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Menopause Matters…Let's Start Paying Attention to Racial and Ethnic Differences: Current and Emerging Treatment Approaches

Announcer:
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Dr. Kagan:
Now, I'd like to welcome you to this module on current and emerging approaches to treating vasomotor symptoms. And again, I'm Dr. Risa Kagan, and it's my pleasure to introduce to you Dr. Ekta Kapoor.

Dr. Kapoor:

Thank you, Dr. Kagan. As you said, I am Dr. Ekta Kapoor. I'm an Associate Professor of Medicine at Mayo Clinic College of Medicine in Rochester, Minnesota. I'm also the Associate Director for Mayo Clinic Women's Health. So in this module, Dr. Kagan and I will discuss available and emerging hormonal and non-hormonal therapies for vasomotor symptoms, and how we identify women who are eligible for these therapies.

But first of all, let's hear from another patient, Mary Kim, who experienced vasomotor symptoms and tried hormone therapy for treatment.

Patient:
Hi, my name is Mary Kim. I'm a 55-year-old woman. I started going through menopause or some menopause-like symptoms in my late 40s. I went through official menopause when I was 51 years old. So I've been approximately in menopause for 4 years.

Well, I think it was in my late 40s When I was starting to get an inkling I was heading into the peri menopausal phase of life. I just proactively went to my OB/GYN during one of my appointments and just asking are there any, you know, special things, I need to look for, tips and tricks just as I'm starting to get into this process. And basically, my OB would just look at me and she's like, 'You're beautiful, you look fine. Everything is good, you know, like, you'll be fine.' And, you know, again, the next year when I started having, what for me were not hot flashes, but were these sort of simmers that would linger for days, I started talking more and more about again, those symptoms, what to expect, what can I do, what are some options? At that point, you know, my doctor still didn't seem to have a lot of interest in what I was saying. She just kind of kept moving on to another topic, and then eventually actually sent beyond to an endocrinologist for further testing, whether I was or was not going into menopause.

So when I went to the endocrinologist, the irony is she had asked me what I was there for, and I kind of told her and she looked at me great quizzically, and I hate to say this, but I kind of told her, I said, I think it's just because my OB didn't really want to do her job and take the levels. She chuckled. She did take my hormone levels. And when I came back for a follow-up appointment, she did state that I was, you know, pretty much in menopause. And since I discussed some of my symptoms with her. And again, predominantly, you know, some of it was the weight gain. But the biggest thing for me was these - the night sweats as well as these just long simmering days where I was just hot. And it was being very disruptive. It's just you're just always hot, and there's really not a lot you can do about

it. So she did put me on a low dose of ___and a subsequent prescription of progesterone. And we went to go see, you know, how that would help my symptoms.

As it turns out, I stayed on for I believe somewhere between 4 to 6 weeks, ended up having some side effects to the prescriptions. And basically, at that point, she said that I probably would not be a candidate for hormone replacement therapy, did not offer me any other options at the time, and basically kind of left me to go back to my OB/GYN.

Dr. Kapoor:
So as you heard from Mary Kim, what a frustrating journey for her and what is sad is that Mary Kim is not alone in this kind of an experience. Very often in my practice, I hear from patients that they enter menopause with little or no knowledge about it, leave alone, knowledge about strategies to manage their symptoms. Worse still, as Mary Kim brought out a lot of times patients bring up these concerns that their providers and they are unfortunately dismissed. So very sad situations.

As we were discussing in the previous module, there is a huge unmet clinical need in terms of how we educate our patients about menopause, what their options are, and what to expect. And as Mary Kim shared, that even though, for a given symptom or a concern, if even if you do not have very effective treatment options out there, I think it's very important to let the patient know and to have that transparency, because that itself empowers patients and gives them that knowledge base to know that this is an important change that's happening in their lives. And this is what they have to live with versus this is something that can be managed. Because a lot of times there is this negative messaging that there is nothing that can be done about menopausal symptoms, and they had to live with those symptoms, which is so far from the truth.

So in terms of management strategies, let's first of all talk about the hormonal agents that we have at our disposal. And hormonal therapy is actually the most effective treatment for menopausal symptoms, as Dr. Kagan was sharing with us in the first module. So what are our options when it comes to hormone therapy?

So you know, the main hormone that is lacking after menopause, which causes not only the bothersome menopause symptoms, but also the long-term adverse consequences, is estrogen. So that obviously has to be a component of any type of menopausal hormone therapy. Now the estrogen can be given via an oral route, transdermal, meaning through the skin or the vaginal route. In terms of oral preparations, we could use bioidentical estradiol, which is the hormone that's made by the ovaries, or we could use conjugated estrogens. In terms of transdermal preparations, the ones that are given via the skin, it could be a patch, gel, or a cream. And the vaginal rings typically contain estradiol.

Now in women who have an intact uterus, we do not use unopposed estrogen because of the risk of endometrial hyperplasia, and potentially uterine cancer. So those patients have to be on a concurrent progestogen. So in terms of our options for progestogen therapy, we could use oral micronized progesterone, which again, is the natural hormone made by the premenopausal ovary, we could use synthetic counterparts of progesterone, including the medroxyprogesterone acetate, or other synthetic progestins. Another option is levonorgestrel-containing IUDs.

Now in terms of how we give hormone therapy to our patients, it could be either in a continuous fashion, meaning the estrogen and the progestogen given continuously at all times, versus what we call sequential regimens, wherein there is a time period when estrogen is given unopposed, and then followed by estrogen plus the progestogen. So there are pros and cons of each approach there.

Then, one last thing that I want to mention about hormone therapy is this relatively new product, not that new now, which uses a combination of conjugated estrogen and a SERM. So selective estrogen receptor modulator, bazedoxifene as opposed to a progestogen. So those are our hormone options.

Now, I was telling you earlier that hormone therapy is the most effective treatment for menopause symptoms. So it looks like we have an effective tool. But why is it that most of the patients with menopause symptoms are not being treated? I mean, leave alone treatment with hormone therapy, most of these patients, overwhelming majority, even if they have severe symptoms, are not being treated. And again, going back to Mary Kim's story, she was told by many people that there was no effective treatment for her symptoms.

So what has the landscape of hormone therapy used been over the years? How has it evolved? So back in the 1990s, hormone therapy was given to pretty much every woman that went through menopause, it was the so-called default intervention, if you will. And that was because back then, as Dr. Kagan was telling us, that people who were practicing at that time, this was standard practice, because it was believed, based on fairly strong observational evidence, that hormone therapy protects women against heart disease. It protects against dementia. It protects

against osteoporosis. So again, based on very strong observational evidence, the thinking then was that not only is this the best treatment out there for menopause symptoms, it has preventive health benefits. So based on that premise, the practice at that time

would be that a patient would walk in a doctor's office, and if she was postmenopausal, the default discussion would be that okay, regardless of symptoms, patients were very often put on hormone therapy because of the preventive health benefits.

So then the WHI, Women's Health Initiative trials were conceived, and the idea at that time was that okay, we know of all these benefits of hormone therapy based on very strong observational evidence, let's test this out in a randomized control trial model, meaning let's look at the pros and cons of hormone therapy in a clinical trial. So it was conceived - these trials were conceived with a lot of enthusiasm, and with the hope that we would see a reduction in cardiovascular risk, we would see a reduction in dementia risk. But the WHI didn't quite bring out both results.

So why did that happen? Why was WHI, in a sense, the wrong model for testing the hypothesis that it thought it was testing? Well, the reason for that was as is shown on the slide, the average age of the woman in the WHI was 63 years. Now, as we were talking about in the previous module, the average age of menopause is 51 years. So these women were more than the average woman in the WHI, was more than a decade older than the average woman who goes through menopause.

So if you think about your clinical practice, when do you sit down with a 63-year-old patient for the first time to talk to her about hormone therapy? That almost never happens, right? The patient that you typically see in your office to discuss hormone therapies, the woman in her late 40s, or in her early 50s, not a 63-year-old; 66% of the women who were involved in the WHI trials were actually more than 60 years of age, and were more than 10 years from menopause. So again, the point being, this was not the typical patient that we recommend hormone therapy to.

Most of them had pre-existing risk factors for cardiovascular disease, including hypertension, diabetes, high cholesterol, and obesity. So it's not a surprise that the WHI really did not bring out the results that we were hoping it would. So what we saw was, which actually led to premature termination of these trials, that there was an increased risk of cardiovascular disease, there was an increased risk of breast cancer. And this was like allcomers, all patients, all participants looked at together.

But then the data were stratified. So the devil is really in the details. When these data are stratified by age, it became very clear that for that young patient between the ages of 50 to 59 years, within 10 years of menopause, even in the WHI, there was a significant reduction in the risk of coronary artery disease. There was a significant reduction in the all-cause mortality risk. Now, no other intervention known to man actually causes such a significant reduction in mortality for women in that age group. So hormone therapy stands out in that respect. There was the high risk seen for cardiovascular disease, it was the women who were older than 60 years of age and that trial.

So again, the point being, the reason why the WHI disappointed us was because it wasn't designed to show us the outcome that we were hoping it would show. So if this study were to be done all over again, and the average age of the participant is 53, we're very likely to see very different results. But no one is really jumping out of their chair to do a trial again on a concept like this. But, again, when we stratify these data by age group, it's pretty clear that the benefits of hormone therapy use in that patient who's between 50 to 59 years of age, and within 10 years of menopause, the benefits far, far outweigh the risks even in a patient who doesn't have a contraindication to hormone therapy, because obviously, so contraindications would mean that she has pre-existing cardiovascular disease, or she has a history of estrogen-sensitive malignancy like breast cancer or endometrial cancer, or a prior history of an unprovoked deep vein thrombosis. So again, working on the premise that there is no contraindication, the benefits outweigh the risks in the right patient.

So because of these facts that I shared with you, most professional societies, including the North American Menopause Society, the American College of Obstetricians and Gynecologists, the American Association of Clinical Endocrinologists, The Endocrine Society, and the U.S. Preventive Services Task Force, all of them - all of them endorse the use of hormone therapy for management of bothersome menopause symptoms in the young patients less than 60 years of age and within 10 years of menopause.

Now again, the important thing to understand is that the way things stand in 2022, we are recommending hormone therapy for treatment of menopause symptoms only. We're not quite prescribing it for its preventive health benefits, like the practice used to be back in the 1990s. But who knows, we may come full circle and that might change. But that's not how we are currently practicing. But definitely for the patient who's having bothersome symptoms, this is the frontline therapy. So patients like Mary Kim should not have to suffer through night sweats. So provided there is no contraindication to hormone therapy use, this should be discussed with patients like herself.

So in terms of determining who is the right patient for hormone therapy, if she's sitting in your office having bothersome symptoms, so I'm going to turn it over to Dr. Kagan. If you can walk us through how you determine whether hormone therapy is appropriate for the patient sitting in your office, Dr. Kagan?

Dr. Kagan:
Well, a lot of this depends on whether this is a new patient or a return patient. But I think it's essential, and I am one of those old-time docs that really I don't mind if it's a return patient doing a video or telemedicine visit, if it's somebody I know them. But if it's a new patient, I mean, and with COVID, I may have to do a telemedicine visit.

But I will say, I do believe that a complete history is so important, not only symptom based, but medical history, social history, finding out family history. And then I do like to do some evaluation of the patient before just prescribing hormone therapy. And what I like to do is do a full comprehensive evaluation, by careful history taking, finding out what they've been on before, finding about their menstrual history, find out - it's essential to find out what they're - if they're hormone sensitive. Many women who have PMS, many women who have postpartum depression. Many women will describe, you know, sensitivities to a progestogen that they may have tried. And if they have a uterus, clearly, we might need to use that. So this is very important. We need to find out what their lifestyle is like, or do they smoke? Are they drinking alcohol? Could I be concerned that maybe they have an underlying liver disease?

So you already heard, as you elegantly presented, the contraindications, the absolute contraindications, but there are these things called relative contraindications. So we do a lot of education. So if somebody comes in and says, 'Oh, I have a family history of breast cancer, family history of, you know, thromboembolic disease,' it doesn't mean that that patient right then and there, if they are severely affected, can't use hormone therapy for some period of time.

So I do recommend a complete history, medical, family, surgical, finding out what they've tried in the past, find out what alternatives they're trying right now, finding out, really, are they sleeping? Are they ready? It's shared decision-making. And in order to do that, there needs to be a fair amount of education as well.

So after that, well-woman exam, I may send them out with some reading material grade level. NAMS, North American Menopause Society does have some very good, something called MenoNotes, while I'm gathering the laboratory data, the mammogram, trying to get a family history of bone health.

And then we set up another visit face to face, clothes on, whether it be on video, or whether it be in person to really do the shared decision-making. Because no matter how many prescriptions I could give somebody, if they are not involved in that decision process, they will not stay on it. And I've seen it over and over again, they'll never fill the prescription. They'll come back 6 months later saying, 'oh, I never took it. I was too afraid. I went to my book club, and everybody scared me about breast cancer.' So if women are really suffering, I don't want them to suffer in silence.

So I start the process of even educating people prior to that last menstrual period. Even if someone is having a lot of symptoms at this time, I do that usually use that perimenopausal time of life as a really good hallmark to look at what symptoms they may have now, what could happen, find out a little bit about their sisters, their mothers, what their biases might be, and really attack it head on.

But before starting, I do believe that it's important to do some evaluation medically, besides taking the big history, and even doing a physical exam, because periodically I will pick up a breast mass and need to evaluate that prior to going on any kind of hormone therapy.

Dr. Kapoor:
Correct. Correct. Thank you so much for that, Dr. Kagan. So yeah, medical school approach, a detailed history is very important. So I think if we were to summarize that, we are first trying to assess the severity of the menopause symptoms, which dictates the need for interventions like hormone therapy. So the breadth of the menopause symptoms, what is it that they're experiencing, and how severe are those symptoms? Number one. And then trying to assess if hormone therapy is right for them. So basically, a detailed assessment for any contraindication for hormone therapy. And that's via history-taking, examination, like you said, and laboratory workup. And then the third thing is okay, the decision is made to do hormone therapy, what form of hormone therapy? Like you were alluding to, patients with high triglyceride level, for example, you go with transdermal as opposed to oral, etcetera. So I think those are the three questions that we are trying to answer when we are making this assessment. Wonderful. Thank you.

So the next question do, Dr. Kagan, is, what challenges and barriers do you see in prescribing hormone therapy? For example, if your patient questions the use of hormones, and as you know, that happens quite a bit, because of all the information that they have received from friends, family, the media, mostly the aftermath of the WHI, or they are experiencing problems accessing therapy, how do you approach situations like that which are very common in clinical practice?

Dr. Kagan:
There's no question that we really have to overcome the biases that have happened post WHI. There are lots of studies showing that at least 80% of people just went off hormones, never went back on, and we're suffering and suffering in silence.

And so some of the challenges and barriers besides their personal fears, I do open-ended questions. I mean, I really try to get a sense as to your suffering. And the absolute, you have no contraindication, please share with me what your fears are. And usually, the number one is breast cancer. So we really do go into a lot of education, shared decisions, give reading material. Sometimes I'll even do a risk assessment as far as their future risk of breast cancer is concerned. And the more information I can give, the better.

But some of the other challenges and barriers has to do with their access to healthcare. I mean, and cost. Nowadays, there are a lot of choices to be made about putting food on the table, or are they going to go on something that may help them sleep at night? And so, you need to give it their sense as to again, those social determinants of their health to find out what is realistic, and what is affordable, and really, what is stopping them from trying hormone therapy.

Dr. Kapoor:
So you know, as we were talking earlier, that hormone therapy, effective as it is, and all the preventive health benefits and the right patient, it's not for everybody, right? So there are situations where we cannot use hormone therapy, we should not use hormone therapy, or the patient just, even after all these long discussions is just not comfortable using hormone therapy for whatever reason. So then the question is, what are the options out there for a patient who cannot be on hormone therapy? Can you speak to that a little bit?

Dr. Kagan:
Yes, I can. And we can talk about what has been available, what has been used over the years. And we can say that, for the ones who cannot be on hormone therapy, you really get into all of the different options, more because if they're suffering, you really have to educate them about all these different options.

For those who choose not to go on hormone therapy, many of them don't want to go in any of these either, because they're afraid of the side effects. And you know, what we have here is a list of options that have been, you know, studied in small studies, but we have literally one, and only one, that has been FDA approved and studied in a randomized control trial against a placebo showing efficacy, and that is a very low dose of paroxetine 7.5-milligram dose that is actually approved for hormone therapy. There are many, many other selective serotonin reuptake inhibitors that have been studied against placebo with efficacy, none as good as hormone therapy. Escitalopram, citalopram, fluoxetine, sertraline, and most - then we have SNRIs, like venlafaxine and desvenlafaxine.

Most of this literature and studies though have come from our breast cancer survivor population. There's small studies. There are the other challenge that we have with all of these randomized controlled trials is that they have to be better than a placebo response. And we really know from clinical trials, there's a very large placebo response that can be even sometimes 40 to 60%. Having been an investigator and some of the gabapentin trials, and one of those trials even saw a 60% placebo response. So if we could package that placebo, and I mean, these are the worst severe hot flashes, both in number and severity, compared to placebo.

But if you explain the mechanism of action to the patient, some may open their mind up to trying some of these agents, especially if they are also suffering from some new mood disorder, anxiety disorder. And reassuring them that these are not necessarily going to give you the same side effects, the doses may be lower than some people use when they have had a long history of depression or anxiety.

Now, the gabapentin pregabalin and gabapentin as I said, is an excellent agent that when some people actually need to use an SSRI/SNRI in the morning, and even use a little gabapentin at night for sleep, combination therapy. There the randomized control trials again, but smaller numbers showing efficacy again, none like hormone therapy.

And then there is another agent. Generally, we use it as a transdermal delivery, clonidine, which is a antihypertensive medication. So you have to be careful that a patient needs to be instructed that if it lowers their blood pressure too much, they may have side effects from that.

And then, more recently, there's randomized controlled trials using oxybutynin, which many of us use for overactive bladder. And in the proper dosing, this has also helped a number of our patients.

So we do have alternatives, especially for those who absolutely can't use estrogen, or choose not to use estrogen, or are afraid to use estrogen. But then you need to go through the potential side effects, how long it takes to work, and the different dosing. But then again, I must admit, the only one that really has been studied in any large numbers, RCTs is the low-dose, LDMP, the paroxetine of 7.5 milligrams, which unfortunately is very hard to get because it's not on any formularies.

So Dr. Kapoor, now in talking about alternatives, because we definitely need to have a good alternative, because not everybody can or will take hormone therapy, I understand that you are going to now educate us a little bit about a new pathway for hot flashes, and a new mechanism of action that has been found and certain agents that have been targeted at this new pathway, if you don't mind, and they're in during clinical trials at present. So if you don't mind reviewing that for us?

Dr. Kapoor:
No, happy to. This is an exciting thing in menopause medicine.

So as much as we talk about vasomotor symptoms and the impact that they have on the lives of our patients, and we have a reasonable handle on our management strategies, in terms of the pathophysiology of vasomotor symptoms that's still incompletely understood, even in this day and age. So what we do know for a fact is that estrogen deficiency is a key player. But then how exactly it does that,

that's not very well known. And then studies have previously looked at estradiol levels and the correlation and the frequency and severity of vasomotor symptoms, and there isn't a perfect correlation. There seems to be some correlation with the FSH level, gonadotropin level, and the intensity of hot flashes. But estradiol level itself does not seem to corroborate. So that doesn't make sense at some level that if it is the main pathogenic factor level, should probably have something to do, but we just don't know that yet.

So while of the relatively novel mechanisms that has been proposed in the pathophysiology of vasomotor symptoms, which could potentially be either the only or one of the mechanisms by which the lack of estrogen causes vasomotor symptoms, involves a group of nuclei, a group of neurons in the hypothalamus that reside in the infundibular nucleus of the hypothalamus. And as you know, that the temperature-regulating center of our body is also located in the hypothalamus. So this new group of neurons as shown on the slide, these are known as the KNDy neurons, K-N-D-y. Now the reason why we have this name because these neurons they contain neuropeptides, kisspeptin, neurokinin B, and dynorphin A. So that's why the short term, the acronym, KNDy neuron.

Now these KNDy neurons are very interesting. They have estrogen receptors on them, and they have neurokinin 1 and 3 receptors on them. Estrogen perhaps exerts an inhibitory influence on these neurons, and neurokinin exerts a stimulatory influence.

Now, post-mortem studies in postmenopausal women has shown hypertrophy of these neurons so they are hypertrophied in comparison to premenopausal women. So something changes after menopause that has a stimulatory effect on these neurons, causing them to hypertrophy.

Then some research has also shown that if you infuse neurokinin B, and it activates this receptor on the KNDy neurons, that leads to the whole hot flash response. Then if there is estrogen deprivation, because estrogen has an inhibitory effect on these neurons, if there is lack of estrogen, these neurons, not only hypertrophy, they get stimulated, and that causes the hot flash response. So, it is likely that estrogen is exerting its effect or lack of estrogen causing the vasomotor symptoms is being exerted via these neurons, because they also project on to the median preoptic nucleus in the hypothalamus, as you can see on this slide, which is the temperature-regulating center of the hypothalamus.

So, some very intricately conducted experiments, they've all come together to show us that this group of neurons called KNDt neurons, inhibited by estrogen stimulated by neurokinin B, so, lack of estrogen causes stimulation of these neurons. And since they project onto the temperature-regulation center, lack of estrogen causes the hot flash response. So I think physiologically makes a great deal of sense. So one of the novel mechanisms.

Now, so what investigators have done knowing that neurokinin B stimulates the KNDy neurons, they have looked at neurokinin B receptor antagonists as a way of treating hot flashes. So the three agents that have been tested in clinical trials, which are neurokinin 3 receptor antagonists include fezolinetant, elinzanetant, which is NT-814, and SJX-653. So fezolinetant is a neurokinin 3 receptor antagonist, elinzanetant is a dual neurokinin 1 and 3 receptor antagonist, and SJX-653 is a selective neurokinin 3 antagonists. So in the next few slides, I'll show you some clinical trial data which appears very promising as to how these agents can change the landscape or modify the landscape of treatment or vasomotor symptoms significantly, potentially.

So this first slide here shows the results from a phase 2a study of fezolinetant. So basically, here, the investigators compared placebo to fezolinetant given at the doses of 90 milligrams BID, and looked at the effect on vasomotor symptoms over a period of 12 weeks. So as you can see, at baseline, the daily total VMS score was comparable in the two groups. And within 4 weeks, there was a significant reduction in the total daily VMS score, as you can see, actually both in placebo and fezo, but definitely much more dramatic in the fezo group, kind of preserved at week 8 and slightly more pronounced at week 12. But the point to make here is that the favorable effects - the dramatically favorable effect of fezo is seen as early as week 4, and is maintained to week 12 at the dose of 90 milligrams BID.

And the phase 3 SKYLIGHT-2 study was a double-blind placebo-controlled 12-week, which was followed by 40-week active treatment extension. The investigators engaged 500 women between the ages of 40 to 65 years who had moderate to severe vasomotor symptoms with a minimum average of seven hot flashes per day. And the participants were randomized, 1-1-1 to fezo 30, 45, or placebo given once daily. And what they saw with that, the results are summarized here on this slide. So if you look at the reduction in mean frequency of moderate to severe vasomotor symptoms versus placebo, fezo 30 was effective, as you can see that these very significant P values. And again, effective as early as 4 weeks, which did not change significantly by week 12. But fezo 45 was even more effective, again, getting to nearly maximal efficacy at 4 weeks itself, and preserved at the 12 week mark. If you look at the reduction in mean severity of moderate to severe vasomotor symptoms versus placebo, fezo 30 was effective as seen by the as seen by the significant P value here. But then again, fezo 45 was more effective. And then the efficacy really did not change from week 4 to week 12. So the point again, being higher doses seem to have a greater effectiveness. But regardless of the dose, the beneficial effect of this antagonist is seen early on in therapy as early as 4 weeks, and then preserved throughout the duration of treatment, which, you know, based on these clinical trial data is in the range of 12 weeks.

And this next slide here talks about the pharmacokinetics and preliminary efficacy of NT-814, which is the dual neurokinin 1 and 3 receptor antagonist. So again, they're comparing different doses of the agent, 50, 100, 150, and 300 versus placebo. And here on the X axis are the number of days. So again, while these graphs bring out that the response to treatment is pretty early. So within 7 days of treatment, we can see a reduction in the number of hot flashes, and not so dramatic when it comes to severity. But still, the response whatever has to occur, occurs early on within 1 week of starting treatment, which is very encouraging. And then again, in terms of the most effective dose based on these graphs presented here, it looks like 150 milligram turns out to be the most effective dose paradoxically, and not the 300-milligram. So there's perhaps a little ceiling effect there and things swinging a little bit to the other side with the 300-milligram dose.

The phase 2b SWITCH-1 trial of NT-814 is a randomized, double-blind placebo-controlled 12-week trial engaging 199 women with at least seven moderate or severe hot flashes per day. And the least or mean reduction in average hot flashes frequency are shown on this slide here. So 6.7 for NT versus 2.7 for placebo at week 4, and then slightly more effective, but then again, not very different. So again, the ___ seems to be that all these agents work rapidly, maximal response, nearly maximal response at week 4, and not significant differences after that.

So again, in a nutshell, Dr. Kagan, I think this is a very promising line of therapies. And not only is it exciting from the standpoint of a new agent, and we've waited forever for something like that after hormone therapy. What is also exciting about this line of treatment is the pathophysiology piece, how it is shedding some light on what may be the underlying mechanisms of how estrogen mediates the whole pathophysiology, the whole process of hot flash temperature regulation. That is another exciting piece that comes out with these new novel therapies.

Announcer:
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