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### Mining the Outer Reaches of Migraine Science

#### Announcer:

Welcome to CME on ReachMD. This activity, entitled "Mining the Outer Reaches of Migraine Science" is provided by Forefront Collaborative and is supported by an independent educational grant from Lily.

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#### Dr. Caudle:

Due to the fact that it's often underdiagnosed and undertreated, migraine has become the second leading global cause of years lived with disability. But the good news is that there is hope for clinicians and patients who are frustrated by the challenges of relieving migraine's crippling pain. And today, we'll be taking a look at some of those new pathophysiologically-targeted treatment options.

This is CME on ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to discuss these advances in migraine treatment is Dr. Wade Cooper, who is the Director of the Headache and Neuropathic Pain Program, and Associate Professor of Neurology at the University of Michigan in Ann Arbor.

Dr. Cooper, welcome to the program.

#### Dr. Cooper:

Thank you very much for having me.

#### Dr. Caudle:

Absolutely. Migraine has previously been thought of as a problem with vascular spasm, causing subsequent pain and throbbing sensations for patients. But how have recent breakthroughs led to a shift in our understanding of migraine?

#### Dr. Cooper:

We know migraine is incredibly common, over 36 million people in the United States have migraine. And it used to be thought of as a blood vessel spasming issue at the surface of the brain that was generating all the symptoms. And there certainly is a vasoconstriction element to migraine, but we also know that migraine includes a sterile inflammatory response to the lining of the brain. When you think of your patients who have migraine, I'm sure you know they're uncomfortable. And this can include things like light and sound sensitivity, and nausea, in addition to the headache component as well as having some mood change and fatigue elements. And what we understand is happening is like a sterile meningitis. And as we

study this further, we've been able to identify inflammatory peptides that are released from the surface of the brain and irritate the pain-sensitive nerves that send a signal to initiate and maintain a migraine attack. And this is resulting in central activation; turning on the features of migraine that you and I see in our patients. This pain signal is sent from the sterile inflammatory mechanisms on the surface of the brain by A delta fibers, these pain-sensitive trigeminal fibers that go deep into the brain itself and propagate that migraine attack.

Dr. Caudle:

And that's really helpful to understand the pathophysiology. In turn, how has this improved understanding of these inflammatory mechanisms led to the development of targeted therapies for the prevention of migraine?

Dr. Cooper:

CGRP receptors and the CGRP ligands have become key targets. If you use a CGRP-targeted monoclonal antibody, you can reduce days of headache per month, and some patients get more than 75% reduction in their days of headache per month over the course of time. When you use these once a month, and in the case of fremanezumab once every quarter, if you use these therapies, you can see a separation from placebo within one week, although typically our patients need to be on these treatments between three to six months to identify how much benefit they're going to get. Many times, you can see improvements in their disability scores. When these came out, we were worried that if you block CGRP, it would have consequences not just on the nervous system to reduce migraines, but maybe it would affect other areas of the body. It turns out, CGRP is active in our lungs, CGRP is active in our blood vessels, CGRP is active in our heart, in our kidney, in our skin; all kinds of areas. One of these studies that just got published showed us that people on one of these monoclonal antibodies; in this case it was erenumab, over the course of five years in their open-label trial extension, showed that it was very well tolerated and also very safe. The only thing that came out of long-term studies for these was the addition of severe constipation as a warning for erenumab, and that was also in the label for the other FDA-approved medications for prevention of migraine in this class; that's galcanezumab and fremanezumab. The side effect list can include constipation or injection site reaction. Of interest, galcanezumab was also found to be effective in the prevention of episodic cluster headache. Cluster headache is quite different from migraine, but shares the same CGRP inflammatory pathology. The FDA is reviewing a fourth medicine, Search Results

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Eptinezumab, and that one is going to be an I.V. infusion scheduled to be given once every three months.

Dr. Caudle:

As a family doctor in practice for over 10 years. I think about all the prevention medications that we've been using over the years. Dr. Cooper, how are these new CGRP monoclonal antibodies different from what patients have experienced before, and what we as doctors have been prescribing before?

Dr. Cooper:

Our patients, our migrainers, are warriors. Previous prevention therapies such as the FDA-approved topiramate or valproic acid were medicines that were designed to prevent epilepsy, and they had a side effect or an additional benefit of lowering migraine. But they came with baggage; things like weight gain, cognitive impact, having numbness or tingling of the hands and feet. Other medicines commonly used in the prevention of migraine like propranolol or tricyclic antidepressant class medicines. None of these medicines were specific for migraine; they were just used because they had a consequence or a side effect of improving migraine. And this really frustrated our patients, because our patients had to cope with a lot of side effects, and sometimes had to choose what's worse: having disabling bouts of migraine or having weight gain, with some of these medicines adding 10, 15, 20 pounds of weight on our patients. As a provider it's important to individualize your patient selection for prevention therapy. So using tablets like topiramate or valproic acid can be appropriate in the right situation. Propranolol and other medications can be appropriate, as can onabotulinum toxin A. And all this has to be determined by your clinical skill-set. Trying to match what the patient's looking for, what their clinical symptoms are, and what you think they're going to do best with.

Dr. Caudle:

Those are really interesting points that you mentioned about the idea of patients sometimes choosing between the side effects of medications versus what the medications are intended to treat. I think a lot of clinicians out there can relate.

For those of you who are just tuning in, you're listening to CME on ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Wade Cooper about advances in migraine pathophysiology and treatment. Dr. Cooper, we spoke a bit earlier about the inflammatory mechanisms of migraine, but now let's shift over to how these pathways affect the way we treat migraine. Is there a role for medications targeting CGRP for the acute treatment of migraine attacks?

Dr. Cooper:

The field class of medicines are known as the gepants. The gepants class of medicines limit the ability of CGRP to activate the receptor; therefore, receptor antagonists in the peripheral nervous system before it sends pain to the deep brain structures. And their design is that when you take the tablet within two hours, you should separate from placebo in items like pain freedom, pain reduction at two hours, as well as improvement of other associated migraine symptoms, what they call their most bothersome symptom of either nausea or light sensitivity or sound sensitivity. And what's interesting is previous standard of care agents used for treating acute attacks of migraine like sumatriptan and DHE are known to lower the effect of CGRP in the peripheral nervous system.

Dr. Caudle:

Are there other acute treatments for migraine that have similar targeted mechanisms of action?

Dr. Cooper:

The standard of care currently using triptan-class medicines such as sumatriptan or rizatriptan or naratriptan or using other medicines such as dihydroergotamine can be very effective for the acute attack of migraine. And these work on serotonin receptors; 5-HT<sub>1B</sub>, which is located along the blood vessel, and 5-HT<sub>1D</sub>, also a serotonin receptor, which is located along nerves as they send signals into the brain. And those medicines have been remarkably effective, and a lot of situations return someone's quality of life within a couple hours of their use. They've identified a second receptor group, the serotonin 5-HT<sub>1F</sub> receptor. And this also exists in the peripheral nervous system along nerves as they send their pain signals deep into the brain. But 5-HT<sub>1F</sub> receptors also are located in areas of the brain that are part of the central processing of migraine. Areas like the thalamus, which when you take care of your patients, you'll be thinking of light and sound sensitivity, which are located in this area. 5-HT<sub>1F</sub> receptors are located in the hypothalamus, which is where we generate our response to triggers to migraine, like sleep deprivation, like hunger. And when our patients describe these things, they're telling you the nervous system is being wound up through these regions that activate a migraine. There's even 5-HT<sub>1F</sub> receptors that are located on the descending turn-off pain signal of the brain, what we call the periaqueductal gray region. We have some patients who, when they get stuck in a migraine, they're going to have symptoms for a long period of time, they just can't turn off the attack when it started. Sumatriptan and other medicines are pretty effective at stopping the signal to turn on the migraine attack, but once it's been activated, it's very hard to shut that off. 5-HT<sub>1F</sub> receptor targets may promise to do just that. There's currently a medicine called lasmiditan, which has been FDA approved and is just waiting to be cleared through the DEA from a scheduling standpoint, which seems to be effective in people for acute migraine. We know that this medicine is overall safe, and can be used in people with cardiovascular diseases, you can develop CNS side effects, central nervous system side effects. This can include dizziness or somnolence. Patients on lasmiditan are asked to not drive for 8 hours even if they feel completely fine. We do know that lasmiditan did show efficacy for two-hour pain freedom, as well as two-hour improvement and bothersome symptoms such as nausea or light and sound sensitivity.

Dr. Caudle:

To kind of wrap this up and give us some takeaway points for clinicians with an interest in migraine what are some of the guiding principles that we just need to keep in mind in this age of treatment options?

Dr. Cooper:

It's important to know that when you treat people with migraine, know that it's first of all just unfair. It's unfair that our patients

with migraine have to have episodes where they're incapacitated because of pain or nausea or light and sound sensitivity. It's unfair that this is unpredictable, so that people don't know when one's going to attack, and it disrupts a lot of their quality of life and a lot of aspects of their day-to-day living. We know migraine is common with about 36 million people in the United States have migraine, and it's a systemic neurologic disorder. It affects different areas of the nervous system, and impacts people in lots of different ways. But the best part about this is our recent breakthroughs in understanding molecular science has led to specialized treatments that focus on key aspects of the migraine machinery. We've seen impressive results of prevention therapies from the three monoclonal antibodies that are just recently being used in this country like fremanezumab, erenumab, and galcanezumab. And these have minimal side effects. We've got the promise of acute therapies that work on CGRP like the gepants class medicines that we expect to be FDA approved. We have the promise of lasmiditan and other medicines being developed on 5-HT<sub>1F</sub> receptors And these have shown substantial pain relief, pain freedom, and improvement of overall symptoms at two hours. This is a very exciting time for those who treat migraine, and most importantly, a very exciting time for our patients who have migraine.

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You know, I couldn't agree more; those are certainly some great principles for us to take with us as we come to the end of today's program. And I'd like to thank Dr. Wade Cooper for helping us better understand the mechanisms of action of new therapeutics targeting the underlying pathophysiology of migraine. Dr. Cooper, it was great speaking with you today.

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Caudle\_Cooper

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[SC1] This one worked out ok.

[LZ2] You can add this one back in. it sounded jumpy as though more was cut out than a simple 'And'

[SC3] KYLE: Add back in

[KC4] Added