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Dyspareunia: Best Practices in Counseling, Diagnosis, and Therapy

ANNOUNCER

You're listening to ReachMD and welcome to the Omnia Education CME activity, entitled Dyspareunia: Best Practices in Counseling, Diagnosis, and Therapy presented by Dr. David Portman and recorded live at the Women's Health Annual Visit in Chicago, Illinois.

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DR. PORTMAN:

Dyspareunia and female sexual dysfunction, two things that both our patients and clinicians seem to not want to really talk a whole lot about, so you're going to hear me talk a lot about it today. So, we all know about male sexuality and the aging male, but the neglected part of that diad is really the female. It would be a crime to treat a male partner without first addressing whether or not the female partner is

sexually functional. And that really is the painful truth that vulvovaginal atrophy is significantly underdiagnosed and also associated with sexual dysfunction. It's not a sexual dysfunction, per se, and fortunately the Center for Medicare and Medicaid Services realized that and now is going to allow for treatments of dyspareunia associated with menopause because they recognized that it is a pain disorder associated with some sexual problems. So, it's a chicken or the egg story, is that "What comes first?" Is it the pain and then the decreased sexual function? Or vice versa? In this instance, it's almost always associated with the pain, the dryness, urogenital symptoms, and subsequent problems with arousal, desire, and orgasm. This is some patient-reported data and this is interesting because it not only queried the female patient, but the male partner as well, so this "He said, she said" survey you see is fairly aligned in that the male partner recognizes that their partner is having pain, loss of desire, and they even seem to perceive even a greater avoidance of intimacy. Let's delve a little bit deeper into GSM. So I was fortunate enough to work close to a dozen interdisciplinary professionals, urologists, gynecologists, endocrinologists, sexual health experts – because we were very frustrated by the lack of awareness on the part of clinicians, as well as patients, that there was a common condition that was associated with genital and sexual and lower urinary tract symptoms associated with menopause, and our patients weren't aware of it, clinicians were underdiagnosing it, and yet, in the aging male, there seemed to be great acceptance of erectile dysfunction, and we thought that language is really quite important, and if you term something vulvovaginal atrophy – first of all, most men don't know what a vulva is; many women don't – and atrophy is pretty demeaning, so the idea of that kind of diagnosis we felt would be akin to calling something impotence or something even more pejorative, and it also didn't recognize the constellation of signs and symptoms that these patients suffer from. We concluded that it really was a syndrome. It was a constellation of signs and symptoms that were associated with a decrease in estrogen and other sex steroids, namely androgens, and it involves the entire lower urogenital tract, including the urethra and the bladder, and, therefore, dysuria, recurrent urinary tract infections, and urgency, we felt, were part of this syndrome, as well as the cascading effects and impacts on sexual health, which are initiated by the dryness, burning, and irritation in the genital tract. So, we do have a very high incidence – 50-70% in most surveys, so you're looking at about 30 million U.S. women – largely seeing primary doctors. The most common symptoms that they describe are painful intercourse and dryness, although they may present very differently in each woman. Some may say, "I'm really bothered by burning," "When I now exercise, my exercise clothes bother me," "I can't sleep because of itching or irritation," certainly want to exclude other conditions, but the challenge with this, as opposed to vasomotor symptoms, is that a lot of the time those will go away and become more mild with time. This, unfortunately, is the gift that keeps on giving, and it really doesn't improve over time and usually gets worse without treatment. And patients, unfortunately, often see it as a normal consequence of aging. They may be embarrassed to talk about it. They're concerned about treatments

that are available if they're hormonal and have significant negative associations with those hormones, and they may also have dissatisfaction with other products. In this survey, you'll see a very consistent pattern, about half of the women will initiate a conversation if they have symptomatology. On the other hand, the clinician, only about 10% of the time, even when women present with symptoms, are querying those patients. It's almost a don't ask, don't tell – the clinician may not want to spend the time. They may feel ill-equipped to counsel. The burden of talking about hormones becomes a day-long discourse to convince somebody that it will not cause great harm to them. You should really ask all your patients who are in this menopausal transition. We've seen this in the epidemiologic studies, that there's a great inflection in urogenital symptoms at that perimenopausal time, so that's a good time to start asking not just "Are you having problems with hot flashes, night sweats, sleep disturbance, emotional changes due to lack of sleep or hormonal fluctuation?" but also ask about urogenital symptoms and see what type of onset that those patients are describing. So, talking about the well-woman exam – the annual exam – I think this is critical that as gatekeepers you really are a first line of defense. If these patients don't get some counseling and good information from you, they may go on to assume that this is all there is and live with, unfortunately, a very chronic and debilitating condition. So, ask about all of the symptomatology that they could present with, the timing, and see if it is, in fact, GSM. Sex steroids are greatly implicated in this condition. If you look at immunohistochemistry and gene expression analyses, there is very clear expression of androgen and estrogen receptors in the lower and upper urogenital tract, and you see changes in these distributions with changes in circulating sex steroids, so the receptors are very responsive as well as all the enzymatic machinery in the tissue to utilize sex steroids, and when they become less available, the consequences are quite obvious – the epithelium gets injured, it becomes dry, decreased mucus production, less elasticity because of changes in collagen, and here you see on the right, these are the areas where the most estrogen and androgen-rich areas of receptor density are found, right where all the problems with GSM are – in the bladder trigone, in the urethra. We can see this microscopically in that the superficial layer of the vaginal epithelium is replete with these glycogen-rich superficial cells. Those can turn lactobacilli into lactic acid and, therefore, maintain an acidic pH and prevent pathogens from colonizing. In the menopause, you get a very thin layer, which leads to easy injury, an alkaline pH, and susceptibility to infections. And this is really a shame when a patient comes in for her annual exam – if you're going to do a Pap, if it's indicated – and you see this. You basically just see a urethra replacing the introitus. And this is not unusual. This patient's clearly going to have painful intercourse. If you look at the labia, they become infantilized. So, it's almost the bookend of prepubertal lack of sex steroids; the labia regress, the urethra becomes prominent, you can see that the tissue does not have much elasticity, and this is really a recipe for all of these symptoms and signs of GSM. This is a very classic presentation what you don't want to do is assume that all of this is due to sex steroid changes. There

are some pathologic conditions that you should put in your differential, but common things are common. If there's a pigmented lesion, certainly rule out vulvar cancer, but these other dermatoses are more rare and more associated with severe itching and more diffuse or patchy types of changes in the skin. You can do a simple pH test, and if it's alkaline and the patient had these symptoms arise during menopause, it's almost certainly vulvovaginal atrophy or GSM. So, looking at treatment options – the first thing that patients will do and the first thing I think that you as clinicians can do is recommend some lubricants or moisturizers. Lubricants are for on-demand use to apply to themselves or their partner to help aid with intercourse and penetration. Moisturizers, with some new ones with hyaluronic acid, are out and available. They're used twice a week and used on a maintenance basis. Unfortunately, that does not reverse the physiologic changes, so it's kind of a Band-Aid rather than a cure. It may, with mild symptoms, help patients get through some of the discomfort, but it may not improve the blood flow and the underlying muscular changes that may lead to pain and sexual dysfunction. As I mentioned, I've done a lot of the research that got these therapies approved and into the clinic and into patients' use, but we want to make sure we are measuring what we need to measure, and a lot of the treatments that were approved decades ago essentially said, well you have a high pH and you have superficial cells that are absent, so you have vulvovaginal atrophy. If we can change those, then that treatment works. The FDA has since, in 2003, mandated that you not only change the underlying objective findings of vulvovaginal atrophy, namely an elevated pH and decreased superficial cells and elevated parabasal cells, but you also have to improve the patient's symptom, and that makes good sense is that we want patient-reported outcomes and we also want objective findings that support use of a medical treatment. And really the classic treatment for this is estrogen, so, this isn't the place to debate the Women's Health Initiative, but that genie is out of the bottle and, unfortunately, I don't think we'll ever see patients' comfort with pure estrogen therapy's return, but it is a highly effective treatment for urogenital atrophy. It does not necessarily address the fact that there are androgens present, and many clinicians, especially in the sexual medicine field, feel that that's a neglected steroid that may benefit from supplementation in GSM. This table may or may not – it's been updated because there's a new treatment in here. There's a vaginal insert that was recently approved, but really, up until 2012, 2013, when a serum was approved – an oral serum for VVA/dyspareunia, and then an intravaginal DHE-approved – all treatments have really been estrogen based, so we had our hands somewhat tied. One could say there was flexibility – well do you want a vaginal tablet, which is a little bit easier to dose I actually wrote a paper that patients did prefer and refilled vaginal tablets more often than creams, which were perceived as messy. Patients were concerned that maybe they weren't dosing themselves right. The creams, however, are able to be applied externally, and that may be an advantage. The ring is easy to use in that it only needs to be placed and removed every three months with very low exposure to estrogen. And now the newest

entry, a soft vaginal insert without an applicator gives patients another option, needless to say, another estrogen option. The biggest challenge with estrogen is estrogen-related side effects that we see systemically. You have a patient who starts on vaginal estrogen - she can say that she is having some breast tenderness. She might have a burst of estrogen systemically that she'll actually get symptomatic with, and I think that those are important symptoms to acknowledge and warn them about, but the first thing they're going to do is look at the box label and say, "Well, if I'm having breast pain when I put my vaginal estrogen in, what is that doing? There's a box warning here about breast cancer and endometrial cancer. This is just too much worry." NAMS had submitted a petition to the FDA and said, the Women's Health Initiative looked at high-dose oral estrogens and progestins, how can you possibly assign the same label to vaginal estrogens? It's just a totally different animal." The FDA, said, "Well, we still are going to have this labeled because we need more data but clearly the consensus from clinicians is that local vaginal estrogens to expose patients to much lower estrogen levels and likely confer greater safety, but that message has not gotten through to our patients and, unfortunately, it's a very challenging consulting issue in the office. And just to show you a few other photos from what you might see – how the vaginal estrogen and the other therapies can improve the exam, and these are quite dramatic. These are from Murray Freedman's clinic, and you can see, again, the very classic presentation – the attenuated labia, the lack of elasticity, the very prominent urethra, the stenosis of the introitus – you see all of this and it's almost pathopneumonic for GSM or vulvovaginal atrophy. And you can see that same patient is highly responsive to the estrogens. The mucosa looks much more moist and pink. The urethra much less prominent. The labia more defined and elastic. Unfortunately, that same patient decided, well maybe I don't want to take my estrogen, and you can see that when those changes were improved – this is actually a different patient who was on estrogen here, she goes off and the changes all come back quite markedly. So, the good news is patients can go on and off therapy, but when they do go off therapy, the medication stops working. So, let's talk about some alternatives. When you see your patients in the office, and 1) they're having trouble discussing this issue with you, and 2) it's a little bit challenging to bring it up – I think having other options is certainly going to serve us and our patients much better. So, let's look at some of the recently approved therapies to see if we can't begin to diversify the way we counsel our patients. First, it's important to recognize that these new options are now available – should be available soon – to patients over 65, and that was a challenge in that because the FDA mandated that a bothersome symptom be included in the new guidance, instead of approving products for vulvovaginal atrophy writ large, and therefore that's a medical condition, what the drugs such as Ospemifene and intravaginal DHEA did was that they studied the most bothersome symptom and the most common bothersome symptom that was the best to measure, which is painful sex. Patients are pretty good at saying, "It hurt really bad before, and now, not so much. So, the center for Medicare and Medicaid Services recognize that, that just because

a product is approved for dyspareunia, it's not approved for a sexual dysfunction, but it's approved for a medical condition associated with menopause, these therapies may be, in fact, be available quite soon, if not already, to your Medicare Part D patients. So, let's look at the first one that came to market, and I think that it really did appear and was studied because everybody knew that women and clinicians were looking for alternatives to estrogen. Estrogen, which stimulates breast tissue, it stimulates the endometrium; however, it also has favorable effects on the bone and urogenital tissue, so how do we optimize that? Well, we optimize that by intelligent drug design and identifying drugs that combine to the estrogen receptor in certain ways that can turn some of the receptor on and others off. And that's exactly what Ospemifene does is that it's a partial estrogen agonist/antagonist depending on the target tissue, and it's a 60 mg tablet taken once daily with food. It is not that bioavailable, so it is recommended to take with food and not on an empty stomach. There are a few drug-drug interactions and it does carry similar warnings as estrogen, unfortunately. So, while they were trying to finesse a way to have something that wasn't quite – was a kinder, gentler estrogen, unfortunately, because of small studies, they were unable to take some of the risks of the class label away from us. It's a triphenylethylene serum, so it's in the tamoxifen family, very similar to toremifene. This is from one of the pivotal studies that we published, and here you see very clearly that the superficial cells improve with treatment. This is after 12 weeks compared to placebo, and the parabasal cells are also regressing, which is very normal when you give the patient back the sex steroids that they need. And then the pH, likewise, decreasing by about a point, becoming more acidic, and then the patient's most bothersome symptoms improving statistically beyond placebo. I think it's really important is the placebo response, and this is seen in just about any patient reported outcome study. Here you see, however, that the active treatment arm significantly improving when it came to less pain. Also, there was a trend, although not statistically significant, towards improvement and dryness, and I would venture to say that really, if you're hitting the right target tissues, which are all the receptors in the lower urogenital tract as well as the bladder and urethra, you're probably going to see improvement across the board, but here you do see that one of the symptoms of dryness is improving, and I would venture to say that most symptoms will improve with these treatments. This is a paper that was published looking at what about if we improve lubrication and we decrease pain, shouldn't that improve sexual health? Won't those patients be more responsive sexually with greater blood flow? And, in fact, here you do see at both 4 and 12 weeks at all domains of the female sexual function index, which asks about 6 domains of sexual function – desire, arousal, lubrication, orgasm, satisfaction, pain reduction – all of these improved. You do have side effects – hot flashes because it acts as an antiestrogen on the vasomotor complex, likely from the hypothalamus. You do see about a 7.5% incidence of hot flashes; you have some vaginal discharge, which is really almost a class effect in most of these drugs that increase secretions and lubrications, and leg cramps and sweating. So, kind of your classic raloxifene or

tamoxifen side effects, but a pretty reasonable safety profile. It does have a box warning about endometrium, but I think that the endometrial profile looks very reassuring, but any postmenopausal bleeding should be evaluated. It does treat dyspareunia and, as I mentioned, that is good enough for Medicare Part D now to allow patients to take this, and we have safety data out to 52 weeks. But it does have warnings similar to estrogen – venous thromboembolism if there's a history. There's contraindications as well for vascular concerns as well as estrogen-dependent neoplasms. So, it's a label not dissimilar to estrogen. So, even though we were really trying to get another option out there and a more friendly label, that didn't happen, but it does work by a different mechanism, and hopefully, if you have patients who want an oral tablet and want something other than estrogen, this is certainly something in our armamentarium. What I want to spend a little bit more time now, in the last portion of the program, is the newest kid on the block, and that is intravaginal DHEA, or prasterone, and it's a steroid indicated for the treatment of moderate-to-severe dyspareunia symptom of vulvar and vaginal atrophy due to menopause. It's a once-nightly insert that comes with an applicator. It's in a Witepsol case, which is kind of a hard fat which liquifies at body temperature, and it's given to the patient and she takes it nightly as part of her routine, so before she goes to bed. So, what is prasterone? Well, prasterone is the generic name for DHEA and it's identical to endogenous DHEA, so it's a synthetic DHEA. And a little bit of background on why one would think that DHEA should be even considered when we talk about urogenital atrophy, and that if you look at a woman's production of DHEA, it's probably 60% decreased by the time she gets to menopause, so she does have less availability of this precursor steroid. So, to take you back to a little bit of your biochemistry, DHEA is a precursor to both estrogens and androgens. When it circulates in very large amounts in the circulation, produced largely from the adrenal as DHEA or its sulfated counterpart, it's inactive, so it only will activate if the tissue that it gets to, has the enzymes that can convert it into usable estrogens or androgens at the local tissues. And this schematic kind of shows you how that's done, is that it enters the cell, it can be turned into either estrogen, estradiol or estrone, depending on the enzymatic pathway, and then aromatized from androgens into estrogens. So, it allows for both bioavailable estrogens and androgens. And there's minimal systemic exposure. Just like we saw with estrogen and with Ospemifene, these are the data on the superficial cells, improving in both trials, and it just shows you why the FDA requires you to have two well-controlled studies is that a scientific experiment should be reproducible, and here you do see that both studies showed statistical significance; however, one was less robust than the other. It could have been a power issue or a simply different patient population. Let's take a look at parabasal cells. Here you see nice decrease in parabasal cells as well as a decrease in the pH. And this is all driven largely, these changes, by the conversion of DHEA intravaginally into the estradiol and estrone as well as into androgens – testosterone and androstenedione. And here you see very similar results. Placebo responding to the patient using a

nightly moisturizing suppository, and then the actual active treatment arm giving them greater relief of their moderate-to-severe dyspareunia. Just another comment about placebo effect – and here I think it's even more marked – if you think about the Ospemifene study where they're taking an oral tablet and that's what their placebo is, that may, in fact, not really give them any objective vaginal relief. Here they're using a nightly moisturizing suppository in the placebo arm, and then the active arm actually has the DHEA in it, 0.5% DHEA, and it's able to separate even from a woman who's using a nightly moisturizer. As I showed before, there's a lot of overlap between symptoms, and here you see that 80% of the patients who had dyspareunia also had bothersome vaginal dryness, moderate to severe, and they changed by close to a – here you see the point scale – they went from 2.3 to 0.8, and we'll talk a little bit about how you make sense of these types of small changes when we talk about HSDD because it's very challenging for clinicians when they look at a clinical study is that how meaningful is that to the patient? So, this was identified by these patients as meaningful in that they said that they were pleased with the treatment and that their own subjective symptoms were improving and going from moderate-to-severe to mild-to-none. A very similar type of analysis looking at the female sexual function index, and here you see, again, every domain statistically significant – desire, arousal, lubrication, orgasm, satisfaction, and pain. This needs to be investigated a little bit further because we all know that androgens drive sexual desire quite a bit, both centrally and locally, and we need to learn a little bit more about whether or not that added sex steroid that is metabolized from DHEA, namely testosterone and androstenedione, in the vulvar and vaginal tissues with minimal systemic exposure, would perhaps impact desire and arousal and orgasm in a different way than other therapies. It was well tolerated. The most common adverse reaction, as you would expect when you're using a nightly insert, is an increase in vaginal discharge. Here you see roughly 5% versus 3.5% in vaginal discharge with prasterone. In a 52-week study, which was looking largely at safety, about a 14% increase in vaginal discharge reported. We recently published this data in the Journal of Menopause, and unlike other therapies which have seen proliferation and hyperplasia, there was absolutely no stimulation in the endometrium in the patients we obtained samples from, and this was not a huge surprise, given that we know that DHEA is largely an inactive steroid precursor, and in order to get estrogenic effects, you need to have expression of aromatase, and since there's been no identified aromatase expression in normal endometrium, you essentially really wouldn't get any conversion intracellularly in the endometrium to cause proliferative changes and, therefore, there is no box warning. If you look at the pharmacokinetics, the amount of both estrogen as well as DHEA and testosterone after 24 hours is very close to placebo range and well within the range of postmenopausal women, and I think that's really likely what led to a much more user-friendly label. I think largely because of what I just explained to you, as well as the fact that the systemic levels are so low that they felt there was no reason to have the contraindications or warnings around VTE or stroke or heart disease, dementia, and all the other

baggage that we've inherited from the Women's Health Initiative. So, I hope that everybody recognizes that genitourinary syndrome of menopause is a common condition that affects at least 50% of postmenopausal women. We'd like to make this a socially acceptable and medically well-defined and characterized condition, just as ED and overactive bladder have helped patient overcome some of the discomfort and stigma of impotence and incontinence. I think having a medical syndrome allows the clinician to focus on the symptoms at hand, whether or not they're genital, sexual, or urologic in your mature patients. GSM is the most common cause of dyspareunia in menopause. You can do a lot to improve the patient's quality of life as well as their overall urogenital health, and, hopefully, after today, it won't remain as underdiagnosed or undertreated.

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