer which can be measured, we'll talk about this in clinical trials, that is full of glycogen. That glycogen is broken down to lactic acid, which gives you an acidic pH, helps prevent pathologic colonization with bacteria, and in a smear of a postmenopausal woman, there is an increase in the immature parabasal cells and a decrease in that superficial layer, which leads to the kind of physiologic and anatomic damage that we see.

So if you look at the photo, and these are all courtesy of Dr. Murray Freedman from Augusta who was part of our consensus panel, and he has really helped us. His patients are very kind in allowing for these well-controlled photographs. These are dermatologic and almost, you know, when you go to plastic surgeons who control for lighting and reproduction of the photographs, have identified some of the signs that we can identify for GSM. There's a decrease in moisture and elasticity, and I really want to stress that this is probably one of the biggest reasons why patients have such discomfort is that the tissue loses its stretchability. In a healthy premenopausal woman, the introitus and the vagina can expand to accommodate childbirth, and in a postmenopausal woman, that elasticity is almost completely gone for many women, not all women, which that might be due to the bioavailability of their own sex steroids. You see that the labia minora are absorbed, the opening loses its concavity, and then the urethra becomes very prominent. So if you're examining a patient because the vulvar introitus is contracting and becoming more stenotic, this urethra is really becomes almost like a target for intercourse, and trauma might lead to some of the urologic symptoms that we're seeing, so you're going to see some even more dramatic presentations of this, but you know it when you see it, and I think that, you know, if you have a patient who comes in, even if she hasn't brought this up, you can say, "You know, I've seen some changes in your exam. Are you experiencing any, etc.?" And I think it's a great way to discuss that with them.

But based on our consensus, you know, women may present with some or all of these signs and symptoms. You might say, "Are you having any burning, irritation, pain with sex, loss of interest due to pain, dysuria?" She'll say, "Yes, yes, yes, yes," or she might just have one isolated symptom, but you do want to exclude other causes. So this is not necessarily a diagnosis of exclusion because I would say nine times out of ten when a patient presents with these types of symptoms post-menopausally, it is GSM, but you want to make sure that it's not an infection. You can simply do a wet smear and make sure of that. Make sure it's not a dermatologic condition, such as lichen sclerosus, which is going to respond to very different treatments. Lesions should be biopsied to make sure there's no

neoplasia, and make sure that it's not vestibulodynia or vulvodynia, primary or secondary, but that it is, in fact, this particular syndrome.

So now let's talk about treatment. I hope that we've at least raised the awareness that you've got to talk about it. You've got to engage the patient because there is this disconnect. What are the options? Well, if you go to CVS and you see a whole row of lubricants and moisturizers, his and hers and flavored and colored, it's because, one, there is a need, and two, a lot of women avoid medical treatments, and we'll talk about why that is, but these really don't treat the underlying physiologic changes. They can certainly help with short-term relief. They can be a sexual aid used at the time of activity, or they can use moisturizers on a scheduled basis to improve retention of fluid and water in the vagina, but again, we've shown you some of the damage that the epithelium can undergo, so it's critical to reverse that, and that is really only going to respond to treatment.

So, what does the FDA tell you you have to do in order to prove that your treatments work? There is actually guidance for this. These drugs just don't, you know, come out of thin air, but there are very strict requirements, and actually in this particular therapeutic area the requirements are a little bit confusing, and the labels are very disparate. If you look at some of the products, it'll say it treats atrophic vaginitis. Another says it treats dyspareunia. Another says it treats urgency associated with vulvovaginal atrophy. Others say it treats vulvovaginal atrophy. It's treating the same thing. It's treating GSM, and the reason why there's that confusion and the reason why the FDA changed their guidance is because of that and that one, you have to demonstrate objective improvement in these physiologic parameters. You have to improve pH and the superficial and parabasal cell counts, and then you also have to improve a patient's symptoms. It's not simply enough to tell your patient, "You know, I think you're cured. Your pH is better." They want to know that they don't hurt anymore or that it's not dry anymore. So the FDA has mandated that a patient reported outcome be achieved, and they've identified the five most common as what patients might choose as their most bothersome symptom. As I've said, it's often a huge overlap, so to isolate one symptom and to treat that and to approve for one isolated symptom is a little bit challenging, and I think that's something that is being looked at from a regulatory standpoint.

So I hope that they provide you with these slides because this has got a lot of information, but the long and short of it is that there are available estrogen-based local low dose vaginal estrogens, creams, tablets, rings. They have advantages and disadvantages, and the advantages of tablets and rings are that they are scheduled dosage regimen so the patient can't under or overdose, although obviously with a tablet they may use it less frequently. The low dose vaginal tablet has, at least in my clinical experience and a lot of clinicians who I've talked to, been, in fact, it may be a little bit too low of a dose and that it doesn't treat the entire vulvovaginal area, so it doesn't give you the coverage of introital benefits, so often these patients end up using cream on the outside, tablet on the inside. Patients often complain about creams as being messy and are confused about how much they use, how often do they use it. The oral estrogen agonist and antagonist, ospemifene, does increase some menopausal symptoms, such as hot flashes, but it does have the benefit of acting as an estrogen on some tissue and an antiestrogen on others, and then a new treatment, vaginal DHEA, a daily dosing, which some may find either inconvenient or a good schedule to follow as opposed to, "How do I divide seven by two? Do I do it Monday/Thursday or is it a half a day?," and also the advantage that it doesn't have any box warning. So we'll talk a little bit about all of these and see if we can't help you at least distill this into a conversation that's manageable for you and your visits with your patients.

So, estrogen has been studied for decades. These have been approved for decades, but unfortunately when you look at the uptake, it's still very low. Patients are, since the Women's Health Initiative, are very fearful of any form of estrogen, which is unfortunate, but that's the hand that we were dealt in 2002 with the publication of the Women's Health Initiative. We do know that estrogen reverses changes. It lowers pH, improves blood flow, capillary growth, and thickens the epithelium. It'll change all those parameters that we discussed. It alleviates most of the symptoms, and that's why some of these products have labels that describe a variety of symptoms that it's treating. The side effects are usually minimal, but oftentimes patients, especially early on in treatment when that epithelium is very thin and there's a systemic absorption, patients may also have some systemic side effects. They may complain of breast tenderness. They may have some cramping or discomfort with these products, so don't assume that just because it's local and vaginal that the patient may not be experiencing some side effects.

The biggest side effect is the product label, so even under the best of circumstances when you counsel these patients, they go home and they read the boxed warning. They say, "This is just not worth it, dear." The husband or the partner is going to say, "You know, I love you too much. I don't want you to get dementia and have a stroke when you use your low dose vaginal estrogen." Now NAMS has tried to approach the regulators to tell them that, you know what, there's a difference between systemic and local, but until there's very large prospective data, I think that we're going to be living with this for quite a long time, so no matter how much, and I have used a lot of these treatments in my day, it's still a challenge no matter how much time you dedicate, and I think that until we can figure out a way to overcome this label, this is probably the biggest side effect to the local vaginal estrogens, but they work, and again, this is courtesy of Dr. Murray Freedman. Again, looking on the left, you see a patient with the signs of VVA/GSM. You see that lack of elasticity. That labia is barely able to stretch, and then on the right after estrogen treatment, color, the concavity improves. The urethra becomes less prominent, so this is really something that you can see and identify in your patients. They can come back. Often colleagues will use

mirrors to let the patient know, “Hey, there’s a change here. Let’s follow this and show that you are improving.” But it can be dramatic, and you can imagine how uncomfortable the patient is before on the left and relieved on the right, but unfortunately these changes can reverse. This is a patient who was using her estrogen in July and then the following year had gone off, either decided that she was afraid or perhaps her partner was no longer functional, but you see how this can reverse and go back and forth, so the ideal treatments are going to be the ones that patients take and can take for a while and stay on it indefinitely as long as they are sexually active or as long as they are having symptoms.

So let’s talk about some of the recently approved products because they do differentiate from estrogen in some ways and not in others. So the first one we’ll talk about is ospemifene. I’m going to be showing a lot of my data. I participated in a lot of these approval trials, so I’ll share with you some of the slides from my publications. Ospemifene is an estrogen agonist/antagonist formerly known as a SERM, a selective estrogen receptor modulator, for the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause. So again, here you see it says it’s treating a symptom, not treating a condition, and therefore it is approved for dyspareunia but not for those other symptoms. I would beg to differ. I think it’s treating all those symptoms as well. It has to be taken daily, 60 mg with food. It’s not absorbed as well without food, so if you have a patient who you’ve given this to seem to be responding but is not, maybe something’s changed. Maybe she is taking it on the run, forgot to take it with breakfast or dinner, and there are some warnings and some interactions. Don’t use it with other estrogens. Fluconazole will increase serum concentrations. Rifampin will decrease those.

So, what is ospemifene? It was actually originally studied as a triphenylethylene. It looks a lot like tamoxifen molecularly. It’s structurally changed just slightly and doesn’t have the same profile, doesn’t have the same stimulation of the endometrium, although there is a little stimulation of the endometrium, but it was originally studied for osteoporosis, and that was because it reduced bone turnover and increased bone strength. It’s not approved for any of the osteoporotic conditions, but another SERM as you know, raloxifene, was approved and is available for osteoporosis treatment and prevention. It induced mucification and changed the benefits in animal models, and so they said, “You know what, maybe this is a SERM that’s different than raloxifene. Maybe it helps urogenital atrophy,” and that was really, you know, that’s the beauty of SERMs is that they can block estrogen like tamoxifen on the breast, and unfortunately tamoxifen stimulates the endometrium. Raloxifene helps on the bone but doesn’t do much for the vagina. This one looked to be beneficial at the breast bone and vagina, and it was the vaginal benefits that were ultimately studied and approved.

So, here you see, we’re going to run through some of these slides quickly because they all kind of look the same, and I think that’s why I would venture to say that even though there’s no head-to-head data comparing all these products, you often hear clinicians or patients saying, “Which one’s better?” I think it’s not which one’s better as in which one’s right for you. So if you look at the changes, and this is both the intention-to-treat population and the per-protocol population, they look pretty similar, so I, and just pay attention to one or the other. You see that the maturation index of superficial cells increase. Parabasal cells decrease. You’re reversing the physiologic changes, and then the pH improves. You’re lowering it to that acidic pH, which again creates a healthy epithelium, a glycogen and reduced pathogens, and will likely translate into fewer vaginal and urinary tract infections, and then the symptom. It’s interesting because the objective parameters in placebo don’t change hardly at all, but when a patient’s in a clinical trial, they do, and in fact, in these clinical trials we had to allow patients to use lubricants on demand. So, you’re really, your placebo group is a lubricant control group, so they’re going to improve a little bit, too, but statistically, it’s highly statistically significant compared to placebo, and as you see, the P value 0.0001. These patients are improving. Their most bothersome symptom of painful sex has improved at 12 weeks.

Well, what about dryness? And this, in fact, is why ospemifene is not approved for dryness and dyspareunia is that they looked at it, and the P value is 0.08. So does that mean that it doesn’t improve dryness? It means statistically it wasn’t demonstrated, but I think most of us would agree that if the pH improved, if the epithelium improved, these patients are getting symptomatic relief. It’s just an unfortunate disconnect the way that these drugs are studied and the way that the label ultimately reads. Well what about the other component? We mentioned that genitourinary syndrome of menopause are genital, sexual, and urologic symptoms. What about the sexual symptoms associated with VVA? And again, Dr. Kellogg, who really understands this space really well, is going to talk to you about primary hypoactive sexual desire disorder where you have patients who don’t have any underlying cause. These are women who have VVA and subsequent sexual dysfunction, that there’s a nice tailwind here for patients and their sexual function. They didn’t necessarily have dysfunction at baseline, but you do see that from 4 and 12 weeks compared to baseline that their total FSFI, which is a validated survey for sexual function, the Female Sexual Function Index, did improve statistically, and all the domains of sexual function – desire, arousal, lubrication, orgasm, satisfaction, and pain reduction – all improved. You’ll notice that the biggest delta is with lubrication and pain because that’s what we’re treating is this pain disorder, but if the patient is saying she’s got a lot of these things going on, I think you can tell her that these treatments may in fact improve them. We’ve seen this with estrogen as well. The side effect profile: hot flashes, vaginal discharge, and leg cramps. One of the big challenges, though, is the label.

While we did look at histology, this is a paper that Steve Goldstein and I published, looking at the endometrial biopsies, these patients are very kind to allow pre and post biopsies. It’s no picnic to be in these trials, and you see a little bit of a shift in the ospemifene group

at week 52, the third column, where you had a little bit of weekly and active proliferation, one case of hyperplasia, but it does look like the majority of this is atrophic, and none of this believe that this is a tamoxifen on the uterus.

However, the FDA begged to differ, and they said, “Well you don’t have enough long term safety data to tell us that, so we’re going to put a boxed warning for endometrial risks, endometrial cancer there even though there were none seen,” and it does have, unfortunately while you would think it has the best of both worlds of being an estrogen agonist and an antagonist, it also has the worst of both worlds when it comes to the label, and it’s labeled like an unopposed estrogen for the endometrium and some of the risks, vascular risks, that were seen with some of the SERMs. So it does improve symptoms, but it does pose some challenges for patients who don’t want systemic risks.

So what I want to conclude with, there will be time for some questions I think after the next speaker, is a just-approved treatment which we also studied at our center and published some of this data – prasterone – which is a steroid indicator for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause, again isolated dyspareunia, but we’re going to run through very similar data that I just showed you because these studies are all designed identically. So even though there are no head-to-head comparisons, we can compare across trials. Well first of all, what is a DHEA? Dehydroepiandrosterone is a prohormone. It’s secreted by the adrenal in huge amounts. However, there are no identified functional DHEA receptors. It has to be converted locally in local tissues to the active hormones, and that’s done very efficiently intracellularly. So here you see a DHEA is administered vaginally. It’s converted to testosterone and estradiol within the cell and likely also deactivated within the cell. So, the reason, and we’re going to talk a little bit about the label, is different is at very, very small amounts. Less than the 95th percentile of postmenopausal norms were identified in these patients, so incredibly safe profile because it seems to be all this intracellular conversion seems to be done locally, and the metabolites are put back into circulation and hopefully with little to no systemic effects. It looked at all the parameters we talked about – pH, MI, and moderate to severe dyspareunia – and we’ll run through these again rather quickly. Here you see superficial cells improving. The first smaller trial, not quite as a robust effect, but there you seem very similar improvement in superficial cells in the large registration trial. You see the pH and parabasal cells also mirroring other studies that we’ve shown you, so the objective parameters are improving. The most bothersome symptom again almost identical. So you see that whether or not this is just the limitation of the study designs, we really do demonstrate that these drugs are similar in their efficacy. What’s interesting is that it seems like no matter how you give these drugs, orally, intravaginally as an estrogen, or here daily as a precursor insert, they all seem to appear quite effective. There was dryness looked at in this population. As I mentioned, there’s a lot of overlap between the patients who suffer from these symptoms. 80% of the women in these studies who presented with pain with intercourse as their most bothersome symptom also had dryness, and that improved. It went from a moderate to severe level at 2.3, severe being 3, down to 0.8, so it was either none or mild, and this was not even a dryness study. So you do see that it is treating the constellations of symptoms.

Again, the FSFI total improving across the board at 4 and 12 weeks, so sexual symptoms did seem to improve, although these patients are not being studied for sexual dysfunction. They just had that overlap as we discussed. And then all the domains – desire, arousal, lubrication, orgasm, satisfaction, and pain. So, as I mentioned, these are all very similar in efficacy, but I think a big differentiator here is the side effect profile and the label. Discharge – this is a daily vaginal insert, so the placebo group did have higher rates of discharge. The patients on the active treatment had slightly higher rates in an uncontrolled, non-compared about 15% vaginal discharge. Sometimes these patients say that’s good. “I was so dry, I need some lubrication.” Discharge is a pleasant side effect. Others would say, “It’s not something that I really wanted.”

And then the endometrium was completely inactive. This is a biopsy study that again we published. We saw no proliferation, and the FDA, also, I think, was very impressed with this. This could be due to the fact that intracellularly you need to convert DHEA into estrogens, and the normal endometrium has not been identified as containing aromatase, so maybe that’s why we didn’t see any activity. All bets are off for abnormal endometrium, so that’s why you want to make sure the patients don’t have abnormal bleeding before you start them on any of these products. So, how about the label? And I think this is really very helpful, so if you have patients who have a label phobia, and when you hand them, you have to give them the package insert. No boxed warning. It talks a little bit about before you treat them they shouldn’t have any abnormal uterine bleeding, and if they have a current or past history of breast cancer because it hasn’t been studied, and that estrogen is a metabolite of DHEA.

So, I think that you have a variety of options, and I think that’s the critical aspect of the point that I’d like to drive home is that GSM is going to affect at least 50% of postmenopausal women. Let’s talk about it. Let’s identify it. It affects quality of life, both urogenital and sexual health. It remains underdiagnosed and undertreated even though we have many, many proven therapies that are effective, and so hopefully this has been an awareness-raising session and you can go back to your offices and start to engage your patients and identify them and hopefully help them improve their quality of life. So with that, I thank you very much for your attention.

ANNOUNCER CLOSING

Thank you for participating in the Omnia Education CME activity, entitled *Postmenopausal Dyspareunia: Innovations in Therapy and Patient Management* presented by Dr. David Portman, recorded live at the Women's Health Annual Visit in Philadelphia, Pennsylvania.

This activity is supported by an independent medical educational grant from AMAG Pharmaceuticals.