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Understanding Emerging Options for Managing Vasomotor Symptoms

Announcer:
Welcome to CME on ReachMD. This activity, entitled Understanding Emerging Options for Managing Vasomotor Symptoms is provided by Omnia.

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Dr. Santoro:
Thank you for joining us. This is CME on ReachMD, and I'm Dr. Nanette Santoro, professor and E. Stewart Taylor Chair of OB-GYN at the University of Colorado School of Medicine. During this program, we will look at the burden of vasomotor symptoms, briefly review current hormonal and nonhormonal options for management, and explore a new class of nonhormonal agents called selective neurokinin-3 receptor antagonists.

Hot flashes are a major burden for women as they are traversing the menopausal transition, and they actually reach their highest prevalence before a woman is actually defined as being menopausal. This is important because patients may come in for treatment before they have actually experienced their final menstrual period. You can see on this slide, which amalgamates several different studies, the premenopausal is somewhere between 20% to 45% of women will report having hot flashes mostly concentrated to around the time of their menstrual period. Hot flashes begin to increase in prevalence with 25% to 55% of women experiencing them as they begin to get some of that early menstrual cycle irregularity associated with the early perimenopause. But remember, early perimenopause, women have at least one menstrual period within the past 3 months, so there isn't prolonged amenorrhea. As women progress to that late perimenopause, where amenorrhea of 60 days or more is more common, 50% to 80% of women will report hot flashes. From that late perimenopause transition to the postmenopause, after a woman has had 1 year of amenorrhea, the prevalence begins to go down again. And in the late postmenopause, more than 5 years after the final menstrual period, 16% to 44% of women will report hot flashes. So it looks like it begins to go down, but this just tells us about the frequency or the prevalence but not severity of hot flashes, which we know for some women, many in that 15% range here at the low end, will continue to report severe hot flashes long after menopause.

The high prevalence of vasomotor symptoms also speaks to their burden. And that has also been looked at in some studies. Another study reported that two-thirds to almost 80% of women, similar to the percentages in the SWAN study, report having hot flashes; 7% to 9% will report the very severe hot flashes, more than 7 moderate to severe daily hot flashes, which is usually what qualifies women for studies of hot flash treatments.

In one quality-of-life study of almost 3,000 women, hot flashes were reported as negatively affecting sleep, which is a very common clinical complaint. Many women feel that it affects their concentration, their mood, their energy levels, work, and social activities. Many of these burdens of hot flashes are also intertwined. So hot flashes are thought to maybe initiate a cascade of negative events that then has quality-of-life compromise. And most distressing is that 44% of women will report decreasing their social activities because of hot flashes, and a similar percentage find that it causes them difficulty at work.

There are some factors that we also know of that influence how long hot flashes are going to last and can give us an idea of who will have the most severe hot flashes. The 2 most important factors are the timing of onset as well as race/ethnicity. The median duration of Vasomotor symptoms for African American women in the SWAN cohort was 10 years. Vasomotor symptoms that start before a woman even has any menstrual cycle changes associated with her menopause transition also last longer, and that's almost 12 years. So how bothersome they are is really going to dictate the wisdom of applying treatment, as opposed to someone who gets them much later in the transition who may want to tough it out and is only going to have a couple of years to deal with it.

So other predictors of long duration of hot flashes are younger age at onset, cigarette smoking, high body mass index, worse overall symptoms. So women who just have more of what we call symptom sensitivity are also likely to have a longer duration of hot flashes, and women that have other forms of stress.

Vasomotor symptoms that start post menopause, in contrast, have a median duration of only 3 to 3½ years. So those women are much more likely to have a milder, more short-lived course of hot flashes. And that is going to influence the decisions regarding treatment. Other predictors of short duration of hot flashes are being of Japanese or Chinese heritage, being married or partnered, having less financial stress, and experiencing more social support.

So you can see that evolving from that discussion is that there really seems to be a health disparity in hot flashes, duration, severity, and impact.

So let's talk about some of the treatments for menopause and hot flashes being the biggest and baddest of symptoms. And hormone therapy, we know, is currently the most effective treatment that we have. We know that adequate doses of hormone therapy can certainly improve and, in many women, completely eliminate hot flashes. This in turn tends to improve sleep. And in studies done of women that get GnRH agonists to induce menopause – and these are young, premenopausal women that are just given the GnRH agonist – when you add back a treatment, hormones being one of those treatments, one of the first signs that you see is that women given the agonist will have decreased ratings in mood surveys. As soon as you give hormones back, their sleep gets better, and sleep predicts improved mood. So sleep is an important component and something on the axis of how hot flashes are disruptive. We know hormones also improve blood flow to the vagina and the vulva. And this may increase sexual sensation in women who are having some sexual dysfunction or just a change in sexual function that they are not happy with as a result of menopause.

Typical doses of hormone therapy are also effective as a bone antiresorptive. Although they're not considered a primary agent, this is a secondary benefit that this will reduce bone resorption and prevent fractures. And there's some evidence that collagen content and skin thickness can be improved with hormone therapy, although that is a little more mixed.

So hormone therapy can be appropriate therapy, we know, for many women, especially early in the menopause transition when women are exposed to hormones anyway. Preventing them from having those periodic dips may improve their symptoms. Estrogen used with SERMs or local progestins, so that would be a progesterone IUD, may eliminate the breast cancer risks associated with progestins. That's somewhat controversial, but it's definitely a good thing to explore. And the ability to treat vasomotor symptoms in women who don't or can't use hormones, we also have some nonhormonal therapies that will allow wider use. So women who are hesitant to use hormones or who have increased risk can also be offered these treatments.

But all of them can be used and they have a place. And I encourage clinicians to get some facility with a few of these and move patients through them because it really is worth trying a few different treatments. You may be able to arrive at something that's going to work.

For women that primarily have nighttime hot flashes, gabapentin can be very, very helpful. I typically will start my patients at very low doses. If you look at the clinical studies that have been done, they sometimes start with doses of 600 to 900 mg, but there are some women who are much more sensitive to this, and you don't want to turn them off to the treatment permanently by giving them a dose that's going to make them dizzy or sleepy so that they can't wake up or they get adverse side effects or have a fall as a result. So I will have them start slowly and move up because relief with agents like gabapentin is very rapid. So it's usually within a matter of days. And a patient will know if she's having side effects. They usually consist of dizziness, disorientation, dysphoria for some patients, but many patients will notice that they sleep more deeply. They're not awakened by their hot flashes. And if most of their hot flashes are happening at night, or the most bothersome hot flashes are at night, that may be all that’s necessary.

For women that are 24/7 hot flashers and that are having disruption during the daytime, the SSRI/SNRI class of drugs has been shown in a number of randomized trials to be helpful. Only 1 is FDA-approved. I also encourage clinicians to get comfortable with a couple of different agents in this group of drugs because one may not work and another may work. It is worthwhile to switch back and forth or among different drugs within this class of drugs to see if you can get one that a patient is comfortable with.

Clonidine has had mixed results in clinical trials. But again, it's worth trying for some patients, particularly if you can get what I call a twofer. If the patient has hypertension, and she does well with clonidine for her hot flashes, you may be able to just go back to one agent

and she can go off her antihypertensives.

The weekly patch seems to be a little more free of side effects and is very convenient for patients to use. They place the patch on their shoulder, and they can forget it. The biggest side effect that I see in the real-world use of clonidine is that some patients will get postural hypotension. Others will get dry mouth. But otherwise, you can push the dose from 0.1 up to 0.3 in the weekly patch. There's also oral dosing that can be higher. I usually have patients have a blood pressure cuff at home and watch for side effects and make sure that they're not getting any postural hypotension. And again, similar to gabapentin and the SSRIs, relief begins to happen within days.

One of the newer kids on the block is oxybutynin. So in doses at 2.5 to 5 mg twice a day, has been shown to have some efficacy over placebo in some randomized clinical trials. So again, another great opportunity to get a twofer in a patient who has some irritable bladder symptoms; this may treat both things with one treatment.

So among the prescription nonhormonals, there are some alternatives. And I think it's very important for patients to know that and not to just assume that all they can be given is hormones. They have a reasonable track record of efficacy and safety, but again, only 1 is FDA-approved. So all of these other treatments are off label, and I think it's generally good practice just that the patients know that. SNRI/SSRIs have been used in hundreds to thousands of women in reported clinical trials. Gabapentin at least in hundreds. Clonidine has been reported in at least 100 women and oxybutynin similar. And that's usually the number of patients that you need to really determine is this treatment better than placebo. The typical efficacy of all of these compounds is about one-half of that of estrogen. So in several of the studies, they just appear to edge placebo. And for many women who just cannot take hormone therapy, that is the best that we can do. And we can take the edge off of their symptoms. So it's actually very encouraging that we have some new agents for vasomotor symptoms.

And targeting the neurokinin-3 receptor is a highly specific treatment that may address vasomotor symptoms at their origin. So that's been a new exciting development in the science of hot flashes. We have been in the dark for decades about where hot flashes begin. It's always, somewhere in the brain we have a thermoregulatory center; it’s not really known where it is. Well, it has now been localized to that NK3 receptor, which is on hypothalamic KNDγ neurons for kisspeptin, neurokinin, and dynorphin. They have superior efficacy to all of the nonhormonals, and they seem to be comparable to hormone therapy itself. So we may now be entering an era where we have a highly effective nonhormonal treatment that we can offer patients.

The KNDγ neurons kisspeptin, neurokinin, and dynorphin are in the hypothalamus. Kisspeptin works north of gonadotropin-releasing hormone and helps to initiate puberty by stimulating the production of GnRH. The other receptors and peptides in these neurons have not been well understood, but the dynorphins are known to be in the endogenous internal opioid system as well. The KNDγ neurons were first noticed to be increased in the brains of animals and humans after the ovaries had been removed. So women that have oophorectomies have a vast increase in these neurons. And that's where the extra NK3 input comes in. And in one very elegant experiment in mice, blocking that receptor reduced the coolness-seeking behavior in mice that had their ovaries removed. So it then became applied to humans very quickly because this was a very exciting discovery, that blocking the neurokinin-3 receptor could abolish hot flashes.

Thank you for joining us today. I hope I've been able to convince you that vasomotor symptoms are a truly bothersome symptom that causes women a substantial amount of loss of quality of life, that we currently have satisfactory hormonal options but not entirely satisfactory nonhormonal options, and to stay tuned for the newest of the nonhormonal options targeting the NK3 receptor, which may prove to be highly effective. Thank you.

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