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Not Just a Headache: Migraine Across Women's Lifespan

Announcer:
Welcome to CE on ReachMD. This activity, titled Not Just a Headache: Migraine Across Women's Lifespan, is provided by Omnia Education and supported by AbbVie, Inc.

Dr. Pavlovic:
Well, good morning, and welcome to my home city, New York City. So it's a pleasure and privilege to be here among you, especially for this first in-person in a while meeting. It's a pleasure to share the stage with my friend and colleague, Dr. Amaal Starling. Wae happen to be the 2 neurologists probably in the room, and we're headache specialists, and there are very few of us in the country, right, Amaal?

Dr. Starling:
There's only 900 of us trying to serve 40-plus million women and men and children living with migraine. And so we are here because we need to recruit all of you to be also helping us taking care of women across the lifespan, across their life stages.

Dr. Pavlovic:
We can't do it all ourselves. The 900 of us are not sleeping, so you got to help us. So we're ready to start. We are? Okay.

So this will be somewhat of a whirlwind through a lot of slides, and some of them are neurology specific. They are there for your reference. We will point the most important points from them, but some of the complex slides serve there as your reference points to a future material, and we will just spin over them, and we can discuss them later more in the questions and answers.

These are our disclosures.

And these are the learning objectives. We want to focus on the diagnosis of migraine in women. We want you to focus on optimization of migraine care across a woman's life stages. As we say, we are not retrofitting old treatments into women's care. To reduce disparities—obviously here, disparities are significant, gender and race based—and improve the quality of migraine treatment across all special patient populations. And then integrate these goals into shared decision-making, which we really need you for—you are the first line here. Again, only 900 of us.

The first part of the talk will focus on really hormonal aspects of migraine that are highly relevant to this conference and highly relevant to the issue of women. So since the ages, we've known that hormones have affected migraine. And this is a slide that summarizes the 1-year prevalence of common headache disorders. And as you probably know, tension headache tends to be the most common headache. Migraine, only about 20% of women are thought to have migraine, or at least in a large epidemiological study. In our practices, obviously, that's different. And that's about 3 times more common than men.

However, when you study primary care offices, when you study any type of interplay with the medical community—who is in the waiting

rooms, who is in the urgent care seeking help for headache—it's actually migraine. It's just that it's often not diagnosed.

So if there's 1 slide from my some 30 slides that I would like you to really focus on, it's this one. And that is, that migraine is a global problem. It affects globally about 15% of the population, probably about 1/4 of women globally of reproductive age—1 in 4 women of reproductive age has migraine. Probably more than 50 million Americans, because these are data from a few years ago.

And this is truly the disease of women. And not only of women who are aging, but of women of reproductive age, women in peak prime years of their life—30 to 39 years is when the prevalence peaks in midlife, and then also the burden of migraine peaks. So this is something that's never lost on us, and this is not lost on us when we talk to others why this is important.

And then the last point here is that about 20% to 35% of people who have migraine have 4 or more attacks per month, and this qualifies them for preventive treatment of migraine. And Dr. Starling will focus on various treatments and the revolution of those treatments that we've had in the last couple of years.

Focusing on the gender- and age-specific prevalence of migraine, we really see that—what I've already told you, that about 1/4 of women of reproductive age have migraine. You see how that curve really peaks for women and how men kind of stay at almost the same prevalence throughout the lifespan. And what I'd like you to focus on is here, that right, like the peak of this curve really overlaps with entry into perimenopause. And then, as women are postmenopause, this is when typically migraine prevalence drops off.

How does migraine affect women compared to men? This is relevant when we talk, especially—I think this is an audience that probably understands this. But this is relevant when we talk to others who sometimes question this.

First of all, not only women more commonly have migraine than men, the higher rates of most associated symptoms of migraine is in women versus men. They're more frequent, longer-lasting attacks. The migraine severity tends to be the same, but the attacks are much harder to treat and often refractory to treatment. Therefore, they're more disabling. There's inability to perform daily chores and daily activities of living, many missed family activities, which women really don't like to report—the women underreport them consistently—but still, even with the underreporting, we see much higher rates of it.

And while women are more likely to seek medical attention, they are less likely to get the correct diagnosis. That's something that really needs to sink in— more likely to seek attention, which makes sense because they're so burdened, but less likely to get the correct diagnosis.

Okay, how does this all work through the lifespan? So I mentioned earlier that we've known for a long time that hormones and migraine are intimately connected. You're all familiar with hormones here, and so I'll just point out that progesterone is in this bright purple, the color of WHAV, and estrogen is in the navy blue. And we see the fluctuation in estrogen and progesterone mostly because those are the two hormones really that are most relevant. That is estrogen primarily. And in the gray background is the headache frequency.

So migraine affects women on two time scales in life. And one is the monthly time scale, or the menstrual cycle time scale during the reproductive age, and then the other one is just the lifetime, right? So during pregnancy and then lactation, how it generally helps out, and then in perimenopause and postmenopause, you see increases. So fundamentally, migraine likes steady and increasing levels of estrogen, dislikes—or the brain that has migraine—and dislikes drops and dramatic fluctuations of estrogen. That is the point of it. So when we see perimenopausal fluctuations in estrogen, we see a significant increase in frequency of headaches and migraine in those who already have migraine.

So there are many triggers, and I'm sure that patients who you see for headache and migraine, whether they recognize it or not, they will often probably tell you, “I wonder why I have these headaches. I wonder what's triggering them. I wonder why I have them.”

So one of the reliable triggers are sex hormones, primarily estrogen, right? This is the ultimate endogenous trigger. We know that the onset of symptoms typically occurs 2 days prior to the onset of bleeding—menstrual bleeding—and the symptoms generally continue for about 5 days. We will get into the specifics of the diagnosis. We in the field refer to this as -2 to +3, +1 being the first day of bleeding.

This is highly predictable in women with regular cycles, which really offers an opportunity for effective short-term treatment while minimizing the exposure to medication. And I'll give you like a short example. A woman who might have 8 migraine attacks a month,

which is a lot, if 5 of those happen to be perimenstrual, and if she's even uncertain and unwilling to go on one of the preventive treatments that Dr. Starling will be telling us about, but if she's willing to at least to have a provider who will recognize the perimenstrual migraine attacks and then willing to treat those in this mini-prevention concept, she will significantly decrease her headache frequency.

This is more of a reference slide explaining how we came to realize, historically—these were experiments done in the 1970s by Somerville in England—treating women with estradiol and realizing that the drop in estradiol is what led to headache occurrence. And this is where this concept of estrogen withdrawal hypothesis, which is highly relevant in our field, was derived.

And this is more as a reference to know in the future. And this is my work showing actually that women who have migraine—from SWAN, the Study of Women's Health Across the Nation, which is an amazing study—showing that the women who have migraine, who have history of migraine, seem to have a faster drop in estrogen in the late luteal phase—the first 2 days of the late luteal phase—than women who don't have migraine—core controls—and that this could be a natural kind of a 2-step hypothesis that predisposes women to migraine.

This is from Anne MacGregor which showed really this very straight correlation between estrogen levels and headache occurrence. You see estrogen in the fluctuation in the background, in black line, and then the purple headache frequency. And this is really where menstrual migraine occurs. And the highest number of headache days occurred on the first day of menstruation. And so therefore, inverse relationship between estradiol levels and migraine.

Let's focus. I know that that was a lot of concepts very quickly, but just to track back into what exactly is migraine and what are the criteria, because we always have to go back to the criteria. Though a lot of it is also—we were talking yesterday how vibes these days seem to be, going through a lot of medicine. It's not quite drugs. But when a woman comes to your office and she keeps complaining about severe headaches, and if she's not even—asking her, Are you sensitive to sound? Are you sensitive to light? She may even deny it. I have patients who come in, but I'll be like, you're not sensitive to lights, but you're wearing sunglasses. Can I point this out? And, well, okay, you say you're not sensitive to sound, but do you go to the movies, to the concerts? What happens? "Oh, I never go to those places." What happens in restaurants? "Oh, I don't go." So people have designed entire lives.

So I will step out of the physician-scientist hat that I wear and say that sometimes listening to the vibes of burden in migraine can bring you a long way along in the diagnosis.

Dr. Starling:
I will add that one of the questions I ask people is when you have your most severe head pain, would you rather be in a dark room that's quiet? Would you rather sit and rest or lay down? Because most women will be like, "Well, I can't—I'm at work, I'm taking care of the kids. I can't sit. I can't rest." Okay, I understand there's so many things that people have to do, but I say, if you could, would you rather be in a dark room that's quiet? If you could, would you rather rest? If they say yes to both of those things, this is most likely migraine.

Dr. Pavlovic:
Absolutely. That's so well put.

But for the diagnosis, a woman needs—or a man, anyone—needs to have at least 5 lifetime attacks. So 1 or 2 are not enough because they may randomly happen for no particular reason, but 5 lifetime attacks fulfilling the criteria where the headache should be at least 4 hours long. That means untreated headache, laying down, sleeping, and so on is treatment. So untreated headaches should be at least 4 hours long, so 72 hours is most low, because if over 72 hours, it's status migrainosus.

And headaches should be at least 2 of the following 4, and that's the unilateral location—it doesn't have to stay unilateral, it can spread around, and in most people, it does after a while; pulsating quality, generally; moderate or severe pain intensity; and be aggravated by causing or avoidance—or there should be avoidance of routine physical activities, but not precipitated by them. Finally, during headache, there should be at least nausea and/or vomiting. Sometimes that's just a queasy feeling. And this photophobia and phonophobia that we were explaining. Obviously, we don't ask patients, do you have photo- and phonophobia? This is what we teach residents and fellows not to do, but to really try to tease out the sensitivity to light and sound.

And the migraine with aura is the same as migraine without aura, it's just that having an aura—which is fully reversible aura symptoms—visual being the most common, but sensory motor, even a speech aura can occur, and that can be very scary, and that requires full

stroke workup. But the typical visual and sensory auras you can typically handle in the office without much concern. And that requires at least 2 lifetime attacks. Because 1 attack is not enough. When they asked neurologists if they've had an aura in their life, 85% of neurologists said that they had an aura. So, meaning people who know what an aura is will frequently have auras, it turns out.

Now, in terms of what we were talking about—the perimenstrual attacks and women-relevant migraine diagnosis—there are 2 entities in this International Classification of Headache Diagnosis, ICHD-3, and those are pure menstrual migraine and menstrually related migraine. Both are classified as without aura, but they can occur with aura as well. And these attacks occur exclusively during the -2 to +3 days that I was talking about in pure menstrual migraine, with at least 2 out of the last 3 menstrual cycles. So there's room to miss, right? Because it's a time sampling that may not be consistent.

And then the menstrually related migraine occurs during that women who have menstrually related migraine—that's the majority of the population, that's about 60% of the population of women with migraine—they have the -2 to +3, but they also have headaches at other times.

Dr. Starling:
One thing that is always good to remember with the criteria is you only have to have 2 out of those 4 things.

Dr. Pavlovic:
Exactly.

Dr. Starling:
Often, people will think that a migraine is unilateral, and a tension-type headache is bilateral. But in fact, 60% of migraine attacks can be bilateral, and 50% of migraine attacks can be tension-like or pressure-like. I find that's one of the areas of misdiagnosis often.

Dr. Pavlovic:
That's a great point. Another thing is that not all migraines have to be the same, right? So sometimes it will be unilateral; other times there will be nausea in the same person. Sometimes they will be photosensitive; other times they will not be. So as long as, in general, this seems to be the flavor of their headache, that qualifies.

So some of the treatment options, which I'll touch upon just in respect to hormone therapy, and Dr. Starling will focus on more in. So first, we have to start with the approach to diagnosis, right? And we'll focus on menstrual migraine here, as highly relevant to this audience. We tell the patient to keep a diary for at least 3, 4 months or longer. I really like 6 months, if possible. We have patients who keep it for years. They come with all the data. And that helps us learn which days are at risk—not only the perimenstrual headaches, but other times as well, like Saturday morning headaches and such other things beyond the scope of this talk.

We make a treatment plan, and then we follow over time and adjust if needed. This is really incremental approach of treatment. That's what the art of headache medicine is based in. So the tool is simple. The most important tool, and we cannot overemphasize this, is the calendar. There are many apps for this, but sometimes just the plain paper calendar works the best. And you just tell them, mark when your period is, mark when you have headaches. If you don't want to put other things and be bothered with it, don't; just give me this information.

So if we identify predictable perimenstrual migraines, we can attempt perimenstrual prophylaxis. What's important is that currently there is no product licensed specifically for this indication. This may start trials in the works, and hopefully that will be changing.

We generally try 3 cycles of treatment at least before abandoning. First-line are often NSAIDs, especially if there's comorbid dysmenorrhea and menorrhagia and stuff. Perimenstrual triptans have also been used, perimenstrual estrogen supplements, and various contraceptive strategies. Most trials have been, at this point, done with short-term prevention with naproxen and perimenstrual triptans, long-acting triptans like naratriptan. This is more for reference.

And contraceptive strategies have included various concepts, such as low-dose OC just with supplementation during the menstrual week, or in the case of extended cycle, OC with supplemental estrogen during the menstrual week, and then not treating if they're natural menstrual cycles, with perimenstrual application of estradiol patch just during that interval.

That's all good when we have predictable ovarian cycles, or somewhat predictable. But what happens when we enter perimenopause and various menopausal transition fluctuations in estradiol and progesterone and various symptoms that I know all of you deal with in your practices? From Women's Health Initiative data that we worked on, we've seen that, actually, vasomotor symptoms are more common among women with a history of migraine.

So one point—you don't have to pay attention so much to this busy slide—but one point I'd like you to take away is what was hit upon in the introduction: there are a lot of comorbidities here, and women with migraine seem to be especially susceptible and have comorbidities with endometriosis, IBS, and have many more symptoms than women who do not have migraine. So no wonder you will see these women with a lot of burden in your practices.

There are a lot of challenges in available knowledge, mostly from the lack of studies. We really haven't had good longitudinal studies in this space, and we need them. What we do know is that migraine in menopausal transition—there's a trend toward fewer migraine attacks and milder symptoms in menopause but worsening during perimenopause. And that women with menstrual migraine and perimenstrual syndrome tend to have best prognosis postmenopause because they seem to be most hormonally responsive. Right? So once hormonal settling down occurs, they do best. And it's really unclear, the full association with other menopause symptoms.

Medical menopause is something I'll touch upon just because, at one point, women were so desperate that actually elective oophorectomies were being done for women with chronic migraine. We now know that this is not a way to go forward. That sudden menopause worsens—whether medical or surgical—worsens migraine—existing migraine, and often it's very hard to bring these women back to state.

This is more for reference point, but one of the challenges of migraine treatment in your space is that OCP's consensus guidelines for use of migraine by the WHO and ACOG are very, very stringent and really limiting. These are because of perceived cardiovascular risk, particularly stroke risk, in women with migraine of increased ischemic stroke. But though the relative risk is actually somewhat high, the absolute risk is very, very low. And here are the specific numbers for your reference.

The important point of this is that, really, the dose matters, and that the information that we have is all based on very high doses. We've tried to do studies to really come up with new urgent guidelines in this space, but we couldn't because we don't have new studies that we urgently need to be able to formulate new guidelines.

So as I said, hormone therapy, however, is not contraindicated in migraine and can be used, and, therefore, there are many risks and benefits of hormone therapy. But you can liberally use it in women with migraine. That is one take-home I want you to remember—there are no contraindications against hormone therapy dosages in migraine. And the effects of it on women with migraine can be various.

So in summary, current knowledge, we currently do not have really helpful, new, updated guidelines for use of exogenous estrogens in women with migraine, particularly migraine with aura. We need new guidelines. There's no contraindication for use of hormone therapy in women with migraine, and we really need more updated studies.

I'd just like you to remember that ovarian hormones have a complex role in migraine pathogenesis and presentation of migraine and can be used for treatment of migraine, that they impact women through stages of life, as it's not surprising. The prevalence of migraine is highest in perimenopause—again, goes along with estrogen fluctuations. And that women who have menstrual migraine worsen the most and then resolve, but because the predictable attacks allow for mini-prevention. Sudden menopause is never good for the brain, and we really need to tailor these treatments to individual patients and do more studies.

Thank you for your attention, and I pass this to you.

Dr. Starling:
So I'm going to stand because I'm so excited to be here, and if I sit, I'm just going to be wiggling around.

I love talking about migraine, because at the end of the day, what we are doing is 1 in 5 women who are living with migraine throughout their life stages, we are figuring out what they want, what they need, and, most importantly, what they absolutely deserve.

Now, we mentioned that 1 in 5 women have migraines, so the prevalence is high. I also want to mention that based on the Global

Burden of Disease study from the World Health Organization in women age 15 to 49, it is the number one leading cause of days lived with disability. Number one, yet we are only effectively diagnosing and treating 12% of women living with migraine, and men and children. So we really have a lot of room for improvement, and that's what we're talking about.

So when we're talking about the treatment of migraine, I think it's important to take a step back and talk about how migraine is a chronic disease that has episodes or attacks. My analogy that I really like to talk to patients about, as well as my trainees, is think about migraine like asthma. Asthma disease, it's a lung disease that's present every single day, but then they will have individual asthma attacks. When they have infrequent attacks, they'll need a rescue medication or a rescue inhaler. And if they have more frequent attacks, they need a controller or a maintenance medication to manage the underlying disease. And they also need a rescue inhaler to manage the attack. Similarly, in migraine, it is there every single day.

This is a great teaching point for our patients, because patients often come to us and they say, “I had migraine yesterday, but I don't have migraine today.” And it's a great time to be like, no, migraine is a genetic neurologic disease. It is present every day. You had an attack yesterday. Fortunately, you're not in an attack today. And it's helpful so that we can increase the number of people who are on prevention to manage the underlying disease.

So we have acute treatment that treats the individual attacks, and then we have preventive treatment options that treat the underlying disease of migraine. And I'm going to highlight this number 4 that was already brought up—that 20% to 30% of people have 4 or more headache days per month with migraine features, and that is the number for whom people need to be on prevention. Because data has shown that if there's a higher number of attacks, it leads to disease progression.

So it's a chronic disease that can result in disease progression if individual attacks are not treated effectively. If the over-the-counter medications—Tylenol, ibuprofen, Excedrin—if they're just taking the edge off and helping that woman get through her day, that is ineffective treatment. And ineffective treatment of individual attacks leads to disease progression.

What is disease progression? Disease progression is when people have more frequent attacks. If they have more frequent attacks, they're using those medications that may or may not work so well more frequently. And that leads to further disease progression until patients end up in our office with daily migraine symptoms, a high interictal in-between attack burden, and they develop chronic migraine, as defined as having 15 or more headache days per month.

So how do we stop disease progression? It's effective treatment of those individual attacks and initiating prevention so that we can reduce the frequency of attacks, we can reduce the severity of attacks, and we can also make those acute medications more effective when those attacks do occur.

And so how do we choose from our toolbox of medications which one is going to be right for our patients? And I really do think that it would be great if we had a woman-specific, shared decision-making tool. So we'll get working on that. Add that to our to-do list. But right now, based on the American Academy of Neurology guidelines, we do have these 5 questions for choosing the right treatment option in a shared-decision manner: Which drugs work the best? What are the side effects? How are they affecting the quality of life? And also, the cost of the medications. Those are all really important.

All right, here's the meat of the talk. Let's talk about acute treatment. Acute treatment is for those individual attacks. We have migraine nonspecific treatments, many of which are over the counter and migraine-specific. Really want to focus on those migraine-specific treatments, because by the time they're in your office, and definitely in my office, they've already tried many of the migraine nonspecific therapies.

So let's get to the medications that actually go to the migraine parts of the nervous system and actually normalize that function. And that is what triptan medications do, dihydroergotamine, gepants—which are some of the more novel therapeutics we have available—as well as the ditans, or lasmiditan.

So this is a nice slide that goes over all the 7 different triptan medications that we have available, all of which are available oral. You'll see that some are available as nasal sprays as well as injectables. Why is this important? It's important because nausea is one of the features of many migraine attacks.

Why does nausea happen? Because of gastroparesis. If someone is having gastroparesis, how effectively are they going to absorb an oral medication quickly to stop that migraine attack? Not so well. So let's bypass the GI tract, use the nasal mucosa or an injectable to be able to effectively treat that attack.

I've also highlighted the 2 triptan medications that were mentioned before that can be used for mini-prevention for menstrually related attacks or pure menstrual migraine. However, even though triptan medications do work quite well, there are contraindications for triptan medications, specifically with vascular disease, because they work on the serotonin 1B, 1D, 1F receptors. And 1B receptors are located on coronary and cerebrovascular blood vessels. And so that is why there are contraindications in the setting of vascular disease, stroke, heart attack, as well as other individuals who may not benefit from a triptan or may have side effects from triptans.

So we need other options. And fortunately, now we do have other options. Gepants are CGRP, calcitonin gene-related peptide, receptor antagonists. These do not have any vasoconstriction. There are no vascular contraindications. There's been no serious adverse events in cardiovascular spaces in all of the clinical trials.

And remember, there was that other piece that I mentioned about if someone has frequent migraine attacks and they're using either over-the-counter medications or triptans too frequently, it can add to this concept of medication overuse headache. Fortunately, gepants, which are acute treatment options, do not result in medication overuse. And so this is another benefit of these gepant medications.

We currently have 3 different gepant medications that are available: ubrogepant, rimegepant, and then a nasal spray option, zavegepant. And then we also have another option called lasmiditan.

So let's talk a little bit about lasmiditan. I mentioned triptans are agonists for 5HT 1B, 1D, 1F. And 1B is located on blood vessels, but 1F is not. So lasmiditan actually is an agonist to 1F, has no effect on the blood vessels, can be used in the setting of vascular disease because it has no effect there, and can also be effective. I like to use this in patients who had great benefit from triptans but now have vascular contraindications.

One of the issues with this medication is that it does cause some sedation, and so there's an 8-hour driving restriction. So often people will use this at night or when they're able to rest.

For acute treatment and preventive treatment, we have 5 FDA-cleared neuromodulation devices. I love neuromodulation because the brain is a big circuit board, and migraine is a disease of abnormal brain function in the setting of normal structure. And so how about we adjust the electrical abnormal function in the brain of migraine with a neuromodulation device?

Many of these are available both—FDA-cleared for both acute and preventive treatment. The main barrier, from a clinical perspective, is reimbursement is quite challenging, but that is continuing to improve over time.

Now let's talk about different life stages. So what about acute treatment in the setting of pregnancy? You know that there are studies that have shown that women with migraine have decided to not get pregnant because they have migraine? Because they are told by clinicians, “Well, when you get pregnant, you're going to have to stop all your migraine medications.” And they're like, “Well, then I can't function. So there goes family planning for me with regards to getting pregnant.”

So the goal here is to say that throughout life stages, there are many options for treatment, both acute and prevention. So for first line, we'll typically use acetaminophen and metoclopramide. But triptans are okay to use in the setting of pregnancy.

So here's a case: 40-year-old female, first pregnancy, 36 weeks, and we have worked together at saying when there's a more mild attack, we can use one of those neuromodulation devices and use a biobehavioral technique of biofeedback and progressive muscle relaxation. If it's a more moderate attack, let's use the acetaminophen and metoclopramide. But for a severe attack, her triptans work well for her, and it is okay for her to use it in the setting of pregnancy. There have been studies that have demonstrated that there's not an increased risk of adverse events in the setting of pregnancy to either the mother or to the fetus. So this is really a good second-line, effective, and safe treatment option for our patients who have migraine and in the setting of pregnancy.

What about breastfeeding? What about the next stage with lactation? So an interesting piece of this is there are studies that show that

women who are exclusively breastfeeding may actually have a lower recurrence of migraine during that stage. And that may be related to the degree of estrogen withdrawal that occurs in the absence of breastfeeding or lactation versus in the presence of it, or also delayed ovulation and delayed menstruation.

And there are many options that can be used in the setting of lactation as well, including triptan medications. In fact, the American Academy of Pediatrics has a position statement that reports that you don't need to pump and dump when you use triptan medications. There's quite a bit of data, specifically with sumatriptan, that have really allowed for patients to use the triptan that works well for them. Eletriptan is the one that has the lowest amount of maternal milk transfer, but they are all safe in the setting of lactation.

Now, it has been very recently that both of the gepants—ubrogepant as well as rimegepant—have had some studies to show a very low amount of transfer into maternal milk. And so those, although they haven't received the official risk category, they, if you compare it to the amount of transfer that is occurring, would be in that moderate safety category as well. So even our novel therapeutics can be safe in the setting of lactation.

Now we mentioned vascular disease, right? And which ones are we trying to avoid? We need to avoid triptan medications, but we can use the gepants—ubrogepant, rimegepant, as well as zavegepant—and then also the ditan medications and neuromodulation.

But with the gepants, the side effect profile is also just so much better than the triptans for many patients.

Dr. Pavlovic:
Yeah, that we know. And that patients are now more willing to take the medication because they don't fear the side effects.

Dr. Starling:
Yes, it brings up a good point that for individual attacks, we have data that show that the best time to take the acute medication is right when you feel the symptoms coming on. But if you have a medication that gives side effects, people will avoid the medication until they simply cannot wait. And we know at that point the attack is harder to break, and the medication is not as effective. So we really encourage our patients to use it right when the attack occurs. And if there are no side effects or limited side effects from the medication, that's going to be easier for them to do. So that's another place where the gepants are really helpful.

So this is my kind of workflow for patients. Neuromodulation is always an option. If there's no vascular contraindications, I will go to first-line triptan medications. I will try a second one, maybe a nasal spray or an injectable. I may add an NSAID to the triptan. Or if the triptan is ineffective or poorly tolerated, or if there's a vascular contraindication, I'll go to a gepant or a ditan.

So let's talk about prevention. So with prevention, again, that number 4 comes back. And this number—I keep saying 4—I want you to walk away with, “What did I learn from Dr. Starling?” You learned about the number 4. And the reason I keep saying that is because it is very rare that we are starting prevention in people who have 4 attacks per month.

Even my trainees will come in, “Well, they only have 6 attacks per month, so we'll just give them a triptan.” But 4 is what is based off of guidelines. And the guidelines are based off of evidence that shows if we wait until 6 or 7 or 8 attacks per month, we are contributing to disease progression.

We want to prevent people from getting to chronic migraine. We want to prevent people from getting to 6, 8, 10 migraine attacks per month. We want to prevent people from falling into that vicious cycle of worsening migraine and medication overuse. And the way that we do that is initiate prevention when they have 4 or more migraine attacks per month.

And we want to initiate it when it's 4 or more migraine days per month. How many ways do you have to ask a patient how many days per month they have migraine?

Give me a number.

Dr. Pavlovic:
25? 99?

Dr. Starling:
I know. Because this is the way it goes. How many migraine days per month are you having? “Two.” Okay, how many days does a migraine attack last? “About 3.” Okay, so now we're 2 days or 2 attacks? “Oh, 2 attacks.” Okay, so we're at 6. So you're telling me that the other 20+ days are completely headache free? “Well, no, no, no, the other days I have regular headache.” What's regular headache? “Well, you know, what everyone has.” Not everyone has headache. “Oh, well, then I have headache every day, but it's really bad 6 days a month, which is the days that I have to stay home from work because I'm vomiting, and I have to call in my mother to come take care of the kids.” Okay, so what my favorite question is this: How many days per month are you completely free of any headache whatsoever? Mild, moderate, severe, I don't care?

Dr. Pavlovic:
But hold on, what do you get when you ask them that question?

Dr. Starling:
You still have to ask 3 times.

Dr. Pavlovic:
And you also get the blank face, as in, like, I have not considered that. That's a scary consideration.

Dr. Starling:
No one asks that, right? No one asks about headache-free days. That's actually my favorite question to ask, is headache freedom. Right? How many days are you free of headache? Right?

So I encourage you to really look into that and not ask about migraine attacks but migraine days, and then ask about how many days are free of any headache whatsoever.

So prevention. We have many, many tools available. We have a lot of oral medications that are migraine nonspecific that have been available for many, many years. These are medications that were developed for other disease states but were found in clinical trials to be effective for individuals with migraine as well.

The benefit of these—as we've mentioned multiple times, women have comorbidities, and some of these oral, traditional preventive medications can help with other comorbidities. Candesartan can help with hypertension and migraine. Amitriptyline and nortriptyline can help with insomnia as well as some mood disorders in addition to migraine. So there are benefits of that.

However, in general, the migraine nonspecific therapies are ones that may have side effects for patients, and so it's very challenging for patients to continue these medications longer term for a chronic disease.

Now we have newer options that also target that CGRP pathway. These are CGRP-targeted therapies. We've got monoclonal antibodies and a gepant—atogepant, which is used daily, and rimegepant, that's used every other day—and then the 4 monoclonal antibodies—eptinezumab, erenumab, fremanezumab, and galcanezumab—as well as for chronic migraine, onabotulinumtoxinA injections. And we can layer multiple of these therapies to get women to their goal.

So how do we choose out of all these toolboxes? This all comes down to the patient preference, which medication is going to fit their lifestyle, fit their life stage, reduce the risk of side effects that they may have, or treat the comorbidities that they may have as well?

So some of the treatment considerations are listed here, and one that I want to highlight for this women's health-oriented group is that there are options that can be effective for the treatment of migraine that can also be helpful to treat the vasomotor symptoms present in perimenopause. And as you saw in the data from Dr. Pavlovic, we have many women that may present around perimenopause, and so it's really helpful to have options that can help both with those vasomotor symptoms—which we saw are more frequent in women with migraine—in addition to helping them with that additional consideration that is present as well as their migraine.

Now, let's talk about another case. So this is a 30-year-old female who's 20 weeks gestation. She has a history of chronic migraine. She's been stable with onabotulinumtoxinA injections. She has done okay during pregnancy. She's had some improvement during her second trimester.

She is here asking you, “Should I continue with onabotulinumtoxinA injections during pregnancy?” You going to hold? Are you going to inject? What do you want to say, hold or inject? Hold. Who says hold? Okay. Some. Who says inject? Okay. This is great. I think that there's some people that are thinking hold, and is that because of safety, those people that said hold? Okay, so some concerns about safety.

So let's talk about what are the options that are available in the setting of pregnancy for prevention. The goal of this slide—I should have tried to just like go off the slide—the goal is to say there's a lot available, right? A lot of safe, effective options available, including onabotulinumtoxinA injections. It can be safe in the setting of pregnancy. There's now been animal model data and multiple studies actually looking at human studies, demonstrating that there is, again, no negative effect on mom as well as fetus.

And so in that last case, I do think this is a conversation with the patient, because she's had some improvement. So do we need to continue it from just a migraine perspective, if she's had some improvement? How much improvement is some improvement? But let's decide that her improvement means going from daily migraine days, 30 out of 30, to 20 out of 30. Well, she still has a high burden of disease, and for her, we would inject.

However, if she says, “Oh yeah, I've gone from having about 18 days to 2 or 3 days per month,” for her, we would probably hold. Okay. So this is where shared decision-making is key.

In lactation, again, lots of options, from neuromodulation as well as other medications, including continuing onabotulinumtoxinA injections. And in preventive treatment in lactation—I should have updated the slide—rimegepant every other day can be used for prevention. And there is rimegepant data now that there's a low risk of maternal transfer into milk.

So starting prevention is so important. What was that number I wanted you to remember? Four. Got it. This is awesome. I could just walk off the stage and fly home and be happy. So listen, 4 is so important because of these data—data that show that 2/3 of people who are candidates for prevention—how are you a candidate for prevention? Four, excellent. So 2/3 of people who are candidates for prevention are not on prevention. Two-thirds of people who are candidates for prevention are not on prevention.

And for people for whom we prescribe prevention, within 6 months, 70% of those patients have discontinued therapies. Why? Because of side effects, because of inefficacy, because of access. It's market claims data. So it could be all of the above.

So we need medications that have less side effects, that are accessible, that are easy to administer for patients. And this is another one of the benefits of the CGRP-targeted therapies, is they're very well tolerated.

So I'll give you an example with the traditional therapies. One of the traditional therapies, topiramate. In the clinical trials that led to FDA approval for topiramate for chronic migraine, there was a 20% dropout in the clinical trials because of side effects.

If you look at all of the data from the CGRP-targeted therapies, there was less than 2% of dropout because of side effects. So tolerability is great. They work well and they're well tolerated. We're still working on the access part. However, it is improving. Improving because of statements like this put out by societies like the American Headache Society, who has a position statement most recently put out about CGRP-targeting therapies are a first-line option for the treatment of migraine, which has moved the needle already for a couple insurance companies that are allowing these medications to be used as first-line options.

For neuromodulation devices, these are also available for prevention, and there are biobehavioral techniques that can be effective for both acute attacks as well as the prevention of migraine. No side effects, only positive, positive things. So this is a great option throughout the life stages.

So I highlighted the position statements, and I just want to focus on this again. So in 2021, guidelines about initiating prevention when individuals living with migraine have 4 or more migraine days per month. In 2024 is when the position statement came out from the American Headache Society that CGRP-targeted therapy should be considered first-line options for the treatment of migraine.

And then in 2025, from the International Headache Society—I love this—it's about elevating the care for people living with migraine. It's not about just getting to that 50% responder rate because, goodness, someone who has 20 migraine days per month, if we get them to

10, yeah, that's better than 20, but is that still good? Right? I always tell my patients, how are you doing? And they're like, “Oh, I'm fine.” I'm like, well, fine, that's terrible. I want you to be doing good. How can we get you to good? So what does good look like? Good is less than 4 monthly migraine days per month, or monthly headache days per month. And for that less than 4, they have an acute treatment that works, that within 2 hours of their acute treatment, they're back to normal function. That's where we want our women living with migraine to be at.

So this is my workflow for prevention, which is a little bit more of a mess. It's kind of like figuring out what's going to be the right option for the patient. And then we can go directly to a CGRP-targeted therapy or onabotulinumtoxinA injections, or if there's a comorbidity we need to address, then a nonspecific medication as well. Always, behavioral intervention is available, and neuromodulation. And then, especially in our clinics, we layer. It's a lot of layering of therapies. You can send them to us to do all the layering.

So here are the key takeaways. Everyone with migraine needs an effective acute therapy. Everyone with migraine needs an acute therapy, and you will give me the next takeaway. And who needs prevention? Four, I love it. And there are effective treatment options for women across the life stages. We really just need to consider what is their life stage, what is it that they want, what is it that they need, and what is it that they deserve?

And for referral practices, I would usually say that if you tried 1 or 2 acute therapies and they're having challenges getting a woman to the ideal effect, which is 2-hour pain freedom, or 1 or 2 preventives, and they're still not getting to less than 4 headache days per month, send them to us, the neurologist and the headache specialist. We'll take it from there.

This replay of a live broadcast reviews hormonal, diagnostic, and treatment considerations for migraine across women's life stages, including menstrual and menopausal transitions.

Announcer:
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