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Migraine and Women's Health: Migraine and the Whole Female Patient

Announcer:

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Dr. Ailani:

Hello and welcome, everyone, to our presentation on Migraine and Women's Health: Migraine and the Whole Female Patient. We're going to focus this discussion on a better understanding of migraine, from burden of disease through diagnosis and all the way through how to approach a woman with migraine through all her lifespan, including treatment discussion and options.

My name is Dr. Jessica Ailani. I'm a clinical professor of neurology and the director of the MedStar Georgetown Headache Center in Washington, DC. I'm especially grateful to be joined for this program by my colleague and friend, Dr. Dawn Buse. Dr. Buse is a clinical professor of neurology at Albert Einstein College of Medicine.

These are our disclosures.

And these are our learning objectives.

We're going to get started with a discussion on the prevalence, presentation, and burden of migraine in men and women. Dawn, why don't you get us started.

Dr. Buse:

Absolutely. So thank you, Jess. As we know, migraine is actually highly prevalent. It is very common in the world. In fact, 1 billion people globally are estimated to have migraine according to the Global Burden of Disease study conducted just a few years ago. When we think about the United States, we have about 40-47 million Americans with migraine, about 2/3 of them are women. And as we can see here in this prevalence curve, during childhood, we see similar rates between the sexes. And then at the age of menarche, we really see the prevalence of migraine kind of shoot up, so that in the 20s, 30s, 40s, migraine affects about 1/4 of US women from age 30 to 39.

And migraine can be significantly disabling. In fact, according to that same Global Burden of Disease study, it is the second most disabling disease on the planet according to years lived with disability but actually the first most disabling for women aged 14 to 59.

What does it affect? Really everything, everything from the smallest daily mundane activity like making breakfast for your children, driving them to school showing up at work, to the biggest life choices, like choosing whether or not to have children, whether to go to graduate school, whether to embark on a career path, whether to get married. So virtually all important and mundane aspects of life can be negatively impacted by migraine.

As we can see from data from the CaMEO study, that migraine is more impactful with the number of monthly headache day frequency. And Jess is going to tell you the definition of chronic migraine, but just to give you a sneak peek, it is meeting criteria for migraine with

15 or more headache days per month. And we can see in this slide from CaMEO study that the impacts on work and finances increased significantly in those with chronic migraine but are still substantial for those with episodic migraine with 1/4 of people replying with chronic migraine that they had to reduce the number of hours that they worked; they feel a burden to coworkers, kind of a stigma, uncomfortable there; uncomfortable with their bosses; they often try and hide having migraine; and some of the other potential impacts that I just talked about. In fact, half of people with chronic migraine were worried about covering their household expenses due to migraine, worried about long-term financial security, and worried about losing their jobs. Migraine also impacts the home life, parenting, marital and partner relationships, and every other relationship someone can have.

And again, these data from the CaMEO study, the Chronic Migraine Epidemiology and Outcomes study, a large epidemiologic study of 10,000 people with migraine, we can see that people have talked about migraine affects their marriage or their partner relationship negatively, and that 80% with chronic migraine felt they'd be a better partner if they did not have migraine or headaches, 65% with chronic migraine felt they'd be a better parent, and 10% of people with chronic migraine either chose not to have children or delayed having children due to their worries about the effect of migraine on their children, on their ability to parent, what pregnancy would be like, and for other reasons. And I'll show you a breakdown of those reasons in just a moment here in our next slide.

Here we can see data from the ARMR study, the American Registry for Migraine, that they found actually 20% of their female respondents avoided pregnancy because of migraine. And some of the reasons were they thought that their migraine would be worse during their pregnancy. Now Jess is going to speak to this a little bit, and it is a little bit of a mixed bag with changing outcomes per patient and even within the same patient, one pregnancy to the next. But generally, some people, maybe 1/3, might feel better during pregnancy, especially in the second and third trimesters. About 3/4 were worried about what medications they could take during pregnancy, which are of course quite limited. And we even had some misinformations and misbeliefs: 14% were worried that migraine would cause their baby have abnormalities at birth. And migraine is a genetically carried disease. With 1 parent with migraine, you have about a 50% chance of inheriting migraine, and if you've got 2 parents with migraine, that risk goes up to about 75%.

Jess, is this something that you hear your patients worry about?

Dr. Ailani:

Yeah. I think the bigger concern is after it happens, they very much feel the sense of guilt that I gave this to my child; it's my fault. And, you know, sometimes patients will come in and talk a lot about that, that I did this to my child, or it might be a reason given as to why they don't want to have children: "I couldn't imagine passing this on to someone else. I want it to stop with me." It's pretty awful to listen to because you have to try to explain to them you don't know if that's going to happen and also that treatment options are so much better at this point. And it's something that, as a parent living with migraine, they'll be able to identify it much better in their children and get the child the care that they need much faster than perhaps the person really dealt with themselves.

Dr. Buse:

Good point.

We know from the European study, the Eurolight study, the US study, the OVERCOME study, that migraine carries a lot of stigma with it. People with migraine feel guilty, they feel embarrassed, they often try to hide their condition from others, and they try to reduce and minimize the impact that their migraine has on others. So there's a lot of guilt that goes along with migraine that can affect both parenting and relationships as well as the workplace.

And the burden of migraine happens not only during attacks, which we'll call the ictus, but between attacks as well, interictally. For people with more frequent headache and more frequent migraine attacks, some of the symptoms may never fully resolve. They may still have photophobia, allodynia between attacks. And also there's a great burden associated with anxiety, so people might worry about when is the next attack coming, what kind of impact is it going to have on work, school, special plans, whatever social event they planned, or whatever vacation they planned. And we find a fair amount of people, in fact, avoid making plans because they worry about if they have a migraine attack, are they going to have to cancel, leave early, let people down, which really, in turn, puts people into a bit of a downward spiral with guilt, embarrassment, sadness, and social isolation. So it's really a negative on multiple fronts.

It can be valuable to assess kind of all these things I just talked about, the disability impact of headache. It's valuable for a couple of reasons. One is that according to the American Headache Society Consensus Statement in 2021, a really terrific document that reviews literally all of the recommended approved and data-supported migraine therapies from nonpharmacologic to pharmacologic, of which Dr. Ailani is one of the authors – according to that document, when you look at need for prevention, we think about two things: number of monthly headache days for someone with migraine, amount a disability. So you may need to assess disability at baseline for reasons of treatment planning as well as it's really valuable to assess disability over time and look for improvement or even worsening of disease.

We do have validated instruments, or PROMs, patient-reported outcome measures, that can be used. The MIDAS is one of those

measures, a quick 5-item, paper-pencil questionnaire. In 5 items, you sum it up and you get a disability grade. That's available free of charge. The HIT-6, Headache Impact Test 6-item is copyrighted. That's a paper-pencil 6-item test. Or you can ask a simple single question and actually gather a lot of information. The PGIC is the Patient Global Impression of Change. It's just a single question that's been used more recently in clinical trials, kind of assessing how are you doing now compared to how you were doing when we started this therapy. And the American Migraine Communication study recommends the single question: How are migraines impacting your life? And then the trick with that, wait, take whatever the patient says for the disability information and try not to interrupt them. The good news is, in an observational videotaped study, the average speaking time for patients to that question was about 91 seconds. So I know just sometimes we're all on tight schedules and we worry about opening up an open-ended question and getting into a can of worms. But in fact, people found that single question was really a great way to assess disability, establish rapport early on, and also let the patient get off his or her chest whatever was kind of present right at the top of their mind so they can focus better.

What do you like to use in clinic, Jess?

Dr. Ailani:

Oh, that single question. It actually gives us the most information in the fastest way. Because patients often want to make us feel better, I find. They always tell me, "I'm doing great." I'm like, "Well, how are your migraines doing since your last visit? You know, not how are you doing." Because they'll say they're doing great. And when you start to hone it in to how are your migraines doing, you get a lot more information, especially with the pause and really look them in the eye and wait for them to answer. We will try all sorts of scales, have them answer questionnaires. They will make up answers like you wouldn't believe. The questionnaires take a long time to really make sense of for the patient and for us. And that single question gives us everything we need. And buried in that single question, you'll get a lot of information about their goals, which we'll talk about later in our discussion.

Dr. Buse:

Great points.

So I'm going to pass this over to you to go through the diagnostic criteria now.

Dr. Ailani:

Yeah, so it's important to understand, as we've been talking about, that migraine carries a great burden and is a very common disease, especially for women. In order to really understand if the person in front of you has migraine, we need to make the diagnosis.

Well, it's pretty simple to do. Though if you look at this slide, there's a lot of words and it can seem pretty frightening. But the diagnosis of migraine is simply made by taking a history. And in that history, you're simply listening for words about what the migraine attack feels like, listening for symptoms of pain, and symptoms that are associated with pain. So you're looking for the number of attacks a person has had in their life, how long the attack will last if it's untreated. I will tell you up front that it's almost never untreated. The patient has always tried something over the counter to partially treat their attacks, because there might have been 1 attack in their life left untreated; often that attack has left them completely disabled. So they learned pretty early to do something about these attacks.

With the attacks, there are going to be characteristics of pain. The pain is often one-sided, throbbing or pulsating in nature, made worse with physical activity, can, you know, become very moderate or severe if untreated. They don't need to have all these characteristics, just 2 of them. And it comes with associated symptoms, nausea or vomiting or light and sound sensitivity. So you can listen to the patient describe their symptoms, ask a couple of key questions. Do you ever feel like you need to be in a dark room during one of these? Or if you could be in a dark room, does that make you more comfortable? Does loud music or loud talking bother you during an attack? Do you feel queasy or avoid foods? Do you prefer not to eat during an attack? Because nausea is not something that always makes sense to the patient. So these are some ways you can make a diagnosis of migraine without aura, which is the most common type of migraine.

A portion of patients, up to 30% of patients, will have migraine with aura, and that's when they have a neurological phenomenon that occurs prior to the migraine attack itself. The neurological phenomenon for most patients is visual in nature and that's when they will have often described as a sparkling light or shimmering in one eye or one side of the visual field. They might see flashing bright dots followed by dark spots after. And usually, the symptom lasts no more than an hour and completely disappears and is often followed by the headache itself with those associated symptoms. Outside of visual symptoms, the second most common type of aura is sensory, so numbness or tingling, often starting in the mouth moving down to the hand and then into the leg. Other times, patients can have speech disruption. And a few patients can have motor disruption. This can be extremely frightening to patients, especially the first time they have it. But most often when they do have aura, it's always the same type of an event.

We talked about chronic migraine. Out of patients who have migraine, about 4% of patients will have what's called chronic migraine, and that's when they're having attacks at least 15 days a month with at least 8 of those being migraine in nature. So these are the patients

that tend to have a higher burden of disease because they have more frequent headache attacks.

When people are coming in to see you in clinical practice for migraine, most of the time you're trying to figure out is this a migraine or another type of headache, and do I need to be concerned? Well, it's important to note that the most common type of headache is actually a tension-type headache. These are usually milder to moderate headaches, they often are both-sided, described as a dull, pressure-like pain, where people will often describe it feels like there's a cap on my head or a vise-like grip. They generally don't have any associated symptoms. There generally isn't nausea, or vomiting with this headache or light or sound sensitivity. But if they have some associated symptom, it's either light or sound sensitivity. Usually these are made better with physical activity, moving around, doing some work, distraction tends to make these headaches better. And most patients with tension-type headache will take something over the counter and won't come to see you in clinical practice. Whereas migraine might improve with over-the-counter treatment but tends to get worse over time. And patients tend to come see you in practice to try to find something that's a little bit better that works to treat their migraine attacks.

Dr. Buse:

And Jess, unfortunately, those OTCs that they're using can actually get them into trouble, which I know you're going to talk about in a minute. And the only therapies available over the counter are really acute, and we don't have any preventive medication therapies available over the counter.

Dr. Ailani:

Absolutely. So as I mentioned, to really make the diagnosis of migraine, it seems frightening when you look at all the words, but it's just taking a good history and letting the patient talk through when they've ever had a headache like this before, when it happens, where it's located, what does it feel like? Do they have neurological symptoms that come a little bit before the onset and are predictable? What are the symptoms that come with the headache, the nausea, vomiting, light/sound sensitivity? Sometimes patients can have other symptoms with their headache, like vertigo and cognitive difficulty. It's really hard to focus or pay attention to other things when you're having a migraine attack, so it's not an uncommon symptom to have with migraine. Neck pain is actually probably one of the more common secondary symptoms of a migraine attack. You also want to know how disabled they get with migraine attacks. Are they missing work? Are they missing school? Have they tried other medications before? Are they helpful? Any correlation to their menstrual cycle, any correlation to ovulation in a woman, this is important information to collect. We also want to know about their past history, any history of depression, anxiety, insomnia, trouble sleeping with sleep apnea, any other neurological medical conditions, asthma, or allergies. This is very common in patients with migraine. We want a list of things that they're using, especially over-the-counter treatments, which patients will often neglect to tell us but we are looking for overuse of over-the-counter treatments. And we want to know about vitamins and herbal supplements, because many patients will have read about some vitamin supplements, which we'll discuss later, that are helpful for migraine, and you want to know if they've tried them before. Every woman that comes into the clinic for migraine, we're asking about their childbearing history, but we're also asking about family planning. We want to know if they're considering pregnancy in the future or near future and if they're on contraception of any kind, because we know the easiest way to get pregnant is when you're not planning to get pregnant. And if we are going to treatments, right Dawn, I'm sure you hear about this.

Dr. Buse:

That's right. And I'm sure our audience knows even more than we do how common that is.

Dr. Ailani:

Yes, and you want to make sure if you're going to start any treatment options, whether they're as-needed or preventive options, that your patient's aware about safety if they do become pregnant or if they're lactating.

So what's the simple way to identify migraine in clinical practice? And there's a questionnaire called ID Migraine. It's just 3 questions to ask a patient, and you can even print this out and have this done in the waiting room. Your medical assistant can actually go through it before you're even entering the door. And this is screening a patient for migraine. It's something to consider in any of your women patients between the ages of 20 and 50, since it's so common in women during that age period. Have you ever had a headache that limited activity for a day or more in the last 3 months? Because we're looking for that moderate to severe attack that really disables a person. Are you nauseous or sick to your stomach when you have a headache? Looking for that associated symptom with migraine. And does light bother you when you have a headache? Again, that other associated symptom of migraine. If a patient is answering yes to 2 out of 3 of these questions, you're identifying a most likely person with migraine. It's a pretty simple question.

Dr. Buse:

Yeah. Jess, I know we know we love mnemonics, right? So there's a good mnemonic for this one. This is PIN. PIN your migraine, right? Photophobia, and also phonophobia can get in there as well, impact of migraines on disability, and nausea. So PIN. And those 3 hallmark items, those hallmark criteria are really sensitive and specific for migraine. They're real specific to migraine, so usually you're

going to have a very good likelihood that those are going to be migraine.

Dr. Ailani:

Exactly, and since we're talking about mnemonics, another great one is SNOOPS. This one is looking for secondary features. So here we're looking at headache red flags, and the mnemonic SNOOPS can help us out with that. So we're looking for headache associated with systemic symptoms like fever or weight loss, headache associated with neurological symptoms. A patient comes in and they're confused on exam and they're impaired alertness or they have ptosis or some kind of neurological symptom that doesn't really go along well with migraine. They have a sudden-onset headache, abrupt or split-second, that's very concerning for subarachnoid hemorrhage or an aneurysm rupture or dissection. A patient who's older than age 50 who has a new-onset headache or progressive headache, we're concerned about secondary causes of headache. In particular, we're concerned about giant cell arteritis, but there are other things that can be happening in that age group as well. For P, someone who's got a previous history of headache with new or different headaches, change in frequency, severity, or new-onset aura, we also think of P in patients who have headache with position changes, headache in pregnancy that's new. These are times that you might be thinking about imaging a patient for consideration of secondary causes. And then those that have secondary risk factors like immunocompromised patients, patients who have a history of a cancer that's known to metastasize to the brain, these are all valid reasons to obtain an MRI of the brain for consideration to rule out secondary causes of migraine.

Dr. Buse:

Jess, I remember in 2014, American Headache Society published Choosing Wisely, that in most cases, imaging was not necessary in migraine if you had the typical criteria, a long history. And some people talked about green flags or comfort signs, are there particular comfort signs that make you feel comfortable with a migraine diagnosis?

Dr. Ailani:

Yes, that's a good point. The green signs or comfort signs are like over 50-something of them, so I did not mention them in this clinical discussion. But yes, the things that usually make me feel very comfortable in clinical practice are if a patient has had the same type of attacks for a very long time, like 5 to 10 years and not much has changed, and their neurological exam is normal, you know, you're very comfortable making the diagnosis of migraine without imaging the patient, even if they've never been imaged before. A family history of migraine and then the patient's having migraine and they're very similar between the patient and the patient's family member. Again, this makes you very comfortable. New-onset migraine in a patient who's in that right age group for having migraine with all the typical classic features of migraine without aura. Even if someone has migraine with aura but it's a classic visual phenomenon of, you know, photopsia with the little bright shiny spots and then the dark spots after, and they've maybe had 3 or 4 of identical attacks before coming in to see us in clinical practice. And again, the neurological exam is normal, and they're not on any kind of medications or hormones or treatments and you're not really concerned, I would be a little bit less concerned about this patient. But we still, with aura, you offer the patient imaging just as a baseline, but I would be less concerned about a patient like that.

So I was going to move on to talk a little bit about hormones and hormonal cycling in migraine. And I think in the women patient, female patient, this is extremely important because we know that for many patients, menses is a risk factor for migraine, especially migraine without aura. We know that pure menstrual migraine is less common than migraine that is associated with menses. What is the difference here? Pure menstrual migraine is when a person with migraine is only having migraine attacks around the time of their menstrual cycle and no other time of the month. We might see this early in a person with migraine who is in their teens, started getting their menstrual cycles, and they will only get a migraine attack around the time of their cycle, usually within a day or 2 of their bleeding itself. But as they grow older, they start to continue to have migraine around their menses but other times of the month as well. And this is called menstrual-related migraine. And this is much more common in the general population.

To make the diagnosis of menstrual-related migraine or pure menstrual migraine, this really does require us to have the patient keep a calendar for 3 months. And they're calendaring not only their migraine attacks, but they're calendaring their menses as well. And you want to see that in 2 out of the 3 months that there's an association between migraine and their menstrual cycle, that the attacks are happening about 1 to 3 days before the start of their menses or occurring through their menstrual cycle or up to a day after.

We know the prevalence of menstrual migraine is very variable. The studies show us it can be anywhere from 20% to 25% of those with migraine, all the way up to 60%. So we have really drastic variances in numbers, and that for those that have menstrual-related migraine, they'll often report that the menstrual migraine itself is the most difficult one to treat compared to all the other attacks in the month.

Now we're showing you here the menstrual cycle, but the main point I want to make by this slide is that the underlying theory of what's happening in what's causing menstrual migraine might be the drop in estrogen levels that's occurring right before bleed. But there's actually a lot more theories into what might be the cause of menstrual migraine. We think that there might be not only changes in

estrogen levels, but changes in prostaglandin and also changes in oxytocin, and all of this might affect migraine onset. We also know that estrogen level changes will play a role in levels of CGRP, calcitonin gene-related peptide, which we're going to talk about pretty soon, and that plays a role in migraine pathophysiology.

There have also been some studies that take a look at women with migraine compared to women without migraine and have found that it seems that women with migraine have a faster decline in estrogen levels in late luteal phases compared to those without migraines. So somehow women with migraine are having some kind of alteration in hormonal levels to a greater degree that make them more susceptible to this drop and the migraine that occurs after, compared to those that don't have migraine. Between a combination of all of these things, oxytocin fluctuations, estrogen changes, and prostaglandin, is the reason that people are probably having migraine attacks that are harder to treat around that time period.

Dr. Buse:

Jess, you said a key word, and you said it several times when you're reviewing the slide. Change. Change in hormone levels. In addition to change in hormone levels being a risk factor for an attack, a migraine attack, change in almost anything seems to really be risk factors for individuals with migraine.

Dr. Ailani:

Yes, that's true. A lot of our most recent information about triggers are showing us that it's, again, the migraine brain does not like change at all. And it's not so much that an individual item is a trigger, but a change from daily patterns, [just like what you mentioned with caffeine](#), they're also suggesting might be true about alcohol, that alcohol itself might not be a trigger except for those that don't drink alcohol regularly, and now you're introducing something that the body is not regularly taking. And that might be why it causes the problem. Very interesting science behind what really happens in the migraine brain.

So let's move on to talk about our next topic, which is about the changing landscape of therapeutic approaches to treatment of migraine. So, Dawn, why don't you start us off here again.

Dr. Buse:

Great, thank you, Jess. So this comes from a really terrific review that Jess is one of the authors on it, the American Headache Society 2021 Consensus Statement, which in a pretty concise way reviews all of the evidence supported and FDA-approved and guideline-approved therapies for migraine. And we can kind of fit them into some of these buckets. So lifestyle, there are behavioral therapies, there's certainly the pharmacologic, there's neuromodulation, and there's complementary and integrative medicine.

So here are some of the lifestyle habits that we know really matter in kind of calming and stabilizing the nervous system. Sleep, enough sleep, and the timing matters. Try to have patients go to bed about the same time and get up about the same time 7 days a week. They can have a little variance on their days off, but we really want to keep a regular cycle and enough quality sleep. And we want people to get some exercise or at least movement, try to be physically active, meet them wherever they are, and kind of ramp them up as they work on that. A lot of people may be intimidated or uncomfortable or say migraine makes it painful to exercise. So we might need to find other forms of exercise that don't have repetitive movements like swimming or yoga. Eating and drinking. While there's no specific migraine diet, we do know that keeping inflammation low is important. So diets that have anti-inflammatory, low inflammation, good balance of healthy fats are valuable. But also, we just care about the timing, that someone's keeping their blood sugar steady, that they're eating healthy small meals and snacks at regular intervals, and they're staying hydrated. That diary can be very helpful at the beginning of treatment or when treatment changes are made. That's really helpful to really, as Jess mentioned, with the timing of the menstrual cycle. We can also keep the diary of migraine attacks and sleep and stress levels and any other changes or stressors, which we can use as clinicians and patients can use. We can talk about it together to look at are there places they need to be optimizing healthy lifestyle habits. And then stress management. Of course, I love this quote by Jon Kabat-Zinn, we can't stop the waves from coming, but we can learn how to surf. So we obviously cannot stop all of the major stressors or the minor daily hassles that help, but giving patients tools and strategies for how to manage stress.

And some of those best strategies come from behavioral therapies, which not only are helpful for depression, anxiety, and stress management but helpful for migraine prevention. That's going to include cognitive behavioral therapy, relaxation training, and biofeedback. And we have emerging evidence for the mindfulness-based therapies and acceptance and commitment therapy. If a patient asks, "Which one of these should I start with?" My answer is, "Yes, whatever looks interesting to you." Whatever your patient is motivated to do, whatever she or he can find available locally, go for it, get their foot in the door and get them started. And also, as I mentioned, there are neuromodulation approaches as well, which have both acute and preventive indication.

But let me pass this over to Jess to really dive a little deeper into our pharmacotherapies.

Dr. Ailani:

So we're going to first start by talking about some of the acute pharmacotherapy that we have available to us for treatment of migraine. And you'll notice we're pulling from the Consensus Statement because guidelines are still forthcoming since we've had so many new treatment options that have come to the marketplace in the last several years. And the Consensus Statement was published in 2021, and I can tell you really still struggling to keep up with the needs of the marketplace because there have been just so many treatments that have come about. You can see here established efficacy, which is considered Level A. We have several migraine-specific treatment options available for our patients today. And you'll notice that we really have moved away from things like opioids or butalbital. We do have probably effective or Level B options as well. They include ergotamines, which are DHE [dihydroergotamine], one of our other great treatment options for migraine. Then there are several options that are available for use in an emergency situation, so either in an infusion center or in the emergency room that are available as IV formulations. So this is actually really great news for our patients when they're in an emergency room situation for good evidence that's migraine specific.

So we're going to talk more about some of these migraine-specific medications during this discussion today, but I did want to talk about the fact that some of our migraine-specific medications have been around a long time. And that includes things like triptans and ergotamines. They have had limits because they are medications that we tend to avoid in patients that have cardiovascular contraindications like uncontrolled hypertension or someone who's had an MI [myocardial infarction] or cardiovascular disease in the past, like a stroke. Triptans, however, for our female patients are generally things that we might consider continuing when they get pregnant. Our newer medications like gepants and ditans, lasmiditan, are generally safer to use when patients have vascular issues.

So when do we really consider a newer treatment option that might not be generic versus one of our generic treatment options? No surprise, it's for our patients with vascular disease, as I just mentioned, or patients who have had contraindications or intolerance to triptans, for example, side effects like sedation, or nausea from the triptans. Any patient who's tried 2 or more oral triptans in the past and they weren't effective is another patient group that we're going to consider for these more specific treatment options.

So I wanted to take a moment to talk about frequent medication use. Sometimes patients will get into a point where they're overusing acute treatment. And there's many reasons for this. Sometimes the attack frequency is really high and they need something to treat their attacks in order to remain functional. Sometimes they start to become very anxious about the next attack and start to take acute treatment even before the attack has begun. Maybe when they just start to get the sense that they're about to have a headache, and so they start to treat.

Rates of medication overuse and medication overuse headache can be quite high in some patient populations. And this can be something that can be very difficult to manage. With medication overuse, they can actually have many significant issues. One of which we see frequently in clinical practice is when patients are overusing NSAIDs [nonsteroidal anti-inflammatory drugs], especially those that are over the counter. This can cause many of our patients to end up with GI [gastrointestinal] and renal issues. And we will often see peptic ulcer disease that develops. But another common side effect that can occur is increase in blood pressure over time. And cardiovascular issues can develop as well. In a portion of patients overuse of acute treatment leads to an increase in headache, or what's called medication overuse headache. And this can be a problem to make the diagnosis because it can be really hard for us to figure out if the overuse of acute treatment is causing the headache. The only way we can figure that out is by stopping the acute overused medication. And it's an ongoing debate about how do we really manage and treat this properly?

So I've mentioned some of the acute treatments. I think it's important to realize that for every patient with migraine, not every attack is going to be exactly the same. So often, when they're coming to see us in a headache clinic, what we tend to do over time, not generally the first visit, but over time, we build an attack toolbox, and the patient starts to understand for the different attacks they might have, how they might have different tools to treat the attacks. Now, every patient doesn't get all of these medications. And I don't have any patient that has a toolbox that has everything in it. But usually there might be something they use for a mild attack, something they use for a moderate attack, and then something they use for attacks with nausea or vomiting. And each of these items might be different. And usually, a patient will have something for rescue, and that's to avoid going to the emergency room. Which is really one of the reasons we work very hard with patients over time is to avoid emergency room or urgent care use so that they're very independent and capable to manage this disease that, as Dawn had mentioned, take so much away from them.

So we're going to move on to talk about prevention. And for patients with migraine, most patients really will do well with just an acute treatment for migraine. But we do have guidelines that suggest to us when is it a good time to mention prevention to your patient. And this is really when the patient comes to you and said they're disabled from their attacks; acute treatment isn't working well; the attacks are so frequent, it's stopping them from doing the things they need to do, want to do, or love to do.

We have many migraine-specific preventive options in this day and age. We still have our tried-and-true generic options as well for patients to be on to help reduce migraine frequency and the burden associated with disease. This here shows you just a list of different options available for patients that have Level A evidence and Level B evidence for migraine prevention. You can see a list of many of our

oral generic treatment options including topiramate which has Level A evidence and FDA approval for migraine prevention. And you can see amitriptyline and atenolol, which are actually Level B migraine preventive options.

We're going to focus in on the remainder of this discussion on some of our migraine-specific treatment options which focus in on CGRP. CGRP, which we'll talk about in a little bit, calcitonin gene-related peptide, has been discovered to be very intimately related in migraine pathophysiology. By blocking its activity, we can reduce migraine frequency. Here you can see the development of CGRP-specific monoclonal antibodies to block CGRP activity either by binding to its receptor or binding to the CGRP protein itself, can help reduce migraine frequency, whether this is migraine with or without aura or people who have chronic migraine.

There are 4 different CGRP monoclonal antibodies available for clinical use. Three of them are at-home single auto injectors that can be done monthly. One is an IV infusion that's done quarterly either at an infusion center or, for some patients, there is an option for it to be done as a home infusion. I should mention that fremanezumab also has an option for 3 injections that can be done every 90 days if a patient prefers to do it that way. These are generally coming with limited side effects, mostly injection site reactions. Erenumab can cause an increase in blood pressure for those that have borderline blood pressure and constipation. And eptinezumab does have higher rates of hypersensitivity reaction, but overall as a class, they're pretty well tolerated and easy for patients to use over time.

So when do we consider an oral generic medication for patients for migraine prevention versus one of these newer more specified migraine options? We usually will try the generic oral options for patients first before we move on to some of these specified treatments. If a patient has tried 2 oral options in the past and haven't tolerated them well, we might move on at that point to one of these CGRP monoclonal antibodies or, as we'll talk about in a few moments, the CGRP oral options as well. Now this might change, as there's been some newer data that's come about showing that some of these CGRP options are actually better tolerated than our oral generic options. But until there's more information out, this is really how we're practicing in this day and age.

Now we're going to move on to talk about CGRP, the pathophysiology of CGRP in migraine, and interpreting clinical trial data supporting a central role for modulating neuropeptide CGRP in the management of migraine.

So exactly what happens in the brain when a migraine is occurring? We all were taught in medical school that migraine was purely a vascular disease, that vasodilation with the blood vessels bouncing against the trigeminal nerve is what caused all of the pain in migraine and the symptoms associated with migraine as well. Over time, we've come to realize that that was probably too simplistic of an explanation of what was happening in migraine itself. And that more likely, what we think is occurring at this point is a release of neuropeptides which include calcitonin gene-related peptide occurring through vasodilation. And that activates the trigeminal nervous system, which then goes on and activates a whole series of areas in the brain including the hypothalamus and the thalamus, which then causes several of the symptoms involved in migraine including changes in appetite, confusion, brain fog, and then activation of the cortex which can cause several of the other symptoms involved in migraine. We know that when a person with migraine has CGRP infused into them, this can actually trigger a migraine attack. And for those that have no migraine and you infuse CGRP, a small portion of those people will have a tension-type headache but not a migraine. We also know that if you treat a person who has migraine with a triptan, that CGRP levels go down if the migraine is treated successfully. But if it's not treated successfully, nothing really changes with CGRP. So there's a number of different data points we have that really confirm the role of CGRP in migraine itself.

Let's focus in a little bit more on some of the other CGRP medications that have come about in the last several years, more so on those that block the CGRP receptor. There's a family of medications known as gepants that are available both as acute treatments for migraine and preventives. I wanted to first talk to you about some of the acute treatments that are available as gepants. Firstly, there's the oral treatments, ubrogepant and rimegepant. These are both available as oral options to treat an acute migraine attack when it occurs. They work by blocking the CGRP receptor, therefore not allowing CGRP to do what it's supposed to do. The benefit of these medications is they come with very little side effects. Some of them can cause some nausea, ubrogepant at doses of about 100 mg can cause some somnolence and dry mouth, but they don't cause medication overuse headache. And so this is a big topic that Dawn and I have been talking about. They also don't have any trouble if you're driving since they're not sedating, and they don't work on the serotonin pathway so there's not really a risk of serotonin syndrome or interactions with serotonin drugs. They do work on the CYP3A4 system, so just have to consider drug-drug interactions which are really important with medications like ketoconazole.

Another new CGRP receptor antagonist that's used for acute treatment of migraine is zavegepant. This is our first nasal option for use for acute treatment of migraine. This is great, especially for our patients that have nausea or vomiting associated with their migraine attacks. So this is when we definitely consider pulling this medication out. But it's also a third-generation gepant. It's a lot to really go through for this discussion, but if a patient doesn't respond to ubrogepant or rimegepant, that might be another reason to consider zavegepant for use.

I had mentioned earlier the CGRP monoclonal antibodies as a preventive treatment option for patients with migraine, and they were

different than our oral generic treatment options, and perhaps we had some data to suggest that they were better tolerated than oral generics. We have data that suggests to us that for patients that are on preventive treatments that are on oral preventive generic treatments, examples would be topiramate or amitriptyline, that for every 100 patients on an oral generic preventive for migraine, about 81% will stop their treatment in about a year. What about those that are on injectable medications like CGRP monoclonal antibodies that come with less side effects? Well, we see that in the data we have, about 50% will discontinue over 6 months, and about 23% to 25% will remain on these medications in the course of a year. So that is much better than oral generic treatment options, but not as great as I think many of us hoped in clinical practice. We don't really have a reason for why patients are discontinuing the CGRP monoclonal antibodies. For oral generics, we have data that suggests that side effects are probably the biggest reason that patients stop the medication.

But what are patients looking for when it comes to preventive treatment? And so when it comes to our discussions with patients for prevention, what's important and what do we need to ask when we're going to help them make choices? Well, patients are looking, first and foremost, for reduction of migraine. They want more migraine-free days, less frequent attacks so they can have restored function and feel more like themselves. But what's interesting is they want something that's easy to use, and most patients will prefer an oral tablet option. So this is an important consideration when thinking about prevention, especially those that have never been on an injectable option before, they might prefer a tablet. So this is something we have to ask them when we're considering prevention if we're going to consider a CGRP path.

I had mentioned the CGRP receptor antagonists, gepants, for acute treatment for migraine. It's important to note we also have 2 options for prevention. Rimegepant, which is the same tablet used for acute treatment is also FDA-approved for episodic migraine prevention when used every other day. Atogepant is a migraine-specific preventive treatment option for both episodic and chronic [migraine] and comes in several dose options. For episodic migraine, it's available 10, 30, or 60 mg a day. And for chronic migraine, it's available at 60 mg per day. So these are tablet options blocking CGRP, migraine specific, and tend to be better tolerated and we can consider for our patients who would prefer taking a tablet versus doing an injection and who wants something that's more migraine specific.

Now that I've discussed with you all the different options available to patients, how do we really bring this up in clinical practice, and how are your patients hearing us when we're talking about this stuff? Well, the first thing we always look at, unfortunately, is cost and insurance factors. And while I think that's unfortunate, I do know patients appreciate that we bring that topic up right up front. So we go through what kind of goals and needs need to be met by the insurance, but I also will talk to them about if perhaps they need to try generic alternatives first, that doesn't mean they might not have amazing outcomes and that we will often discuss choosing the best generic alternative for them first, based on their comorbidities. Perhaps I've noticed by reviewing their primary care note that they really needed to lose weight and that was a big goal for them. I'm going to bring that up right away and talk about what options I might have that's going to help with that goal along with helping their migrating attacks. Perhaps they've already mentioned to me that sleep is a really big problem for them and it's making their migraine worse. Well, then we're going to talk about how amitriptyline might be a good option for them because it's going to help them sleep better, but can also help their migraine attacks as well.

If we are going to consider something onabotulinumtoxin, I think comorbidities is important as well. I mentioned earlier that neck pain is a big problem for many patients with migraine, and if they're having a lot of neck pain, that might be a reason we're going to choose onabotulinumtoxin versus a gepant or a CGRP monoclonal antibody, and an honest discussion with the patient, I think, is important.

The other thing we're going to talk about if we're moving on to a CGRP-targeted therapy, like a gepant or a CGRP monoclonal antibody, is their desire for an oral treatment option versus an injectable? And if they want to take an oral treatment option, do they want a daily medication or an every-other-day medication? And really, what are their bowel habits like? Are they having a lot of trouble with constipation, which is a higher problem if they're going with a daily oral medication like atogepant? It does carry a higher rate of constipation. So if we're talking about injections, we're talking about is monthly or quarterly something that they feel is more important to them and how well are they at managing these injections at home?

Amongst all of this in our women patients, the biggest part of the conversation is family planning and birth control. You know, how are they preventing from getting pregnant? Are they considering pregnancy and then how soon? If we're thinking about a monoclonal antibody, we'd have to stop that about 6 months before they start trying for pregnancy. And if their goal is to become pregnant in the next year, I don't really think starting a monoclonal antibody would be the best option for them because we'd have to stop it 6 months after they started it and then, you know, think about what to do for 6 months before they started trying for pregnancy. And that can be a very difficult conversation. In that option, an oral gepant that clears the system in about 60 hours would be a much better option for the patient. We might have other discussions about generic medications, putting them on something that might be a little bit safer in case they got pregnant, like a beta-blocker. We might also be having conversations about onabotulinumtoxin A.

So we talked a little bit about adherence earlier, Dawn. And I know this is a big problem in clinical practice, really making sure we get

our patients to stick on their medication regimen. Do you have any other thoughts about ways we can do this better?

Dr. Buse:

You know, Jess, I'd like to go back to that early conversation we had about asking about disability with a single question. You know, how's migraine affecting your life? And we talked about that often patients will say exactly what is most on their mind or most in their heart. So I like to turn those words into a goal. And now we have a shared goal with the patient. So using the patients words to keep them motivated and tied in, because unfortunately, motivation here is a challenge across all of our therapies. You know, and then when we ask for changes, it's really important that we kind of step it up. We don't want the patient to feel like they're failed in making a recommended change. So whatever goal we set for them, be it sleep related, exercise related, anything, medication related, we make it doable, we let them achieve that goal, and then move up the next step together. So those are a couple ideas I have.

Dr. Ailani:

I think those are great.

So we're at the end of our program. I wanted to take a moment to recap some of the points from what we've been discussing. So individualizing multidisciplinary treatment approaches so they align with the unique needs of women with migraine at different stages of life to achieve the best outcomes; stress the importance of healthy lifestyle habits; consider the use of migraine-specific acute therapies; be careful about medication overuse with over-the-counter treatments and caffeine-containing medications; preventive strategies, especially for those that are carrying a higher burden of disease. These can be pharmacological and non-pharmacological. They tend to be underutilized, but they can be very important for patients. Think about those 2021 American Headache Society Consensus Statements that can be helpful in really achieving some of these goals. Inform our patients of novel evidence-based treatment therapies, stress that if they had prior failures to medication, there are more tolerable options out there that are effective. Motivate your patients to accept treatment; individualize patient care based on recent clinical trial and available real-world evidence; employ shared decision-making strategies; consider who's going to be treating that patient, and if it's not going to be you, the primary care provider, or the neurologist, maybe find a good headache specialist in your region and make that referral. Treatment may change over the course of a woman's life. It's going to look very different in her 20s, it's going to look very different when she's thinking about pregnancy, when she's pregnant, when she's lactating, and when she's perimenopausal and postmenopausal. But we have so many treatment options out there and many people who are ready to really take care of this patient population.

So I just want to take a moment to say thank you so much for your attention and for joining us for this program. And, Dr. Buse, thank you for joining me as well today.

Dr. Buse:

Thank you, Dr. Ailani.

Announcer:

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