Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.comhttps://omniaeducation.com/programs/cme/hypoactive-sexual-desire-disorder-assessment-diagnosis-and-treatments/9865/

Released: 10/31/2017
Valid until: 10/31/2018
Time needed to complete: 45 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Hypoactive Sexual Desire Disorder: Assessment, Diagnosis and Treatments

ANNOUNCER INTRODUCTION

Welcome to the Omnia Education CME activity, entitled *Hypoactive Sexual Desire Disorder: Assessment, Diagnosis and Treatments* presented by Dr. Sheryl Kingsberg and recorded live at the Women's Health Annual Visit in Boston, Massachusetts.

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

Dr. Kingsberg

Well, hello everyone. It is a pleasure to be here. Let me just start by saying that this experience is a little bit like sexual dysfunction in women. Women often have to wait patiently for men to finish before it is their turn and so here we are. This is very exciting for me to be able to talk to you about sex and as we go through some of the data on flibanserin and you want to know about alcohol we can talk about what it feels like to drink shots of alcohol at 9:00 or 10:00 a.m. in the morning. I am sure none of you have done that so far.

So, here are my disclosures. I have consulting fees from AMAG and Emotional Brain Palatin and Valeant Pharmaceuticals, and I am the speaker for various companies. So I have a number of objectives. I do not want to spend too much time going through them, because you will see them, certainly, as we go through, but I want to talk to you about what the symptoms are of HSDD and talk about what the barriers are that get between you and your patients in terms of assessing and offering treatments; talk about what you would do to do an efficient and comprehensive sexual history; talk about some of the screening tools that we have; look at some of the causal factors for HSDD; and think about some of the treatment options that we have, and also talk about the REMS certification process for flibanserin.

When we think about sexual health and why we should be addressing it, think about why it is that your patients would benefit from you addressing their sexual concerns. Well, the fact is that above almost anything else, we all consider sexuality and our sexual health to be important to our quality of lives. Think about whether sex is important to your life and think about the impact it might have on women's lives, and we know that women will rank having a healthy sexual life better than almost anything, including home ownership, travel, or career satisfaction. It is clearly important to women's quality of life. We know that the burden of having sexual dysfunction is pretty significant and is about as equivalent to some of these chronic medical conditions such as having diabetes or back pain and what we really know clinically is that sex is really important to the survival of a relationship. So, think about this clinical adage. When sex is good it is good. It adds about 15-20% added value to a relationship, but when sex is bad or nonexistent, it is hugely powerful, draining that relationship more like 50-70%.

Okay, so think about this in your own heads about your own experiences. You know, most of you probably, at some point or other, have been in another relationship before the one you are in and maybe the sex was really good; it was hot, but you are not with that person anymore. Now, why is that? Well, the sex was good, but you know, you found out they voted the wrong way, you know. It is certain things that just cannot survive, right? So we know that even good sex cannot be enough for everything, but what I see clinically are women that come into my office and say, "Everything else in my relationship is good; we are best friends, we have raised children together, we have the same value system, we are great together except if I do not treat my loss of sexual desire, I do not think our

marriage or relationship is going to survive." That is what I see clinically. So, that is what I mean by the drain on the relationship is huge when sex is poor.

A couple of years ago I did an online survey of women who have low sexual desire to see what the impact is outside the bedroom, and it is huge outside the bedroom. When we think about sexual dysfunction, don't just limit it to what you think about sexuality. Think about what the burden is on these women's lives. We know that 70% of them reported that it impacted their body image. So, it is not that poor body image will impact low desire; it is the other way around in this case. Just the experience of having loss of sexual desire has made women feel less about themselves. Their self-esteem is impaired; their sense of femininity is impaired; their complete body image is impaired; self-worth goes down and in terms of the relationship, they feel less connected to their partner; they have much less communication because of poor sexual function, and at least a third of them are worried that their partner is going to cheat.

Let's talk a little bit about healthy sexual function before we return back to the concept of hypoactive sexual desire. When we think about the sexual response, there are various models that we use to understand the sexual response, and what we know clinically is actually women can relate to any of these models, either they attribute themselves to one or they change over time, so not one is carved in stone as the right one, but it is important to think about how women perceive the sexual response and what we have studied.

So, Masters and Johnson in the 1960s, some of you were not even born then, but were the first two to empirically study the sexual response physiologically in a lab. How they got IRB approval in St. Louis, Missouri, in the 1960s to bring people in and have them hooked up to electrodes and watch them masturbate – I do not know. I would never get that done in Cleveland, but they were able to do that and based on their research, they came up with this sexual response model that is essentially a linear progression, showing that all men and women invariantly will go from the same model starting with excitement to plateau. Excitement really is the idea of becoming sexually aroused; plateau is the peak level of sexual excitation just before orgasm. Orgasm is the release of all sexual tension, usually experienced as satisfying, and then the body moves to a non-stimulated stated called resolution. Now, while this is the same between all men and all women, for women there is an infinite variety of ways in which women can experience this linear progression. The importance for you is that when women come into your office, and they do, not knowing what is normal, they want you to say what is normal, and it is important to validate that for them normal can mean a variety of things, and that the normal sexual response can vary between women, right? So, this could be A, B and C could be three different women, it could be 3,000 women, or it could be the same woman on different occasions. It could be across the menstrual cycle or across their lifecycle or between partners. There is an infinite way for them to experience that arousal, plateau, orgasm and resolution. So, woman A moves from excitement to plateau, she has two orgasms, drifts off to resolution; woman B moves to plateau and never orgasms. If this was the same woman on two different occasions we would say that is pretty normal. We do not expect that women will be 100% orgasmic, so it is helpful to validate that, but if this woman B were the same woman on every occasion where she plateaued and never reached orgasm, she would probably have an orgasmic dysfunction, right? But it is important because women will come in and they will say, "Am I normal? I cannot have an orgasm with intercourse, and my husband tells me that all his prior relationships were multiply orgasmic with intercourse with him, so yes we have a different diagnosis for that condition. We call that delusion disorder, but for her, to validate for her that, you know what, intercourse is not a reliable way for women to reach orgasm, that about 75% of women require external stimulation and that if she happens to reach orgasm that is great, but she is not dysfunctional if she does not. Again, it is very helpful to normalize the infinite variety of ways in which women experience a response.

We also have another model, and in the 1970s, Helen Singer Kaplan, by the way, a psychiatrist in New York, said that Masters and Johnson had this linear progression, but in their physiologic labs, they forgot to measure the most important sex organ that there is, which is what? – the brain, and that desire really was the key component to understanding the sexual response, so in her model it is desire, arousal and orgasm – so, desire being important.

Now, we fast forward to the late 1990s and we have Rosemary Basson's non-linear model that reflects the fact that desire is not always the first step, that this linear progression isn't always how it works and this actually informs the DSM-5 categories of sexual dysfunction, but it says that while spontaneous sexual desire, that want, the desire, may be there initially for many women. It may not be the first thing they are thinking of when they choose to engage in sex. The desire for emotional intimacy may be what drives a woman to either be receptive to her partner's initiation or to initiate it herself. There are a lot of reasons why women may decide to engage in sexual activity, giving this morning's first lecture, maybe it is because that they heard that "you burn calories, and boy wouldn't that be an easy way to lose some weight?" So, there are many reasons why women will think about engaging in sex without necessarily feeling that want for sex.

In this model, she is kind of sexually neutral when she either is receptive to her partner or engages in initiating; she is kind of thinking about the laundry list, doing little things in her head, but with enough sexual stimulation, right, they start to engage in sexual activity and there is no biologic interference, that is no pain – that tends to shut down the cycle; or no psychological interference – they do not get into an argument – or there is not a knock on the door, "Mommy, I need you," or maybe the UPS guy rings the doorbell, unless he is

supposed to be there, and then, you know – it changes things. Those brown shorts do something for some people, but assuming all is okay, then her body gets aroused and it is when her body is aroused that that desire kicks in, and that would be a normal response. What we see in hypoactive sexual desire disorder is the response never kicks in, right. There is never a, "Wow, why was I so hesitant? We should do this more often." That comes when the body starts to get aroused. That would be normal for some women, but without that, that would be hypoactive.

The model that works for my patients and me is exercise. I have no biologic urge to exercise, but I have already today, but I have no urge to do that. My body is not craving it. I am not sitting here fantasizing, "When is the next time I can go to the gym?" If I waited for my own internal urge to work out, I would never go, but I know that if I get myself there, put on my little workout clothes, get on the treadmill, once I am on, once my heart rate has risen a little bit, I have worked up a little sweat, and the smile comes on my face and I am like, "Ah, this feels great. Why was I so hesitant? I am really glad I came." And then, you know, the next day I will think about it again and, nope, no drive. So, for women if they can relate to exercise the way they relate to sex, either they recognize once they get started, they are fine, or if they have hypoactive sexual desire disorder, they recognize that no matter where in that cycle they go, there is just no interest and no feeling of satisfaction.

When we think about the sexual response, it is important for you as clinicians to think about this in a biopsychosocial model. Biopsychosocial sounds complicated, but it really reflects the fact that there are various factors that contribute to healthy and dysfunctional sexual function. There are biologic factors that we will spend some time on, thinking about general physical health, but also neurotransmitter function, hormonal status, all of those things can contribute to sexual problems or sexual health. Psychological factors, depression, anxiety, certainly are contributors to sexual problems; sociocultural factors, thinking about the religious cultural values that contribute to a woman's sense of sex is okay or it is not okay, and then the interpersonal factors – the quality of the relationship that she is in. You could have all the biologic health that you need in order to have healthy sexual desire, but if you do not like your partner, then there is nothing that is going to save that.

What we know is that hypoactive sexual desire disorder has been around for a very long time. There have been naysayers that say this is sort of a made-up condition, but think about this as we think about what depression was like 30 years ago. Before SSRIs were sort of ubiquitous in our world, men and women who had clinical depression were told, "Oh honey, it is all in your head. Just go on a tropical vacation. You will feel better in the morning. Just relax." It was all in their head. But once we discovered the biologic foundations, then we understood that depression was a medical condition – same thing for hypoactive sexual desire disorder. It has long been recognized as in the brain, in the head. Helen Singer-Kaplan actually first published this in the 1970s and it has been in our diagnostic and statistical manual as a condition since the early 1980s and labeled as hypoactive sexual desire disorder in 1987. Today we define it as the persistent, or recurrently deficient or absent sexual fantasies, sexual interests, desire for sexual activity that is also accompanied by personal distress, so we do not diagnose somebody with loss of desire as a diagnosis unless they personally feel like they are distressed or bothered by it.

When we think about the DSM-4, which has hypoactive sexual desire disorder, and the DSM-5, which was published in 2013, which essentially lumped arousal and desire together, what is in a name? Whatever you label it, hypoactive sexual desire disorder or female sexual interest/arousal disorder, it is still the persistent loss of desire and HSDD still exists in the ICD codes, in ICD-10 and will be in ICD-11 as well, so you can diagnose hypoactive sexual desire disorder and not worry as much about the DSM-5. Is it arousal? Is it desire? Did they meet the criteria? But essentially, anybody that would meet the criteria for HSDD would also meet the criteria for FSIAD. All that is doing is lumping desire and arousal based on that Basson model that says sometimes arousal precedes desire and so it is a little hard for some patients to tease that out.

So, what is the prevalence? You say, "Well, not in my practice. My patients all have good sexual function," but the fact is that it may be that you are not asking because the prevalence of sexual problems among women is pretty darn high. When we look at the data, which was a survey of 31,581 women – so it was a nice U.S. representative sample across our nation – we saw that 43% of women had reported that they had a sexual concern. Thinking about that distress component as the key to whether or not somebody meets the criteria for dysfunction, when you ask that, it turns out that about a little less than 12% of women in the United States essentially meet the criteria for having a sexual dysfunction. What is the most prevalent? It happens to be hypoactive sexual desire disorder with about 10% of women across all ages meeting the criteria for HSDD. About 5% have arousal problems, and a little less than 5% meet the criteria for an orgasmic dysfunction. So you say, "It must be all the older women that have HSDD." Well in fact, that is not the case. If you look at how it is stratified by age, you can see that in the youngest population it is still 9% that meet the criteria for HSDD. The peri- and postmenopausal women have the highest rates. Women do not like change and our baby boomers are not happy about things changing, but it is the oldest women that actually have the lowest rate of HSDD. So, either they have more learned helplessness or they have lower expectations about their partner or they have sort of learned to live with it, but whatever their reasons, they have the lowest rate. It is the premenopausal women I want you to pay attention to that have a 9% rate of HSDD.

We are going to talk about how we are going to evaluate it and why bother, because I know that sex is one of those questions that you say, “Okay, I have got 30 people in my waiting room, am I really going to ask her about her sexual function? Do I really think I can do that efficiently and effectively?” So, my question to you is, why would you do that? Why would you take that risk? Well, number one, I will tell we can do it very efficiently and effectively, but number two, the fact is that sexual problems really are quite common in your patients and they do want to talk about it, but they are afraid to talk about it and they need you to open the door and they need you to inquire and legitimize. Really it is up to you. It is not their job, and we will talk about it more in the dyspareunia lecture as well, that women want you to ask them about it, and if you do ask, they are really very satisfied with their office visit. They feel like it improves their trust in you and their relationship overall.

When should you do a sexual screen? Should it be a written intake in the waiting room? Should it be in review of systems, annual visits, or specific problems? The answer actually is any time you are willing, because if I tell you there is a specific time that is best and it does not really fit, you will try it once or twice when you get back to your office and they will say, “Well, this does not fit.” It will drop out of your behaviors, because we are no better than our patients at adherence, right? We have a low adherence rate and we are less likely to adhere if something does not fit comfortably with this, so I am not going to tell you exactly when you should do it, just figure out when it fits best for you, when it flows more smoothly, because then it will be more likely to stick and your patients deserve that.

What are the barriers to addressing sexual health? Well, most of you think it is going to take too long. I know that. It is like, “Oh my goodness, talking about sex?” What is the average length of intercourse? It is five to seven minutes. So, I promise you that talking about sexual health will take much less than the average length of somebody having intercourse. There is embarrassment. Most of you who do women’s health, you can talk about odorous discharge, you can talk about cottage cheese discharge, you can talk about all kinds of interesting things falling out of one’s vagina, but it is not okay to talk about sexuality. We are not comfortable talking about one’s sexual activities. We can talk about genitals. We can talk about parts. We can talk about falling out parts, but we cannot talk about sexual activity. We are still a little embarrassed by that and we are worried that we are going to embarrass our patients by asking them something too personal. We also aren’t really aware of the comorbid conditions that go along with sexual dysfunction. We know that for men, erectile dysfunction is a nice early marker for cardiovascular disease, but we do not think about the same issues with women’s sexual health and the fact that having sexual problems actually might be related to some other comorbid conditions and we consider other things as more important to them, you know, hypertension, right? I am sure women are really more concerned about whether she is on the right dose of her blood pressure medicine rather than whether or not she is going to survive her marriage.

Here is another barrier, which is this lovely diagram that says, “Wow, there’s a lot of comorbidity of sexual problems,” and that is true. If you have a desire problem, then it would not be surprising that you would have an arousal problem, an orgasm problem, and maybe you have pain because you have no lubrication, and so what tends to overwhelm you and think, “It is going to take me forever to tease that out,” is to find out the fact that if you ask one or two pointed questions, you can figure out which is the primary disorder and then all the other comorbidities sort of follow from that. It takes one or two questions.

So, a woman walks into your office and you say, “What sexual concerns do you have?” and she says, “I have no sexual desire.” She is a 60-year-old woman with no desire, and you say, “Look, I just learned – I went to this CME program; I learned about a treatment. I am going to give you a pill and I think it will help your desire and off she goes and she comes back three months later and you say, “So, how is it going?” and she says, “Well, I still do not have any desire, because every time I have sex it hurts like heck.” The fact is, she has vulvovaginal atrophy and nobody had assessed that and so without treatment of her VVA, it hurts every time she tries to have penetrated sex and so she has no desire.

So, the next woman walks in and she is also 60, and you come in and say, “What sexual concerns do you have?” and she says, “It hurts every time I have sex.” And you think, oh, great, redemption. I screwed up my last patient, but I am going to get her treated, so you have got all these new treatments for VVA. We give her one of those. We send her off. She comes back a couple months later and you say, “So, how is the pain?” and she says, “Well, it still hurts every time I have sex; my VVA is gone but it still hurts every time I have sex,” because she has no desire, and without desire, she is dry, does not get lubricated, and then trying to have penetration without arousal, she gets pain.

Two different presentations with one or two questions, you would have figured out one had low desire and one had VVA, not hard to do and both would have had easy treatment paths. So do not get overwhelmed by the overlap.

Here is a nice little screening algorithm that I think works nicely, legitimizing sexual concerns as important. Do you have any sexual concerns? Having sex with men, women or both? And if they do not have any concerns, it opens the door for them to bring it up at some other visit. Please try to use open-ended, sort of ubiquity questions because please know that most women are expecting that if you ask a question, the question is asked standing with your hand on the door saying, “You do not have any sexual concerns do you?” So that is not really the open invitation to address sexual concerns. Please sit down and legitimize it. Most of my patients have some

sexual questions or concerns. "What concerns do you have?" That legitimizes it and says I am okay talking about it. You are not alone to have them and what can I do to help you?

The fact is we have data to show that by asking these open-ended questions, ubiquities or validation, you actually get better functional impairment information rather than those 20 yes/no rapid fire sort of machine gun questions, which are fatiguing for you as well as the patient. You get better adherence to whatever treatment you actually then suggest, because the patient feels engaged in the process – it is shared decision making – and her overall satisfaction with the visit goes way up simply by asking open-ended questions.

Now you say, "Well that is going to take forever," but we actually have data that would suggest that you can get more information by that open-ended question – tell me about it – in less than 60 seconds than you would get in say a five-minute yes/no interview, and it is much less fatiguing. Women are clear about giving you their information. They are not going to want to go on and on about their sex lives and I know you are thinking, "Oh, I know Mrs. Jones, if I ask her an open-ended question, she is going to be there all day." Well, she would have been there all day with a yes/no question as well, so do not think about just her. Most women are very good about giving you just the facts. Do not forget about reviewing safe sex; ask about gender and do not forget to ask about over-the-counter medicines, because we know side effects of those are just as real as prescriptions.

When you do make a referral, because you do not have to treat all patients with all problems, just asking actually makes the big difference, try to make it as a collaborative consult, not, "Oh my god, I do not do sex; you have got to go see somebody else," and not as a dismissal and try to use good language and be comfortable. I promise you will not get kicked in the eye.

What screening tools? We actually have some really well-validated tools – very easy to use. You can put them in your waiting room. Your MA can use them. The decreased sexual desire screener, they are online. It is in the public domain, so you can actually just Google the Decreased Sexual Desire Screener or e-mail me and you can get it, but we are hoping to have them here for you as tear-off pads, because they are very nice. The Female Sexual Function Index, which is a 19-item scale that essentially does not diagnose but would give you a sense of whether somebody is having problems with desire, arousal, orgasm, pain, lubrication or overall satisfaction and then looking at distress, if you are interested in how distressed your patients are, we have the Female Sexual Distressed Scale.

Here is the DSDS, which is what I am hoping you will all have, because it is so nice and easy. It really is a validated tool to get to whether or not your patients have what we call acquired generalized hypoactive sexual desire disorder, which means at one point they had good desire and now it is gone, and so the four questions with the fifth question sort of clarifying and the first one is, "In the past, was your level of sexual desire good and satisfying to you?" Yes or no. "Has there been a decrease in your level of sexual desire? Are you bothered by it?" Remember bother gets to the diagnosis and "Would you like it to improve?" all of that gets to whether somebody is interested in being treated, and then if you look at five, it does all the work for you in terms of trying to screen in, rule in, rule out – all the other factors that might be contributing or be the better cause of the sexual dysfunction, or just sort of alongside that. So you and your patient can go through A, B, C, D, E, F, G to see, would that be a better reason for that loss of desire or is it just sort of something you want to keep in mind? So, just because somebody checks off a yes on any of those A-G's does not mean they do not have hypoactive sexual desire disorder; you just kind of want to look at, you know, do they have no desire because their partner has erectile dysfunction or do they have hypoactive sexual desire disorder and maybe their partner does have sexual dysfunction too, so it is sort of a chicken or egg at that point; but, don't assume that just because they say yes means they don't have it, but it allows you to sort of get to that functional impairment and it does all the work for you instead of you having to think, "I had better ask about health? I had better ask my partner. I had better ask about depression." It is all in there for you.

When we think about interventions, remember that biopsychosocial approach? We have on the psychotherapy end for those with psychological interpersonal factors. We have pharmacologic approaches, sometimes combined is the best. Think about how we treat depression. For some women, an SSRI or an antidepressant is the best approach. For some women, psychotherapy or cognitive behavior therapy is going to be the best, and for some, a combination works really well. We want to think about the treatment approach based on what we think the etiology is, right? If we have low desire because somebody is in marital distress, then we want to think about sending them for counseling, but if she has low desire because we think there is a neurotransmitter imbalance, then we want to think about a pharmacologic approach. So, think about this as sort of what we call a tipping point. When you think about the etiology of sexual function, right? If we have the balance here, we have got factors in green that would be for excitation, and factors on the right that reflect inhibition. What we want is to tip the scales for good sexual desire in the direction of excitatory factors. We have both psychological and interpersonal factors and we have physiologic and organic factors. We have John Bancroft's dual control model that says there are going to be factors that inhibit and excite, and based on which one wins out, will determine whether you have desire or no desire. Puts it on sort of a tipping scale.

On the psychological side, we have things like intimacy, shared values, romance, positive history of sexual experiences – all those would contribute to increased sexual desire. On the physiologic side, we have neurotransmitters and hormones; we have dopamine,

oxytocin, melanocortins, vasopressin, and norepinephrine. Those all are important for excitation.

On the inhibition side, we have relationship conflict; we have negative stress; bad sexual experiences or beliefs about sex. That makes sense that that would inhibit sexual desire. On the physiologic side, believe it or not, serotonin, which is great for treating depression, but not good for sexual desire; serotonin is good for mood not great for sexual desire. Opioids, endocannabinoids all decrease sexual desire. They inhibit reward processing. When we think about how we want to treat it, we either want to increase the factors for excitation or we want to decrease the inhibitors. We work on both sides of that coin there.

All these biopsychosocial factors can be etiologic factors. We have got negative expectations, the context, we have got biologic factors. It seems overwhelming, but patients are very good about telling you what is going on for them. Most of them, if you ask, "What is going on with your loss of desire?" they will say, "Everything is good in my relationship. I have positive values." They can tell you so that you do not have to work so hard to tease it out. You just want to get in the direction of is this more of a biologic factor or more psychological or interpersonal?

If you are going to refer for psychotherapy, you do not have to do it yourself. Just know – because people say, "What are you doing sending to sex therapy? What are they going to do in there?" The reality is that it is psychotherapy with a chief complaint of a sexual problem and although the goal is to improve sexual function, there is a lot of cognitive behavioral therapy that goes on and it is not something they have seen on *Boston Legal* or I cannot even imagine what shows they have out there that tell you what happens in sex therapy.

Here are the things that we do. We would lessen performance anxiety. We do some cognitive restructuring about sexual health; look at what low desire may mean; we give them confidence again; we get to barriers of intimacy, increasing communication. All of those things are important to psychotherapeutic approaches for low desire when psychology is involved.

For you as the clinician who is not going to do psychotherapy, think about your office-based counseling from the PLISSIT model. PLISSIT says that the P stands for permission given. If all you do is give your patients permission to legitimately have sexual health, right, that they are entitled to good sexual health and/or it is okay to talk about it or tell you that they have a sexual concern, you have actually already done part of this process and you are already the hero because you have legitimized their sexuality and that sexual concerns are something they can discuss with you.

If you go to the next level, limited information, now you have got a website. You can give them some reading material. You can actually just show them, for example, what they are clitoris looks like using a mirror. Those are limited information things. Specific suggestions – you can give them some ideas about using lubricants or moisturizers or maybe pharmacologic treatments. You do not have to go into intensive therapy, which essentially, unless you want to be a therapist, most of you, that is not what you do for a living, find one or two people in your city and you can refer them and you also look like the hero because you found them somebody that can help them.

What are our approved products? In 2015, there was the first and only approved pharmacologic treatment for acquired generalized hypoactive sexual desire disorder in premenopausal women. It is only approved in premenopausal women. That is called flibanserin. The brand name is Addyi, the first ever approved treatment for a sexual dysfunction in women. Does anybody remember when the first PB-5 inhibitor was approved, which was Viagra? 1998. So, we are coming on the 20th anniversary for Viagra, and so now 17-18 years later we have the first and only approved treatment. It is called flibanserin or Addyi as its brand name. It is actually a CNS drug. It is a central nervous system acting drug. It is actually considered a post-synaptic 5-HT1 agonist and 2A antagonist, so it works actually works to limit serotonin in the synapsis, post-synoptically and promote dopamine and norepinephrine, which we know are important for sexual reward processing and sexual desire. It was approved based on large clinical trials using over 2,300 premenopausal women in three pivotal trials, all named after flowers. How appropriate – we have got Violet, Daisy and Begonia. There were two postmenopausal studies, Snowdrop and Plumeria. I do not even know what a plumeria looks like, but all flowers. These are the premenopausal studies that were used for approval. They were all premenopausal women; the majority Caucasian; mean age was 36. Most of them had HSDD, hypoactive sexual desire disorder, for over five years, and they were all in monogamous, heterosexual relationships long-term, 11 years on average. They had to be heterosexual because the FDA at the time thought that the female sexual function index, which was a secondary endpoint in some of them, was only validated in heterosexual women and that is why it was a requirement.

Here is how those studies went. When you look at these large clinical trials, you are comparing the drug versus placebo, and you can see that in the first two studies they looked at a diary as a main endpoint, asking women with no desire every single day, "What is your desire today? What is your desire today? What is your desire today? What is your desire today?" sort of like watching grass grow, on a 0-3 scale, and also looking at satisfying sexual events. "Did you have a sexual event and was it satisfying to you?" In the first two studies as a secondary endpoint, and then the third trial as a primary endpoint was the female sexual function index desire subdomain,

which asked about desire, which is critical for the diagnosis, and then they all looked at distress, because what is the critical diagnosis of distress? and as you know, important for the diagnosis; whether or not there was a change in distress levels.

What defines a satisfying sexual event? What women think, okay, so they were asking women, you know, "Did you find this event satisfying to you?" Did not require orgasm and it could include masturbation, partnered sex, oral sex, intercourse – it was what a woman considered a satisfying sexual event.

When we look at the results, you can see that in all three trials, satisfying sexual events was statistically significantly greater in the flibanserin group compared to placebo. A lot of times there the look of, "Well, you know, was that really all that meaningful? You know, what there a huge change? Well, let me tell you why this is a pretty important slide and why it is meaningful to your patients, because you can see that, yes, statistical difference, but these are changes from baseline. So, women coming into these clinical trials, married an average of 11 years, right, with HSDD more than 5, were having sex at baseline coming into this trial, already having sex about two and a half times a month, because they are married; they are having either mercy sex or duty sex or they are having sex and they are rating the events as satisfying. So, they are coming in two and half times already and now when on treatment, when on flibanserin, look at the third trial. The number of satisfying sexual events actually doubled. They are now having five events per month and when we think about what the national average is of how often people are having sex in long-term relationships that is not too bad. If we push them even higher, we then push them beyond what normal women without HSDD are having, and for these women to show a doubling is pretty significant. Now you say, "But the placebo group had some increase," and yes, they did, but think about a CNS drug. We know that every single CNS drug that we look at has a placebo response. We just know that that is how CNS drugs work, usually about a 30-40% response. When you can consistently show that the treatment has an effect above and beyond that expected placebo response, that is pretty significant, and when you are looking at satisfying sexual events, which is actually a downstream event from desire, because women will choose to have sexual activity for many reasons, then you can show a pretty significant impact. For women, this change is meaningful.

When we look at desire, in the first two trials it was not the primary endpoint but it was the primary endpoint in the third trial of the study 3; you can see that the desire subdomain, which is critical to understanding improvement in desire, was significantly better in flibanserin versus placebo and here are the questions that somebody would ask: "Over the past four weeks, how often did you feel desire and what was your level of desire?" That is what the desire domain looks like. In terms of distress, you can see improvement in distress.

When you think about responders, it is not a one size fits all in terms of drugs. The response rate is about 50-60%. When you think about using this with your patients, it will not work for everybody. It takes about 8 weeks to show an effect, but you can see that there is a response in about 50-60%. Here are the side effects: Dizziness, sleepy, nausea, fatigue, insomnia. About 11% were dizzy or sleepy. It is important that you know that flibanserin is contraindicated with the use of alcohol, which I am going to get to in one second, talking about the REMS, so it is contraindicated with alcohol, and feel free in your Q & A to ask me about that, and it is also contraindicated with the use of moderate to strong CYP3A4 inhibitors and with women with hepatic impairment.

Let's talk a little bit about a REMS. REMS stands for Risk Evaluation and Mitigation Strategy. The FDA puts a REMS, which is for you to have to educate your patients about the use of alcohol in patients because they are very concerned that there is a risk of hypotension and syncope if women concomitantly drink alcohol. In order to be certified, and you have to be certified to prescribe flibanserin or Abbyi, you have to go to the Abbyirems.com; the certification takes about five minutes. You go online. You have to read and answer about four questions about the contraindications, particularly around hypotension and syncope with the use of alcohol, and once you answer those questions, answer them right, then you will be certified and then you and your patient will be able to discuss the REMS and she will sign off that she will not drink alcohol while she is taking her medication. Like I said, this was based on some studies regarding alcohol. You can certainly ask me about it. There is an alcohol challenge study that was done preapproval and just hot off the press. I do not even have a slide on it. There was another study done in 90 women that was just presented in Prague about two weeks ago on post-approval study with alcohol challenge.

Let me just talk to you a minute about some other up-and-coming treatments. We have bremelanotide that has finished its phase 3 trials, so like I said it is not a one-size-fits-all. The idea of having more than one option for your patients, I think, is going to be huge because for those women who prefer flibanserin, which is an oral medication taken at bedtime, then that is going to be great for them. If it does not work, you can have another option. This is actually an on-demand treatment. This is actually like an EpiPen. It is a novel melanocortins receptor agonist that works within about 45 minutes to increase desire and arousal and so the phase 3 trials have been completed in this and hopefully this will be the next to go to the FDA and get approved. We are hoping.

Here is the study design – very similar to the flibanserin studies except that they used a placebo run-in as its own sort of baseline to show an effect above and beyond women's own placebo I think is a very clever treatment design. Here is the trial. There were about 1,200 women in these clinical trials, these phase 3 trials, and similar to what we are looking at, the female sexual desire scale, the

FSFID, you can see improvement in the treatment over placebo starting at four weeks. The same thing is shown here. Distress already goes down by four weeks and separates from placebo very nicely. Responders were about 50-60% again responder rate. While you have good efficacy in these treatments, it does not work for everybody. You need to pay attention to whether it works for them and if it does that is great and if it does not you can switch them to something else. It is very safe. Most were mild to moderate. Nausea was one of the bigger causes for dropout in about 11%, but I will tell you that with flibanserin and with bremelanotide you get the side effects very early on and they often attenuate. With flibanserin, within two weeks you saw your side effects and with bremelanotide you actually get it right away, but oftentimes it attenuates. While 20% dropped out or 18%, only 11% were because of GI symptoms.

Let me finish by saying sexual function is important. We need to pay attention to the fact that once you treat your patients, their self-perceptions still may need to change and we need to think about the fact that it is helpful to say, you know, just because you have always thought of yourself now as dysfunctional, it is important to shift that perception now that we have treated it and that we need to pay attention to the fact that desire discrepancy is actually one of the issues that couples need to address and that too much of a good thing is not necessarily a good thing and so that is not necessarily a sexual dysfunction. If you have one person who is higher drive and one person that has less drive, the person who has higher drive feels very put upon that you are always the one that controls this. They do not understand how could you not want sex? It is fun. It is free. It is no calories. If you do not want sex it must be because of me. The person with less desire says, “It is not that. It is not that I do not love you or want sex, I just do not want it every single day.” Push me to want something more than my body wants it, it now feels like a chore. It is very helpful to negotiate with those patients to help them understand what that discrepancy is, and since I worked out this morning, I can tell you my favorite comment is, “To change the concept of drive of sex to drive of ice cream.” The person who has high drive may not necessarily have the same level of drive for ice cream; if they think about it, “Do I want it every single day?” well, you know, the first night it is great; the second night it is pretty good; but the third night, you know, I am a little tired of ice cream and maybe I do not want it. The fourth night they have a headache. It is helpful to change the perspective so that the couple can negotiate because sometimes it is really helpful to get people on the same page with communication. With that, I will thank you and say it is hugely a burden for people. Please ask your patients about sexual function. We have safe and effective treatments and your patients will love you if you ask. Thank you very much.

ANNOUNCER CLOSING

Thank you for participating in the Omnia Education CME activity, entitled *Hypoactive Sexual Desire Disorder: Assessment, Diagnosis and Treatments* presented by Dr. Sheryl Kingsberg and recorded live at the Women’s Health Annual Visit in Boston, Massachusetts.

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