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Hypoactive Sexual Desire Disorder: New Strategies for Patient Counseling, Diagnosis, and Management

ANNOUNCER
Listen to ReachMD and welcome to the Omnia Education CME activity, entitled Hypoactive Sexual Desire Disorder: New Strategies for Patient Counseling, Diagnosis, and Management presented by Dr. David Portman and recorded live at the Women's Health Annual Visit in Chicago, Illinois.

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DR. PORTMAN
Now we're really going to talk about primary hypoactive sexual desire disorder in premenopausal women. Objectives – I think it's important that we try to define our terms, understand the landscape; it's

not really worth having a treatment if we don't think that it matters to the patient or to healthcare, address some of the barriers that inhibit the appropriate diagnosis and management of HSDD, which there are quite a few, identify potential screening tools that allow for the diagnosis of HSDD; some which I think you'll be surprised are very easy to use and user-friendly. And lastly, again very similar type of lecture structure, is look at the data, the evidence-based data, that have both current, as well as emerging therapeutic modalities to manage HSDD. So, let's talk a little bit about the definition. But their definition, which has been around for awhile, slightly modified, is a persistent or recurrent deficiency or absence of sexual thoughts, fantasies, and/or desire for or receptivity to sexual activity. It is accompanied by, very importantly, clinically significant personal distress or interpersonal difficulty. So if it's not bothering them, then it's not a disorder. If it is, and it's causing distress, frustration, grief, withdrawal, anything that really bothers them or distresses them, then it is something that should be addressed by their provider. And it should also not be accounted for by another medical disorder, a drug side effect, psychiatric condition. I think it's also really important to recognize, and I think this is something that I think we've learned from the different models of sexual health, beginning with Masters and Johnson, who had looked at a very linear male-focused model of sexual function, in that they saw an arousal stage followed by orgasm resolution and refractory. One of the things they kind of left out was, well what drives arousal; well, desire. So Helen Singer Kaplan out of New York very wisely said, well that's where a lot of this starts, is there has to be motivation, desire, behavior-seeking activity. So I think it's really important that we recognize the desire is what the component that leads to the cascade of sexual pleasure and orgasm. And then, more recently, Rosemary Basson said, "Well, wait a minute, not every woman has spontaneous desire." And this is played out I think when you look at surveys that differentiate between men and women. There is very much a different approach to what they find leads them to engage in sexual activity. And she came up with rather than the linear model, a circular model where you can enter into a state of desire after arousal, after a sexual cue, after a moment of intimacy that was not necessarily spontaneous; it was more receptive. And I think it's really important when you talk to your patients; it's not all about initiating sexual activity, but could very well be, for the majority of women, just feeling that they want to be more receptive and not think the idea they could just not care less. We are going to be talking about acquired hypoactive sexual desire disorder. When you have a patient with lifelong sexual desire problems or sexual problems, those can be very significant and often psychological in nature. What about the impact? Body image, self-confidence, self-worth are all things that impact functionality and daily living. And then the interpersonal aspect of it of feeling less connected to their partner, less communication, worry about cheating, and even ultimately separation and divorce, so this can have significant socioeconomic and quality of life impact. Someone asked me a question earlier, "Well, when a patient presents to you with sexual dysfunction, what's your go-to?" I think we have to recognize that this is a very complex interconnected type of disorder and multifactorial,

and we also have a very much biopsychosocial approach to how we engage with patients. We are going to be focusing mainly on HSDD today, but very often they may have the coexistent other disorders, as well. This might be one of the reasons why we don't necessarily address this proactively in the office. Because it does involve a lot of interdisciplinary action on the part of the clinician. There's also a lot of psychosocial and contextual issues that you may need to drill down as part of the sexual history. Contextual would be that a woman that says, "I have no libido" in Peoria, but she goes on a trip with her partner to Cancun, and all of a sudden she has her desires back, that's also contextual, and that's not generalized hypoactive sexual desire disorder. Also, when it comes to relationships, if she has no desire for her husband in Peoria, but she fantasizes about Hugh Jackman, that's clearly a partner relationship issue. Somebody who is able to masturbate and fantasizes, but there are problems with their relationship, we're not talking about solving those issues. So those are secondary factors and very important to take into context. There has also been a lot of debate about whether or not this is a real condition, which I think is a disservice to women. As I mentioned, since 1977, it has been recognized in the medical literature, as I mentioned, and the DSM early versions, and then in 1987, clearly listed as a disorder. It's hypoactive sexual desire disorder, as well as there is a female sexual arousal disorder. The most recent DSM-5 has acknowledged that there is a huge overlap, if you have somebody who cannot be aroused and it doesn't feel good, then that may lead to a lack of interest, right? It's a behavioral response and it's actually a normal behavioral response to that. But right now, we really do feel that the isolated hypoactive sexual desire disorder is the best way to identify in clinical trial endpoints, and we're still going to focus on that as the primary disorder, although it could co-exist with arousal. So how common is this? A lot of people experience some sexual difficulty at some point in their lives. What we're talking about is somebody who has had, in their mind and opinion, their normal sexual function and they've perceived a change and they no longer feel the same about their sexual activity than they did. And it's distressing. So if you ask patients if they've had any sexual problems, on the far right you see that close to 43% will say, "Yeah, I've had some problems here and there." But then when you ask if it has been distressing, life-changing, problems with the relationship, that goes down to about 11.5%. The vast majority of that is desire disorder. So about 1 in 10 women will say that they have an acquired generalized lack of interest, where they used to have normal interest in their own perception. We've confirmed very much both in animal and human studies, dopamine is a driver of desire and responsiveness to sexual cues. Oxytocin helps with bonding and closeness, often released after orgasm, which gives a sense of intimacy and closeness. Melanocortins, which we'll talk about a little bit, a peptide that also helps with arousal and desire through the dopaminergic neurons. And then the noradrenergic neurotransmitters, which get our heart racing, get us excited, and get you functional. The things that lead to lack of excitation or inhibition are serotonin. We're all familiar that SSRIs, which increase serotonin because of reuptake inhibition can lead to very

large incidence of sexual dysfunction; opioids, endocannabinoids. So if you have more of these types of agents or hormones or molecules circulating, you may have greater inhibition and not enough excitation to overcome that. And it's this balance, is that if you have enough excitation and not too much inhibition, you're going to tip towards being sexual interested and responsive. Vice versa, if there are other factors that lead to greater inhibition and less excitation, then you won't be able to detect the mechanisms of desire. So a little bit of background on at least the neurophysiology, because we're going to talk about a couple of agents that work in that way. So this is again disheartening survey data, when they come to the office, do they really ask? And oftentimes, they ask right when you're out and getting ready to go out the door, "Oh, by the way" and you have three patients in other rooms, and it's not the best time to discuss something complicated. But only 6% really are spontaneously asking their providers. It certainly could be because of embarrassment. Here's another survey that 80% of women self-reported they didn't even mention it to their healthcare provider. So again, living in silence, conspiracy of silence, suffering in silence, and discomfort and embarrassment, or their unwillingness to seek treatment contribute to that. And our report card is equally poor when it comes to asking patients about this. This is a primary care survey. How often did you ask patients about low libido? 86% of the time had not screed, 90% had not diagnosed, as I mentioned 10% -- 1 out of 10 women have this, and 90% of these clinicians had never diagnosed it, largely because they did not feel confident at all or had little confidence. OB/GYNs, of which I am a proud card-carrying member, are not doing quite as well as we should, because that's what we do, we talk to patients about their sexual activity, we provide them contraception to prevent unwanted pregnancy, we talk about sexually transmitted diseases and the consequences of those, as well as pregnancy, and yet we kind of avoid the big – the elephant in the room, which is sex. We don't talk to them about the quality of their sex life, about if they're having problems with desire, pleasure, arousal, orgasm, so I think that we could do better, as well. This could certainly – the female OB/GYNs are doing it better, and I think we all have a lot of catching up to do. So I think you have to be objective, you have to be sensitive, and as you see the following point is there is a fear of embarrassing the patient. So what do we do? We simply just don't ask at all. When could you ask? Well, it could certainly be part of your routine yearly exam. This is a well-woman's annual exam. I think that this is ideal. Make it part of your intake. Your nurse or your nurse practitioner or in any kind of survey that they fill out. Written intake, as I mentioned, when you're doing a review of systems, it makes sense if you're talking to them about their urogynecologic function, then you should talk about how that is working when it comes to sex. I would not recommend doing it during the exam. That could potentially lead to somebody misconstruing. So how can we measure or identify the disorder? So we're going to talk a little bit in detail about the DSDS, which is a validated simple screener, and that's available online. It's a brief diagnostic tool to identify HSDD. There is the FSFI, which hopefully you're familiar with now. The FSDS, which is a measure of distress. So we can measure this. This is not

something that is beyond measuring. When women come in and complain about low desire, they're usually having sex, and they're having sex at the frequency that their partner wants to have sex. Sometimes they may not be receptive, but they're still going to engage in activity and they are very well going to orgasm, but they never come in saying, "My biggest problem is I'm not having enough sex and that really bothers me." They usually say, "I'm having sex, but I could not care less. It feels fine, but I have no desire, I don't seek it. I'd rather go read a book." So unfortunately, a lot of the earlier trials were done counting episodes of desire or counting sexual activity or satisfying sexual activity; whereas, these patient-reported outcome instruments are the much better way to measure and define sexual function. So this is the one that I think is most likely to be used by our average clinician. It asks four pretty basic questions: Did it used to be good, is it no longer good? Are you distressed by it, does it bother you? Are you concerned? And would you like to do something about it? You can get to the bottom of it very quickly, and this has been validated as good as structured interviews by experts. And then you want to look to make sure there's not any confounders, contextual; lack of interest in that partner, but interest in the neighbor. It's a health-related issue. It's a medication. It's pregnancy. So the number 5 questions are rule-outs. So to make sure it is acquired and generalized and not due to another underlying factor. So I think that's pretty well understood for all of you. So let's talk a little bit now about how we've defined our terms, how do we treat? Psychotherapy and counseling, I'm not going to spend a whole lot of time on. There are not a lot of validated well-controlled studies to show that it worked better than non-intervention, but you do have some mindfulness studies, cognitive behavioral therapy, which looked to help largely around arousal rather than desire, so that might be a place to think about therapy. Pharmacologic therapies, which we'll talk about certainly the two most intriguing ones; one approved and one on the cusp of approval, thinking in terms of also doing this in combination. These could be both a medication, as well as a behavioral intervention, and you often get better results. So let's look at the first approved FDA treatment for HSDD, and it's called flibanserin. It's a mixed postsynaptic 5-HT1A agonist and a 5-HT2A antagonist. And what that does, as I've mentioned, if you can decrease the activity of serotonin, you'll decrease their inhibition. And if you can increase dopamine, you'll increase excitation so it's really that balance. You're trying to tip the scale in favor of prosexual effects, primarily through the dopamine-4 receptor, as well as the decreasing on the serotonergic effects of satiety. And this illustration just shows you how that tipping point would change by decreasing serotonin in an inhibitory way and increasing dopamine in an excitatory way, and hopefully tipping the balance for the right patient. So this is a little bit of the history lesson behind the controversy, and I think we experience this firsthand when we went to the FDA to try to get this drug approved. When you ask people to fill out diaries every day, you don't get real good data. Although there is numeric increase in the first two studies, which showed an improvement in daily desire scores. It then rates statistical significance and, since it was a primary endpoint, if you don't hit your primary

endpoint, you can't get approved. What the sponsor then did was another trial study 3, which instead of looking at daily desire, which they realized was not a good way to measure desire, it was a way of counting desire just like satisfying events as a way of counting, and we really want to measure, you see that the third study statistically significantly did improve the female sexual function index desire domain significantly compared to placebo. You see the scales are very small, and that's really one of the pushback that some of the adversaries said is that here you have drugs that have side effects for only a modest 0.4 increase in their desire domain; how good can that be? What does that change mean to the patient? Because ultimately we don't care if it's a small number if it's meaningful to the patient. And then when you look at the previous two studies, even though those weren't the primary endpoint, you see that the desire domain was a very effective predictor statistically meeting those endpoints even those are nominal P values. Similarly, when they looked at distress as a primary endpoint, in the third study, you see that distress improved as well, decreased while desire was increasing, and similarly for those patient-reported outcomes in the earlier studies. If you can decrease their distress and increase their desire, you're tipping a point in the sexual tipping point in the right direction. So what about how to make sense of these small numeric changes? There is a way to bridge or to anchor these types of endpoints to an anchor that has face value meaning. For instance, in this particular study, the patients were asked about, do they think that they've had improvement on a scale of 1-7. And when patients said that they did have some improvement, if they were on that scale a 3, 4, or a 7, 6, or 5, then that would be considered somebody who responded, and then we look at the rates of having changes and FSFI desire scores and the FSDS distress scores, as well as satisfying events. And if you look, there's about a 10% difference compared to placebo. And again, we can't ignore the placebo effect. When patients get counseling, when they get supportive care, when they're asked to engage in sexual activity, that's a form of behavior modification. We don't do that in the clinic, so I would, rather than say there is a net 10% improvement, I would say there is a 40-60% improvement in these patients who take this drug appropriately. That does, however, come with side effects, and it comes with daily dosing, taking 100 mg at bedtime because it can be sedating. The FDA had some concerns about somnolence, dizziness, and even syncope and hypotension with alcohol, and it has a boxed warning and a REMS program around alcohol because of the alcohol interaction studies. Even though women in the study, about 58% described themselves as social drinkers, there was little to no difference in hypotension and syncope, there is still a very significant REMS program, a risk management program, which requires you to be certified. Just curious, how many of you in the audience are REMS certified to prescribe Addyi? So, a handful. So I think that's really a barrier, and that was one of the things that we were concerned about; when you put a lot of restriction on these drugs, access becomes a problem. There are some drug-drug interactions. So it's not that easy to prescribe and has not had a lot of success, unfortunately, in the market. So maybe the intermittent treatment of desire and trying to get in

the mood and have that loving feeling back just when you need it rather than taking a daily medication the way that men have been using PD5 inhibitors episodically for decades, might be an interesting model to look at. In fact, that's where a new compound that is made, joined the ranks of approved therapies next year, which is a cyclic 7 amino peptide, which therefore cannot be given orally. It was initially studied intranasally. This is an alpha-melanocyte stimulating hormone and, as I mentioned in animal models, when you infuse various areas, as well as give systemically, this particular compound, bremelanotide to rodents, you can actually see solicitation behaviors, lordotic positioning, and it really did stimulate receptivity in prosexual behavior, so there's definitely a mechanism by which we know that it works. It was originally also studied for ED, and worked quite well. The intranasal formulation had some very labile PK and Cmax's, so they decided to go with the subq auto-injector, which was one that was studied in the phase 2 and 3 program, which was very easy to use by patients; very small needle autoinjector and they don't even see it. It's used 45 minutes before sexual activity. Rather than taking a nightly pill that has some significant warnings that really cause challenges, this may be an alternative treatment for patients who really don't want a daily therapy for something that they really would rather use episodically. How does it work? Again, tipping point mostly on the desire spectrum, we don't think it's working on decreasing inhibition, which is a good thing. So diversion and abuse is unlikely to be a problem. But the increase in melanocortin helps with the dopaminergic neurons in the areas in the brain that tend to need to be able to focus on sexual cues. So this is just the study design, the Reconnect study. This is the one that is currently before the FDA; two randomized phase 3 controlled studies that look at patients with primary generalized acquired HSDD. They could have coexisting arousal disorder, had to have it for at least six months, average age was about 36, which as you can imagine is very distressing at 36. This is not something you would think would be normal and, the fact that you felt normal before, and now you don't is significantly distressing. They were willing to engage at least once a month in activity. The questionnaires are similar to the ones that I showed you. The primary endpoints, I think we are learned our lesson the hard way, that we don't count desire daily, we don't measure the number of sexually-satisfying events because women don't really care about that; they're looking more at decreasing their distress and increasing their desire. So those are the two co-primary endpoints. Is the distress and the desire domains of these two validated instruments, as well as an anchor; what would be the minimal clinically important difference. You often see the MCIDs in other therapeutic areas where you have scales that are small, and whether or not that change is that meaningful. So the minimal clinically important difference for a change in FSFID was 0.6, as well as 1 for decreasing on the distress scale. Here you see the results from the Reconnect study. The darker lines are the active treatment from the two different trials, then you see the placebo response. And again, placebo response notoriously present in all patient-reported outcomes. And these are patients that completed. And even when you analyze just based on the completers, if you included all patients

and assume they were treatment failures, this was still significant compared to placebo. And here's the difference in their scales on the FSFID score. You do see statistical significance with both studies, and this was likewise consistent with decrease in distress compared to placebo. Again with both trials showing very consistent results. So, getting back to responders; we kind of showed you the responder analysis from the flibanserin experience, roughly around 50%. Here are responders who answered the question: To what degree do you think you've benefited from taking the study drug? That's a pretty good question to know: Is that meaningful to the patient? If they say, "Yes, I've benefited a little; I've benefited a great deal; I've benefited very much" then that patient is considered a responder. When we looked at patients who answered that question greater than 5, 60% of the patients assigned bremelanotide had a response. So when you think about centrally-acting drugs for depression, for anxiety, other neurologic conditions, 60% is a pretty fair number when we look at response rates in those types of trials, so I think this is very respectable and not modestly effective. Then when we looked at even the minimal clinically important differences, there was significant association of patients who were on drug that had the minimally important clinical difference on both these FSFI and FSDS that were highly statistically significant. So the responder analyses, as well as the consistency across the clinical trial were impressive, and hopefully will enter our armamentarium soon. As I mentioned, there were some labile changes with intranasal administration, which were associated with some modest blood pressure increases. That seems to have been taken care of with the subq administration. It is also only given intermittently, so even very small several mmHg will not likely translate into a significant adverse event. There is some nausea and, in fact, some patients because of the emetic centers are in the hypothalamus, did have even vomiting. So there were some discontinuations from nausea. And that's simply, with any drug, if the adverse events are greater than the benefit, they'll make that decision that that's not right for them. And there were roughly about 18% of women who discontinued due to side effects versus 2% for placebo. So it's not without tolerability issues, but given the intermittent use and no-alcohol warning, it's certainly something to consider. But off-label testosterone is something that many of us turn to, especially in the postmenopause, estrogen to treat the urogenital changes that we addressed in the morning, off-label bupropion which will increase dopamine, as well as arousal disorders being studied with PD5 inhibitors showing some benefit to certain subpopulations. So just one quick look at testosterone; there has been a meta-analysis, and have been many publications. This was largely generated around the Intrinsa transdermal program, which did demonstrates efficacy, but that was right around the time of the women's health initiative, and there were some concerns about using a testosterone hormone chronically for a quality of life lifestyle condition and that was never approved here in the States, but was approved in Europe; no longer available there. But it did show improvement in desire, activity, satisfying sexual events, orgasms, compared to placebo with the concomitant reduction in distress. So to wrap up, hopefully we've

created awareness, we've realized now that this is something that can be part of our evaluation of our patients. It creates a huge burden on their quality of life and their relationship stress. It really is our responsibility that the sexual health is a vital sign. We all think about it, we all talk about it, and yet when we get into the doctor's office, all of a sudden we become quiet. I don't think that's the place to be quiet; I think that's really the place to engage actively with your patients about what normal healthy sexuality is. There are safe treatments, and hopefully there will be more on the horizon and we'll see the graph rise for women, as well.

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