
# FACULTY TRAINING TRANSCRIPT

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### Slide 1 – Title Slide

**Susan Burke:** Welcome to Updates in Migraine Management and Primary Care. This activity is jointly provided by the Potomac Center for Medical Education and Rockpointe, and is supported by an educational grant from Lilly.

Hello. I am Dr. M. Susan Burke. I'm a Clinical Associate Professor of Medicine at the Sidney Kimmel Medical College at Thomas Jefferson University, as well as Senior Advisor and Teaching Attending at the Lankenau Medical Associates at Lankenau Medical Center in Wynnewood, Pennsylvania.

I am joined today by Dr. Jack Schim, MD, who is the Co-director of the Headache Center of Southern California in Carlsbad, California. With us today as well are two residents from my institution, Dr. Matthew Delmonico, who is chief resident of the internal medicine program at Lankenau Medical Center in Wynnewood, PA; and Dr. Christopher Damiano, who is a third-year internal medicine resident also at the Lankenau Medical Center.

### Slide 2 – Please Help Us with the Following

### Slide 3 – Disclosures

You will see the disclosures for the faculty as well as the non-faculty content contributors on this slide. This is also provided in the CME information on the landing page of this program.

### Slide 4 – Educational Objectives

Our aim is to ensure that this program is an engaging and meaningful learning experience for you. At the conclusion of the program, you should be able to examine the epidemiology, differential diagnosis, and impact of migraine within the primary care patient population, describe the pathophysiology of migraine including the role of calcitonin gene-related peptide or CGRP, delineate current standards of pharmacologic and nonpharmacologic management for the preventive and acute management of migraine, and assess clinical safety and efficacy data for emerging therapeutic agents for the prevention and treatment of migraines.

### Slide 5 – Polling Question 1

### Slide 6 – Several Types of Headaches (HAs)

We know that there are several types of headaches. Primary headaches are headaches not

caused by another medical condition. These include migraine, tension type, and cluster. And there are secondary headaches, which are caused by another medical condition. These include infectious etiologies, such as meningitis or sinusitis, space-occupying lesions, bleeding, such as subarachnoid hemorrhage, vascular etiologies, rheumatologic etiologies, such as giant cell arteritis, ophthalmologic, such as angle closure glaucoma or optic neuritis, neurologic, such as trigeminal neuralgia or postherpetic neuralgia, idiopathic intracranial hypertension, and others including acute hypertension or carbon monoxide poisoning, which we sometimes can see in the wintertime in some individuals.

Slide 7 – Migraine Impact and Epidemiology

As stated in the title, our focus today will be migraines. As far as the epidemiology of migraines, one in five US adults has migraine with about 28 million persons having migraine each year in the US. Women have a 25% lifetime prevalence, and men about an 8% lifetime prevalence. Seventy percent or more of migrainers have a positive family history of migraine in a first-degree relative. This is an important question to ask of your headache patients. Up to 9 million PCP office visits per year are due to migraines in the US and about 5 million annual visits to an ED are due to migraines as well with a significant association of cost.

Now you will hear a case presented by my colleague, Dr. Delmonico.

Slide 8 – Lizzy, a 31-year-old Mother

**Matt Delmonico:** Thanks, Dr. Burke. I want to present the case of Lizzie. She's a 31-year-old mother who presents to your office to ask for help with her sinus headaches. She notes that she's been getting them for several years, but they are now occurring almost daily. She notes that they're predominantly frontal and maxillary in location without throbbing. She does take acetaminophen almost daily along with pseudoephedrine preparations and occasional loratadine when she has watery eyes and nasal congestion.

Questions we should be asking ourselves as primary care physicians are what else do we need to know to help Lizzie and what treatments can be offered? We'll hear more from Dr. Burke about this.

Slide 9 – Differentiating Migraine from Other Types of Headache

**Susan Burke:** How do we differentiate migraine from other types of headache?

Slide 10 – Basics of the History and Physical Exam

This highlights the basics of the history and physical exam when evaluating someone presenting with the complaint of headache.

During the history, you're going to want to inquire about the timing and frequency of the headache. Are there any exacerbating factors or triggers? Foods for example cheese, chocolate, alcohol, bright lights, perhaps lack of sleep. Also, what meds have a patient tried already? We find that patients usually come in and they've already had a significant use of over-the-counter preparations. Are they overusing these medications? What is the location, intensity,

and nature of the type of pain they're experiencing? And also, are there any associated symptoms? Visual, motor, sensory, or GI symptoms can be associated with headaches.

With regard to the physical, I like to watch the patient walk in if I can or I certainly like to observe their body language. Of course, a careful neurologic exam is key in your initial evaluation of someone presenting with a headache. You can palpate the head, their arteries, their temporal arteries, especially in an older patient, feel for trigger points especially in the neck, examine the neck for stiffness and range of motion. A rapidly lost art is performing a fundoscopic exam, something that I try and highlight with my residents, especially someone presenting with an acute headache or someone who you're worried about increased intracranial pressure to look for papilledema. You can examine the oral cavity as a contributor to headaches and look or feel for the temporomandibular joint area.

## Slide 11 – Episodic Migraine (EM) Recognition by ICHD Criteria

Episodic migraine definitions by the criteria given to us by the International Classification of Headache Disorders. On the left are migraines without aura and on the right, migraines with aura. To review, the criteria for migraine without aura include at least five attacks with at least two of the following: unilateral, pulsating, moderate to severe pain, and aggravated by or avoidance of routine physical activity. This distinguishes a migraine headache say from a tension-type of headache. And they also need to have at least one of the following: nausea and/or vomiting, photo and phonophobia without any evidence of organic disease.

Now a migraine with aura would have at least two attacks that have at least one fully-reversible symptom without motor, so a visual and/or sensory, and/or dysphasic speech and we've probably all heard stories of people who just seem like they are talking and not making any sense and if it's a younger person, we worry about a stroke in anybody, but a migraine headache may be the contributor in that patient.

They also need to have at least two of the following: at least one aura symptom developing gradually over five or more minutes or they can actually have different symptoms occurring successively over five minutes or more. They could have a visual aura first and then maybe a dysphasic aura second. Each symptom can last five or more minutes, but they should all finish within 60 minutes. Then a traditional-type episodic migraine ensues and again, no evidence of organic disease.

## Slide 12 – Headache Types

There are a couple other headache definitions to be aware of that is chronic migraines and medication overuse headache. Patients will often present to our clinic practice with one or other of these quite frequently. In these instances, I always like to ask about the patient's headache as a teen or a young adult because you usually get a story that they had headaches when they were younger, but now, their headaches have changed and they're presenting with almost a daily headache. Then you have to sort out whether it's a chronic migraine or a medication overuse, and there does seem to be some overlap in the definitions of these, but let's distinguish these now.

A chronic migraine occurs in someone who has a headache at least half of the days a month and duration of a headache of four hours a day or more for three months or more. The important thing to note, it's not just more episodic migraine. These headaches don't quite look the same as their episodic migraine that they may have had as a teen or young adult and that's why I always go back and ask what was the nature of the headaches when they first started getting them. They can evolve as a complication of an episodic migraine. About 2.5% per year will morph from an episodic migraine to a chronic migraine. They're more disabling with higher costs and there are some risk factors to be mindful of, certain comorbidities, such as anxiety, depression, or obesity. Also, iatrogenic factors, medications, medication type, and frequency of use. Very important, these can be reversed. It takes a lot of work, working with the patient, but our goal is to revert these patients back to episodic migraines.

On the other side of the slide, we have the definition of the medication overuse headache, which is a pharmacologically maintained headache again occurring 15 days or more a month with headache and the patients are taking an agent, often an over-the-counter agent, and sometimes they're taking it even before they have a headache. They're afraid the headache's going to come on that day. They've been through about four bottles of an ibuprofen-type product within the last couple of months and they're coming in because they don't know what else to do. They're not getting rid of their headaches anymore.

Regular acute drug use of 10 days or more a month, 15 days or more a month for simple analgesics for 3 months or more and the headache worsens over the time of overuse. The headache resolves or reverts to the previous pattern within two months of overuse elimination, and this requires a lot of conversation between you and the patient that they have to stop the offending agent. There's different things you can do. I would certainly think of starting a preventive agent, which we'll talk about in a moment, but they have to stop the offending agent for you to get them out of this pattern of medication overuse.

Please note that any abortive medication can cause medication overuse headache. NSAIDs are big culprits because that's what the patients have their hands on, but triptans can do it. Certainly, butalbital compounds, anything can cause a medication overuse headache. Once a patient gets to a chronic migraine or a medication overuse headache, they can be more challenging to treat and that's what takes time and effort on our part and counseling with the patient and educating the patient, which we'll get into momentarily.

### Slide 13 - Understanding the Chronology of Migraine

This helps us in our understanding of the chronology of migraine. It also shows us how a migrainer can have different types of headaches, which are all part of the spectrum of migraine. If you look at the bottom of the slide, you can see migraine evolution. Some patients may just have a premonitory kind of phase of headache. They might feel like the headache's coming on, but then it sort of stops in its tracks but they just don't feel well. They might get the aura without a headache.

Then the number three marker there, they might have a mild tension-type headache, so when you talk to a patient it sounds like a lot of their headaches are tension-type, but sometimes they have a migraine. It's all part of the spectrum of this same migraine disease.

Now once you have a migrainous headache or a full-blown migraine out at post number five there, those patients actually have central sensitization and you can see on the left what happens in the pathophysiology. Dr. Schim's going to explain a little bit more about pathophysiology of migraine shortly, but there's neurochemical disruption, electrical disinhibition, trigeminal disinhibition, neurovascular activation, and then in the full-blown migraine, central sensitization.

I don't know if you've ever had a patient who has come in and says, "Well, when I get a really bad headache, I don't even want to comb my hair." Their scalp hurts. That's an element of central sensitization. That's the full-blown migraine. It's a real phenomenon. They don't want to wash or comb their hair and it's a real thing. A patient may have any headache along this spectrum and that's why sometimes it seems as though patients present with different types of headache. They may all be migraine headaches.

### Slide 14 – Migraine Evolution

This shows us how a migraine may evolve or transform from an episodic headache to a chronic headache. On the left, you can see the episodic headache occurring here and causing impairment. The line skirts up into mild and then severe impairment, but then the line comes back down in between headaches so that the patient feels normal.

At some point though, you'll see that the patient's headache no longer comes back completely to normal. The patient state is such that they are mildly impaired or maybe even verging on severe impairment and their headaches are more frequent, their normality never goes back, they never feel good. And what can also happen then is they start overusing medications, they start having sleep disorders, irritable bowel, as well as mood and anxiety disorders and a lot of times we think, "Well, the migraine patient, they're complainers or they're more anxious," or they have irritable bowel, "Oh yeah, they typical migraine irritable bowel." Well, there's a physiologic reason for why this happens. They are not sleeping well, they feel lousy all the time, they never return to normality between headaches. And you can also see where they're not having what looks like a typical migraine once they've crossed over or transformed into a chronic migraine headache.

Our goal with treatment then, you'll see this line come back, is to reset the patient if you will. You want them to go back to where they just have episodic headaches and can feel normal between headaches. This is accomplished with education, with our preventive therapies, with withdrawal of overused medications and so forth.

### Slide 15 – Polling Question 2

### Slide 16 – ID Migraine™ – A Validated Screener

One of the most useful identification tools that I use all the time is something called ID Migraine.

It's a simple three-question validated screener. When you use it on someone who's presenting with daily headaches, you might have to ask whether these patients have had these symptoms in the past because once they're in that chronic migraine phase or a medication overuse phase, they may no longer look like your traditional episodic migraine patient. But you want to ask, when you have a headache or when you've had headaches, do you feel nauseated or sick to your stomach? When you have a headache or had headaches, does light bother you sometimes or at least a lot more than when you don't have a headache? And during the last three months, have your headaches limited your ability to work, study, or do what you need to do? And this also is a distinguishing factor as I mentioned between migraine and a tension-type headache.

I always say that someone who has a tension headache might come home and they might not want to take their kid to soccer practice, but they'll take their kid and they might feel better when they're out and they're away from their job and outside and doing things like that, but a migrainer is going to call and see whether somebody else can take their kid to soccer practice because these migraine headaches limit their ability to work, study, or do what they need to do.

Two out of three yeses for migraine gives you a positive predictive value of 93% in the primary care setting. I find this to be the screener that I go to all the time in my evaluation of a patient in whom I suspect migraines.

### Slide 17 – Polling Question 3

### Slide 18 – Indications for Diagnostic Testing

What are the indications for diagnostic testing? We have some red flags to be mindful of and we have some green flags or comfort flags if you will. Let's look at the red flags. There is something called the SNOOP mnemonic. Systemic symptoms, such as fever or weight loss; secondary risk factors like HIV or cancer; neurologic symptoms or signs; onset that's new, sudden, abrupt, or split-second, such as our worst headache of our lives; an older patient, especially somebody over the age of 50 who starts with headache over the age of 50; and then a pattern change especially if headaches now start occurring at night or awaking them from sleep, that's a red flag and diagnostic testing is indicated if any red flags are present.

Our green flags include a stable pattern of six months or more; longstanding headache history or a family history of a similar headache; normal exams neurologically and perhaps you'll get a story that they're consistently triggered by certain factors like hormone cycle, specific sensory input like bright lights or loud noises; weather changes and yes, weather changes can contribute to a migraine headache. Diagnostic testing is not indicated if only green flags are present.

### Slide 19 – If Indicated, Which Diagnostic Test?

If indicated though, which diagnostic test do we go with? CT or MRI and then with or without contrast? Well, you need to keep in mind that the yield is minimal without neurologic signs. Less than 1% of the time is a cause for the headache identified by imaging. MRI is going to give us greater detail, but we know that we get more false-positives. MRI for posterial fossa disease is the imaging of choice and an MRI/MRA for suspected aneurysm or other vascular lesions. And then for someone presenting with the worst headache of their life for example, a CT without

contrast to rule out that subarachnoid bleed. You always have to weigh radiation exposure with the CT and renal contrast concerns with CT and MRI versus the potential yield that you're going to get out of that study. Remember the Choosing Wisely initiative tells us not to perform neuroimaging studies in patients with stable headaches that meet criteria for migraine.

Now, I'm going to turn it back to Dr. Delmonico who's going to tell us a little bit more about our case.

Slide 20 – Back to Lizzy

**Matt Delmonico:** Thanks, Dr. Burke. Back to Lizzie, you get a further history and she notes that she used to have more common migraine headache symptoms as a teenager and these changed over time to be less intense, but daily, sinus-type headaches. And as we discussed earlier with Dr. Burke, this can still be signs and symptoms of migrainous headaches.

In two studies, 86% to 88% of patients self-diagnosed to sinus headache actually meant ICHD criteria as migraine or probable migraine. Based on a diary review, 94% of headaches that prompt a visit to the PCP are migraine-type headaches. We diagnosed Lizzie with migraines. The appropriate treatment was provided and you helped reduce her headaches by 50% over the next couple of months.

Slide 21 – Key Takeaways

Some key takeaways from this case and discussion: if you have a patient that diagnoses themselves, don't assume they're right, which I think we can always agree with. Migraine is the most common cause of headache that brings a patient to the doctor. Recurring moderate-to-severe headaches is migraine until proven otherwise. Migraine patients can experience many different types of headaches from the same underlying mechanism and prompt treatment may restore normal neurologic function and prevent the evolution of episodic migraine to chronic migraine.

I will now turn it back to Dr. Burke.

Slide 22 – The Many Manifestations of Migraine

**Susan Burke:** Now we're going to hear about the many manifestations of migraine and I'm going to focus on current approaches to management. We're going to hear from Dr. Schim some exciting new therapies, as well as non-pharmacologic therapies that we can use for successful management of migraine headaches. But before I begin the current approaches, let's hear another case from Dr. Delmonico.

Slide 23 – Ricky, a 31-year-old CPA

**Matt Delmonico:** Thanks, Dr. Burke. This case is Ricky, a 31-year-old CPA. He has a history of very occasional migraines since his early 20s and naproxen and/or a triptan usually provided relief; however, he started a new job about six months ago, which is requiring him to work long hours. Headaches have increased and now occur several days a week, especially on most weekend days for the last few months.

He is now taking an abortive medication most days a week. I'm going to turn it back over to Dr. Burke to talk about headache treatment.

### Slide 24 – Headache Treatment

**Susan Burke:** Thank you, Dr. Delmonico. We can break down migraine treatments into acute or abortive; preventive, that is taken to reduce the attack, frequency, severity, and duration of attacks; non-pharmacologic, which includes behavioral, neuromodulation, and complementary and alternative treatments, but the first line is a very important aspect of headache treatment and that is education of the patient.

### Slide 25 - Principles of Management for the Patient

There are several principles for managing the patient. We need to talk to the patient and establish realistic expectations. In general, we can hope for about a 50% reduction of headaches with prevention. We should shoot for about a 70% relief with acute treatment, but it's important to stress to them that there is no cure. We must encourage patients to participate in their care. They can keep a headache diary, try and identify triggers. Some don't want to see that chocolate is a trigger or things that they like, like cheese on the pizza is a trigger, but we have to have them work with us to try and cut down on some of their headaches.

They also have to accept that some treatment side effects are inevitable. We've all had patients come in and say they've had a side effect to everything. "Oh, I get a dry mouth from the tricyclic, etcetera but that butalbital compound or the certain opiate, that is the only thing that takes away my headaches." Well, that's fine but that's not where we're going. You have to help them understand that "Okay, dry mouth or bad headache, you make the choice." The patient has to get involved in their own management to some degree. You want to optimize behavioral management, have them keep that diary. Acutely, you want them to take their medicine early. You also don't want them to overuse the medicine where they start getting into a medication overuse headache situation.

In general, the rule is don't use an abortive agent more than two to three times a week or nine days a month. With prevention, you want to follow the guidelines for the various treatments that we're going to be talking about. And then regular patient follow-up with adjusting the dose, the drug combination, etcetera. This isn't a disease where you'll start a therapy and then say "Oh, see you in six months." We do have to start low with most of the agents that we use and build them up slowly. We might have to use different combinations, but it takes time and it takes frequent tweaking of the drug regimens.

### Slide 26 – Behavioral Strategies

With regard to behavioral strategies, and Ricky is a prime example of someone who has changed his sleep patterns. Now, he's probably sleeping as a CPA in a new job, he's sleeping maybe five, six hours a night weekdays. Then what does he want to do? He wants to sleep in and catch up on his sleep on a weekend. But in sleeping in, he is actually triggering a headache. You want sleep to be consistent, six to eight hours consistent within one hour between going to bed and getting up even on weekends. Any exercise is better than none. Aerobic tends to be a little bit better than non-aerobic. Stress management for any disease

seems to be important and appropriate. Biofeedback and relaxation, there are many apps out there that they can use. There's cognitive behavioral therapies that they can do.

Decreasing substance use, so this is a real kicker for some people who find that caffeine may be some type of trigger and they need to taper their caffeine to a maximum of one six-ounce cup. I don't know whether too many doctors could follow this regiment, but it is something that we need to have our patients aspire to and start to decrease caffeine, especially if they're overusing that agent. Eliminate artificial sweeteners, decongestants, and of course everyone in the world should eliminate smoking. You want them to eat fresh, non-processed foods, maybe small, frequent healthy meals and snacks. Some people might find that if they switch to non-processed foods that might cut down on their headaches. Some people get triggers from the strangest things, monosodium glutamate, sulfates on a salad bar, onions. There are so many things that they need to be mindful of, but non-processed foods in general are going to be healthier option for our patients.

### Slide 27 – Acute (Abortive) Migraine Medications

This shows the acute abortive migraine medications that we should be offering our patients. Non-specific drugs, such as NSAIDs are considered first line, but remember, patients likely already used or unfortunately maybe abused these drugs and already failed them, that's why they're coming to you for help, combination analgesics, neuroleptics, antiemetics, and steroids. Specific drugs include triptans and ergotamine, dihydroergotamine products. We have some new formulations that are FDA-approved mostly sumatriptan, either a dry powder or an auto-injector and there are new formulations in development of agents that we are somewhat familiar with like the triptans and DHE, as well as some new agents on the horizon, the gepants and the 5-HT1F receptor agonist lasmiditan, which we'll hear more about from Dr. Schim in a moment.

Choosing wisely, as I highlighted before, don't recommend prolonged or frequent use of OTC pain meds for headache because of the problems that we can run into, including medication overuse. Also, remember the rule of treating, not more than two headaches a week or nine headaches a month with an abortive or at least not with the same abortive. We really want to try and prevent these headaches from happening. Trigger management, behavioral management, drug management, and then prevention therapy.

### Slide 28 – Polling Question 4

### Slide 29 – Guidelines for Initiating Migraine Prevention Therapy

This tells us our guidelines for initiating migraine prevention. Our goals are to reduce disability and medication overuse. We do find that many migrainers qualify for prevention, but few are offered it. One take-home message from today is I urge you to consider prevention earlier in the course of your treatment of a migrainer from now on. You certainly want to institute preventive strategies if the patient is experiencing two attacks per month with disability totaling three days a month or more. They're getting an attack and it's lasting a day or two at a time and they've got to take a vacation day instead of being able to utilize their vacation day for something much more meaningful. They're taking a day off from work because they're having such severe headaches.

Recurring headache significantly interfering with a daily routine despite acute treatment. Presence of uncommon migraine conditions, hemiplegic migraine, prolonged aura, migrainous infarction where we can tend to be much more reluctant to use an abortive agent, such as a triptan in this situation or they're contraindicated completely. Patient preference. Cost considerations. Triptans are not cheap, even the generic ones. A Patient might say "Well, I'd like to use these agents but they're too expensive for me." We will talk about the prevention agents in a moment. Med intolerance, perhaps they don't tolerate the triptan or the dihydroergotamine or the NSAID or whatever agent you're offering. Finally, acute medications, if they're overused more than two days a week, that in and of itself is enough for me to say "I want to start this patient on a prevention medication." If these meds are also ineffective or they had intolerable side effects or they're contraindicated as I mentioned, these are all indications for the use of a preventive therapy for migraines.

## Slide 30 – Polling Question 5

## Slide 31 - Migraine Preventive Therapies

We're going to hear more about what's on the horizon, but right now, the current migraine preventive therapies are shown on this slide. Those with level A established efficacy include antiepileptic agents like divalproex sodium, sodium valproate, and topiramate. I tend to use topiramate a lot in my practice if I am able to. Beta blockers like metoprolol or propranolol. Triptan should only be used as a prevention for someone with a menstrual-related migraine and the Grade A evidence is for frovatriptan. And then a lot of this information is from the Silberstein article from Neurology 2012, but I'm going to highlight that angiotensin-receptor blocker candesartan has some level A efficacy shown that it wasn't available at the time of the Silberstein publication. It's not in the original paper, but it does have level A evidence of efficacy.

Probably effective, the anti-depressants. Amitriptyline is probably my go-to agent there. Venlafaxine can also be effective. There are a couple other beta blockers and a couple other triptans that you can consider use as well. And then possibly effective include the ACE inhibitor lisinopril, some other beta blockers, alpha agonist clonidine, an antieleptic drug carbomezapine is in a level C category, and the antihistamine cyproheptadine which may be used more often in a younger or pediatric population. I'm going to point out, notice that verapamil is not on this list. Verapamil doesn't really have the evidence for migraine. A lot of people want to reach for that. It can be useful for cluster, but it's not really in the categories of effectiveness for migraine headaches.

## Slide 32 – Treatment for Chronic Migraine

There is a treatment for chronic migraine to be aware of. In addition to starting behavioral strategies and the prevention medications, there is a specific FDA-approved medication, onabotulinumtoxinA, which is approved for prophylaxis of chronic migraine, which as we defined before is 15 or more headache days per month. They found in clinical trials that they were eight to nine fewer headaches compared to six to seven fewer headaches with placebo. It entails giving 31 injections in the head and neck every three months and there is a concern for the OnabotulinumtoxinA spreading, causing weakness in a different area. OnabotulinumtoxinA works by blocking the presynaptic release of neurotransmitters and it might block CGRP

release. We're going to hear more from Dr. Schim in just a moment about other new treatments which target CGRP.

I'm going to turn it over to Dr. Delmonico to give us key takeaways for our current approach to treating migraines.

Slide 33 – Key Takeaways

**Matt Delmonico:** Thanks, Dr. Burke. I think some key takeaways from your presentation are that the successful treatment of migraine includes a comprehensive multimodal approach of patient education, behavioral strategies, pharmacologic therapies, and non-pharmacological interventions. Consider preventative medications for prolonged, severe, or complicated headaches or if abortive therapies are required more than two times a week. We will now pass the presentation over to our colleague, Dr. Schim.

Slide 34 – Insights into Migraine Pathophysiology

**Jack Schim:** Thank you very much. Well, we're going to be talking about migraine pathophysiology but first, we have another case. Dr. Damiano, if you could please present our next case.

Slide 35 - Maria, a 38-year-old Female

**Chris Damiano:** Thank you Dr. Schim. Here, we have a case of Maria. Maria is a 38-year-old female, and she's been struggling with migraine since she was about 14 years old. She currently controls her migraines with topiramate 50 mg twice a day and also uses a triptan as needed. She has noticed that over the last three months, her headaches have increased from about one time per week to about three to four days per week despite her optimal lifestyle management and trigger avoidance. Additionally, her headaches are not always relieved by prompt use of triptans. We will now turn the presentation back over to Dr. Schim.

Slide 36 – Polling Question 6

Slide 37 - Migraine Pathogenesis

**Jack Schim:** Thanks very much. Our next phase of discussion is really going to be about the migraine pathophysiology and pathogenesis.

To frame the conversation about migraine pathophysiology, it's important to look at what we used to think of migraine as a vascular headache with throbbing being a function of vasodilatation to the current understanding of migraine as a neurovascular condition that is facilitated by pain augmented within the trigeminal pathway facilitated through that pathway by the release of a variety of neurotransmitters. We believe the most important is calcitonin gene-related peptide. The trigeminal nerve projects all the way down to the brain stem at the trigeminal nucleus caudalis and is, therefore, responsible for the commonly seen neck and shoulder pain in people with migraine.

Slide 38 - Calcitonin Gene Related Protein (CGRP) First Identified as a Potential Mediator of Trigeminal Inflammation

CGRP was initially identified as a mediator of trigeminal information in the early to mid-1980s and first written up as a migraine neurotransmitter in 1985 by Dr. Edvinsson. He identified that trigeminal fibers contain a variety of neurotransmitters, but the CGRP was identifiable there and when released, attaching to its receptors, resulted in mass cell degranulation and vasodilatation. In fact, CGRP is the most important of vasodilators in the nervous system. Trigeminal fibers also release substance P and nitrous oxide, which turned out to not really be that key within trigeminal pain and within migraine.

### Slide 39 – CGRP Receptors Occur at All Sites Involved in Migraine Pathogenesis

With research, trigeminal fibers were then identified as not the only place in which CGRP receptor is found, but in fact, throughout the nervous system and for that matter, throughout the gut. But as you can see there are numerous areas within the brain that are within the pain pathways and where CGRP attaches.

### Slide 40 – CGRP-Targeted Therapies for Headache Disorders — Three Different Targets of Action

The idea that CGRP could be an important target for migraine treatment was first discussed by Lars Edvinsson. We can see several places where CGRP is relevant. First of all, CGRP is released by trigeminal fibers and trigeminal fiber activation has been known to be the locale for triptan action by binding to the 5-HT1B and 1D receptors, but in fact, as a consequence of that blocks the presynaptic release of CGRP. Onabotulinumtoxin likewise blocks CGRP at the presynaptic release level. When CGRP is attaching to its receptor, a complicated receptor that passes through the cell membrane, the option exists for a direct antagonist effect. There are small molecules known as gepants that are shown under Column 3 and the pathway could also be blocked by an antibody to CGRP itself or to the receptor itself. All of these are active areas of research and medication treatment.

### Slide 41 – New, Emerging and Alternative Approaches to Treating Migraine Headaches

Next, we're going to talk about new emerging approaches to treating migraine headaches.

### Slide 42 – CGRP Induces Migraine

Coming back to CGRP and a little bit more of the story, in people who have migraines, CGRP infusion can provoke a headache, headaches that is a very much a migraine-character headache. If someone has a migraine and we sample their blood from their jugular, we see that CGRP levels are very high and in fact, in people who have migraine, chronic migraine that is, their CGRP levels are tonically high. If they take a triptan, which specifically blocks CGRP release and they get relief, their CGRP levels go back towards normal.

### Slide 43 – CGRP in Migraine

To recap that, CGRP is a potent vasodilator. It's released into the jugular system during migraines and CGRP levels are tonically elevated during chronic migraines. The CGRP infusion can provoke a migraine and new medications, gepants that block CGRP can abort a migraine attack about as effectively as a triptan. The new wave of therapies also includes large molecules that block CGRP either at receptor level or by binding the ligands to CGRP itself.

Because these are antibodies, they are too large to cross the blood-brain barrier, except perhaps at exceedingly high levels far beyond what is given physiologically or pharmacologically. We really do believe that their action is peripheral.

### Slide 44 – Small Molecule Approach

The gepants on the other hand are small molecules and potentially can cross the blood-brain barrier. The first gepants were studied and looked promising when they were compared to placebo, as well as compared to triptans, but when given on a chronic daily basis to try to use them as preventives, they cause liver function abnormalities and those initial molecules were put aside. There are, however, some new gepants that are looking quite promising. Rimegepant and ubrogepant have been effective in Phase II and Phase III trials as abortive treatments, and atogepant and it looks like rimegepant are moving toward in Phase II and ultimately hopefully in Phase III trials for preventive therapies. As a broad statement, none of the CGRP-blocking therapies, both the gepants and large molecules, have ever failed to be effective. The issues have always been safety-related with the initial wave of the gepants.

### Slide 45 – Rimegepant – Phase III Trial for Abortive Use

Rimegepant has been in Phase III trials for abortive use and we can see results compared to placebo where pain freedom, a very high level of success was seen in almost 20% of people given treatment, and looking at two hours post, as well as freedom from the patient's most bothersome symptom, MBS, at two hours post dose. This is a new endpoint that has been requested by the regulatory authorities to try to be sure that we're not talking only about pain but about the other aspects of migraine. And as you can see, this disability freedom can persist for many hours after dosing up to eight hours in this particular study. Looking very promising, effectiveness comparable to any of our triptans and safety and tolerability comparable to placebo, it's looking very promising.

### Slide 46 – Large Molecule Approach

In contrast to the gepants, researchers have now been exploring large molocules monoclonal antibodies. There are many antibodies that have been used therapeutically, here we are looking at antibodies that specifically target CGRP or its receptor. There are four medications that have been in studies, three of which are now FDA approved. Erenumab is now approved and it has been studied for episodic and chronic migraine. The dosing is monthly. This medication specifically targets the CGRP receptor and is fully human. Eptinezumab is still in clinical trials. Uniquely, this is a three-month interval intravenous infusion and is being studied for both episodic and chronic migraine. This targets the CGRP peptide, the ligand itself, and is anticipated to be submitted to the FDA in quarter 1 of 2019 and, presumably, if approved, will be available about a year thereafter. Galcanezumab has been studied for migraine, both episodic and chronic, as well as for cluster headache. This medication was recently approved in September and targets the ligand. It is a humanized antibody and is a monthly subcutaneous injection. Fremanezumab also was recently approved. It has been studied for migraine, both episodic and chronic, as well as for cluster headache. This is a humanized antibody and has been studied in both monthly or every three month injections.

## Slide 47 – Erenumab (FDA Approved): Phase III Studies

Here we can see some of the results of the erenumab clinical trials Phase III both in regards to reduction of migraine days for episodic migraine, the STRIVE trial, and for chronic migraine. Interestingly, with this drug, because the chronic migraine data was positive with the Phase II study, the FDA looking at that as well as the context of the Phase III data approves the drug without a Phase III chronic migraine trial. This is approved for migraine anywhere from four days a month on up to every day.

A couple of takeaways from these slides is that first of all, in the episodic migraine data, there's really a trend but no statistical separation between the two doses that we studied at 70 mg versus 140 mg. There was separation from placebo as early as a month. The results show progressive improvement at least during the course of the six months of the study. In the chronic migraine data, which is on the right side of your slide, the study itself was carried only to three months because investigators felt that it may be unethical to keep people with chronic migraine, a much more disabling variant of migraine, on placebo for as long as six months. In the three months of this study, there's no numeric nor some statistical separation between the two doses of 70 or 140 mg but both doses separated from placebo as early as a month.

## Slide 48 – Galcanezumab (FDA Approved): Phase III Studies

The slide shows the results of galcanezumab, which has been studied for both episodic and chronic migraine, specifically looking at the reduction in migraine days across the course of the trial. EVOLVE-1 was a 6-month study and, as you can see, there is reduction even in the first month compared to placebo, which was statistically significant. Both 120 and 240 mg doses were studied, but they were not significantly different. As a consequence, this is approved at 120 mg monthly, with an initial dose loading of 240 mg. The REGAIN study was a study of monthly injections for chronic migraine, and it continued for 3 months. Likewise, as you can see, there was separation from placebo, statistically within the very first month, and no difference between the two doses of 120 mg and 240 mg, and thus likewise, approved for dosing of 120 mg monthly.

## Slide 49 – Fremanezumab (FDA Approved): Phase III Studies (HALO)

Fremanezumab was recently FDA-approved. Here we see the HALO study and likewise, looking at change from baseline in headache days of at least moderate severity, ultimately we're talking about migraine days, these patients were enrolled, they did an online telephone diary to maintain information about their baseline headache frequency and then they continued to use the same diary throughout the clinical trial. Here what we see is it over two different doses, the results were quite comparable up to three months and separated from placebo once again within the first month. Of note, with all of these medications given subcutaneously, is that their T max, in other words, reaching their full blood level takes about a week. In some studies, some improvement was seen earlier than a month, but statistical information is seen at one month and highly significant at every time point.

## Slide 50 – Eptinezumab Phase III CM Prevention

Eptinezumab is the only drug of this category that is being studied that is intravenous where we see results of two different drug doses with relatively comparable results. This is the chronic

migraine study. My thinking in looking at these medications, for the results between two doses are relatively comparable, is that there really isn't a distinct dose response curve once we get into the doses that are effective and that probably means that once CGRP pathways are blocked, we're only going to see a certain degree of improvement. While I mentioned earlier that CGRP is a pivotal neurotransmitter in migraine, clearly, it couldn't be the only important neurotransmitter for all of these people who would be migraine-free.

Slide 51 – New Abortives in Development

Another category of medications in development are the ditans. These are serotonin 1F receptor agonists unlike the triptans that are 1B/1D agonists. As a result of that property for the triptans, they have vasoconstrictive effects and makes them unsuitable for some patients, for example, people with significant coronary artery disease or ischemic stroke.

The ditans have no vascular constrictive properties. There was a drug studied much earlier that hasn't really moved forward, but lasmiditan, which you see the results of here, is positive in its Phase III studies as an acute abortive treatment. The side effects that have shown up in these clinical trials most prominently have included feelings of dizziness or lightheadedness, as well as possibly tingling or paresthesias and tiredness but overall, the results look quite promising, pain freedom seen here in a range of about 30%, it's pretty comparable to any of the triptans and here without any of the vascular risks that we have to consider when we use a triptan for migraine treatment.

I'm going to turn it back over to Dr. Damiano to give you the key takeaways for migraine pathogenesis.

Slide 52 - Key Takeaways

**Chris Damiano:** Thank you, Dr. Schim. As we just discussed, there are several new agents in development that target molecules involved in migraine pathogenesis. One such target is CGRP, a potent vasodilator, peripheral, and cerebral arteries. An example, CGRP receptor antagonists include very small molecules called gepants that are taken orally for acute treatment, as well as large molecules, monoclonal antibodies, injected monthly or quarterly for preventative treatment. All monoclonal antibodies displayed positive results, have a quick onset, and are tolerated with low discontinuation rates. Another class in development includes the ditans, serotonin 1F receptor antagonists. None of the newer agents are associated with vasoconstriction and as with all new agents, close vigilance is warranted.

Slide 53 - Sophie, a 55-year-old Female

Let's move on to another case. Sophie, a 55-year-old female, is diagnosed with episodic migraines over 20 years ago, now has a history of coronary artery disease, decided to embrace a clean lifestyle. She no longer wants to use naproxen and a triptan. She has been given an aerobic exercise regimen and her sleeping schedule has improved; however, she continues to experience headaches nearly five times a month. She's asking if there are any non-pharmacologic therapies that she could use to reduce her migraines. We'll now head over back to Dr. Schim, who will discuss some non-pharmacologic options for the treatment of migraines.

## Slide 54 – Neuromodulation/Complementary and Alternative Treatments

**Jack Schim:** With time, we've learned that there are new options, some of which are neuromodulation and some of which are complementary in alternative therapies.

## Slide 55 – Neuromodulation Devices

I'm going to turn our attention first to some of the neuromodulation devices and you can see a summary of the three available treatments. There's a single-pulse transcranial magnetic stimulator or STMS. This has been approved now for both the abortive treatment and the prevention of migraine. There's a transcutaneous supraorbital neurostimulation. This also has approval for both acute and preventive therapy.

There's now available a non-invasive vagal nerve stimulator known as gammaCore. This presently has approval both for the acute treatment of episodic cluster and for acute migraine treatment. It is under clinical trial development for preventive therapy. Problematically, insurance coverage and the payers have been quite inconsistent in their coverage for these so that usually people are having to self-pay. There are various regimens with each of them, so for example, Cefaly, the transcutaneous stimulator, that manufacturer has a money-back guarantee. The Spring TMS or transcranial magnetic stimulator has recently announced a money-back guarantee. And the vagal nerve stimulator has an initial free trial and it's looking like they're getting better coverage with payers.

## Slide 56 – Single-Pulse Transcranial Magnetic Stimulation (sTMS)

Here we can see some of the information about the transcranial magnetic stimulator. This is a device that is held at the back of the head. If the patient pushes a button, they get a pulse of about a one and a half Tesla, so comparable to an MRI but unlike the repetitive banging that you might be familiar with if you've ever gone and undergone an MRI. This is really just a single click. You really can't feel anything. You can see the results here in terms of improvement in pain compared to a sham, which basically just made a click. And what I'd seen clinically is some patients having very dramatic response. For example, one person who's having migraine aura, it was initially developed and improved for migraine with aura, she was experiencing migraine aura and with two pulses, the little squiggles went away and her headache never actually developed. We've seen this as potentially viable issue or option, the problem being of course the cost of it is out-of-pocket and for most people, not covered by insurance.

## Slide 57 – Transcutaneous Supraorbital Neurostimulator (tSNS)

You see an image of the transcranial supraorbital neurostimulator. This is really kind of a TENS-like unit that people attach to their forehead. There's a little electrode and the device is attached to that and gives pulsing that can be done for 20 minutes at a time. In its clinical trial, it's a small trial, 67 people, you can see that there was a significant improvement in headache days when used preventively and when looking at acute treatment, there's significant improvement in pain. The negatives are that it feels kind of odd to have a continuing paresthesia on your forehead. Some people really don't like that, but if they find that it's ineffective or they don't like it, they can return it to the manufacturer, money-back. There is a bit of a ongoing cost of replacement electrodes which is estimated as about $25.00 every 2 months.

### Slide 58 – Non-invasive Vagal Nerve Stimulator

The most recently approved device or neuromodulatory device is the non-invasive vagal nerve stimulator. Vagal stimulation has been available for decades as an implanted device for the treatment of refractory epilepsy and for refractory depression and so we know that it's safe to have potentially thousands or millions of pulses. But that's really beyond the needs of most of our patients and so what we're looking at here is a handheld non-invasive device. It specifically activates vagal afferents. It doesn't cause pain, it doesn't cause bradycardia or bronchoconstriction, and in clinical trials, it's been shown to inhibit cortical spreading depression, which is the physiologic correlate of aura, as well as dampen trigeminal vascular overactivity, down-regulating activity at the trigeminal nucleus caudalis and basically reducing the central sensitivity that is the basis for migraine. It's been initially approved for the treatment of episodic cluster headache about a year and a half ago and more recently about a half a year ago for the acute treatment of migraine. This likewise, as with the other devices, appears to have no serious side effects and is considered a minimal risk device by the FDA.

### Slide 59 – Investigational Device

Here you see an image of a new interesting investigational device not yet approved. It's really kind of a skin patch that people put on their arm and by having electrical stimulation, this appears to modulate the dissenting tracks of pain in the brain, turning off migraines. It has really no contraindications that have been shown other than, of course, skin breakdown at the site that one is placing it, so place it somewhere else. This is still in clinical trial, so this is not yet FDA-approved.

### Slide 60 – Complementary and Alternative Considerations

In addition to devices and prescription medications, there are a number of complementary and alternative options for our patients with migraines. Commonly, I will have conversations with patients about the particular supplements that you can see here, riboflavin, magnesium, and there's some evidence likewise for CoQ10 as preventives. Those need to be taken on a daily basis and they're very specific doses that have been shown to be beneficial. In addition, as you can see, there are a variety of other options that people have explored, some of which have reasonably good evidence, acupuncture, some of which have let's say widespread acceptance or a generally good idea like a routine exercise regimen and possibly yoga. Hypnotherapy may be of help. Massage I think is less well-evidence-supported, as I would have to say as homeopathy and maybe Tai Chi. But all of these have advantages that they are patient-empowering, they by and large have little to no side effects, and they can really be layered on along with any pharmacologic approaches that we typically would use.

I'm going to turn things back over to Dr. Damiano to give you the key takeaways for migraine.

### Slide 61 – Key Migraine Takeaways

**Chris Damiano:** Thank you, Dr. Schim. As discussed, recurring headache with disability is a migraine until proven otherwise. We should counsel our patients to institute acute therapies as soon as possible after the headache offset and that the use of acute medication greater than nine days per month can lead to medication overuse, their transformation to chronic migraine. We discussed preventative treatment options and they should be offered early to reduce the

adverse outcomes. We also discussed newer modalities, such as CGRP antagonists, neuromodulators, and complementary options, that may supplement the therapeutic benefits offered by more traditional therapies.

Slide 62 – Residency Connect

**Matt Delmonico:** As part of this educational initiative, Rockpointe is establishing the Residency Connect website. This brand-new destination created specifically for residents and fellows will extend the educational experience and allow clinicians to make connections with their colleagues and invited medical experts. Visit Residency Connect to find the CME-certified online activities, clinical tools and apps, patient resources, and other subject-specific features. Start connecting now on Residency Connect.

Slide 63 – Thank you

**Jack Schim:** I'd like to thank all of you for joining us today. To receive credit for this program, you should take the post-test and evaluation. To do that, close this window to return to the Open Activity screen and then click the Continue button. Taking a few minutes to do this will help us gauge the clinical impact of this activity and try to make sure that our future CME programs are really attuned to your specific interests and needs.