Diagnosis, Treatment and Prevention Therapies in Primary Headache Disorders

Overview

Primary headache disorders are a major cause of disability and a common reason people seek medical care. However, distinguishing a primary from a secondary headache disorder, as well as among primary headache disorders, is often challenging. Focusing on cluster and migraine, **Drs. Jessica Ailani** and **Stewart Tepper** provide criteria and strategies to overcome this challenge in the office setting. Insight is also provided to help guide treatment with evidence-based medications and devices, including new options. The real-world use of shared decision-making to individualize patient management and improve patient outcomes is brought to life through the use of whiteboard animation.

Target Audience

This activity is intended for headache specialists, neurologists, primary care physicians, pain specialists, OB/GYNs, nurses, nurse practitioners, physician assistants, pharmacists, medical students, and residents.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Apply guideline-based diagnostic and evaluation strategies to diagnose and differentiate migraine from cluster headache and other primary and secondary headache disorders
- Evaluate acute and preventative pharmacological therapies to develop an individualized treatment plan
- Foster stronger patient adherence through shared decision making
- Utilize the shared decision-making process with patients who have a primary headache disorder to individualize treatment

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Obtain your CE/CME credit at: https://annenberg.net/headache-disorders-cme

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Editor's Note: This is a transcript of the activity. It has been edited for clarity.

Hello. I'm **Dr. Jessica Ailani**. I'm a professor of clinical neurology and the director of the MedStar Georgetown Headache Center in Washington, DC. I'm joined tonight by my colleague and good friend, Dr. Stewart Tepper, who's a professor of neurology at the Geisel School of Medicine at Hanover, New Hampshire, and also the director of the Headache Center at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire.

Dr. Tepper, and I are going to talk about headache disorders today. And the title of our talk is Diagnosis, Treatment and Prevention Therapies in Primary Headache Disorders.

Dr. Tepper is going to start us off by having a discussion on the burden of headache disorders.

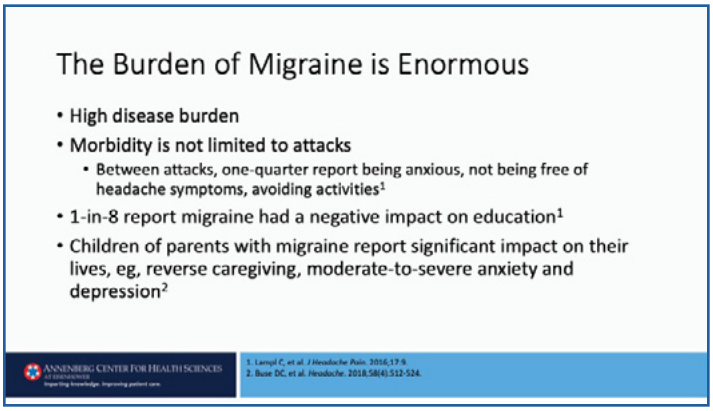
Burden of Disease

Stewart J. Tepper, MD

I think it's useful in headache disorders to follow the International Classification of Headache Disorders, which is now in the third edition. And we'll keep coming back to this. But we think about headache disorders in 3 major groups: primary, secondary, and other.

The primary headache disorders are migraine, tension-type, the trigeminal autonomic cephalalgias, of which cluster is the most important, and other primary headache disorders.

The secondary headache disorders include traumatic secondary headaches, vascular and nonvascular intracranial abnormalities, and those due to substances, infectious diseases, metabolic, or homeostatic changes, facial or cervical problems, or psychiatric.



And then the cranial neuralgias and facial pain syndromes are classified in a third group.

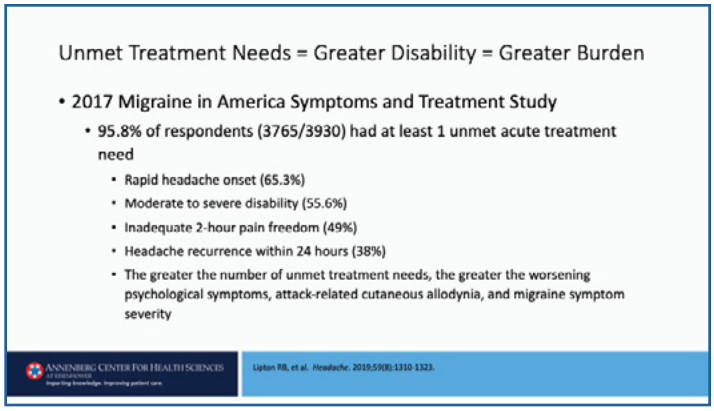
Headache disorders, and migraine in specific, are one of the leading causes of disability worldwide. And the World Health Organization in evaluating years lived with disability rated headache disorders as number 2, second only to low back pain. That's because migraine is a chronic disorder and because it's disabling and chronic, people live a lifetime with these recurrent, disabling headaches.

There's a high disease burden. And as I pointed out, morbidity is not limited to the attacks. Not only are there comorbid illnesses associated, but in between migraine attacks, one-quarter of people report being anxious, not free of headache symptoms, avoiding activities, and cognitive dysfunction and brain fog is often reported.

One in 8 people report that migraine had a negative impact on education, and children or people with migraine report significant impact on their lives. Reverse caregiving, where the children have to take care of the parent, moderate to severe anxiety and depression.

Unmet treatment needs lead to greater disability and also leads to greater burden, and unmet treatment needs account for a significant proportion of migraine burden. Even when taking preventive or acute treatment, migraine patients report moderate to severe headache-related disability.

The Migraine in America Symptoms and Treatment study, or the MAST study evaluated over 3000 patients, and 95.8% of those responding had at least 1 unmet acute treatment need, if you just talk about acute treatment needs. About two-thirds felt that the headache onset was rapid and not met by the acute treatment. Disability spiraled out of control in more than half. Inadequate, 2-hour pain freedom was reported by half and the headaches recurred within 24 hours in more than a third.



And the greater the number of these unmet treatment needs, the greater the worsening psychological symptoms, attack-related sensitivity to skin touch, and other migraine symptom severity. So, approaching acute treatment to try to obtain optimal treatment is likely to reduce disability and burden of the disease. And it's very important to try to get optimal acute treatment.

Optimal acute treatment, which is really getting somebody to get pain-free within 2 hours and not have to retreat and not have the headache recur over the next 24 hours, which is referred to as a sustained pain-free response, can be measured by certain patient-reported outcome tools.

In the American Migraine Prevalence and Prevention study, a very large population-based study, it turned out that poor acute treatment was associated with an increased likelihood of transforming from episodic to chronic migraine. These were people with migraine in the population

and 5,681 of them were evaluated at the beginning of 2006. And by the end of 2007, 3.1% had progressed from episodic to chronic migraine.

That is from less than 15 headache days per month to 15 or more headache days per month. But on the right, you can see that the likelihood of that transformation went up from 3.1% to 6.8% when patients had very poor acute treatment as measured by the Migraine Treatment Optimization Questionnaire (mTOQ) score.

On the other hand, if someone had optimal maximum acute treatment efficacy, that is, a very high likelihood of a sustained pain-free response, then the likelihood of progression to chronic migraine was only 1.9%. So, inadequate acute treatment efficacy was associated with an increased risk of transformation to new onset chronic migraine over the course of 1 year.

Jessica Ailani, MD

As we just heard, managing acute migraine attacks is extremely important to try to prevent disease progression.

When we look at surveys that are done asking patients what are their needs and wants from their acute migraine treatment, we see that complete pain-relief, that's fast in onset, that gets rid of the migraine and the migraine doesn't reoccur, so that you don't have that 3 day, 4 day attack that keeps coming back and you keep needing more treatment for. That's really important to most of these patients. Over 80% of patients in this survey responded that these are the most important things to them when it comes to acute treatment.

It's important since we've been talking a lot about migraine, as migraine is a common reason people come in to see us as a neurologist, but also a common reason people will come in to talk to their primary care doctor about a headache disorder, that we don't forget about other primary headache disorders. And a great example of another important primary headache disorder is cluster headache attacks.

Cluster headaches are known to be so severe that often they're called suicide-type headaches.

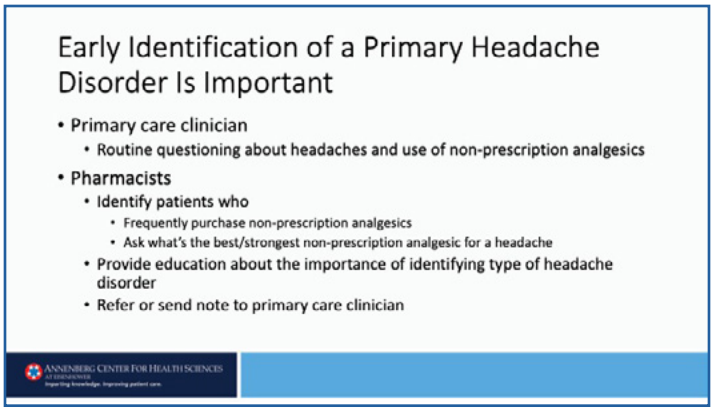
As we've learned from this section that the burden of headache disorders, primary headache disorders, is very high. We see a high burden for patients with migraine, who often are not prescribed migraine-specific treatments.

It's also important to realize that though migraine is a very common type of headache disorder and often the one that comes into the clinical practice most often, that there are other types of primary headache disorders, and a great example of this is cluster headache. And these types of other headache disorders can also carry a high burden, with cluster headache carrying a higher burden of disease than migraine itself. If the appropriate diagnosis is not given, appropriate treatments are not started, so these patients can often go decades without the right treatment plan, leading to an even higher burden of disease.

Screening and Diagnosis

Stewart J. Tepper, MD

Diagnosis becomes a very, very important aspect of this. I mean, does the patient have a primary headache disorder like migraine or cluster, or does the patient have a secondary headache disorder? And does the patient have something more rare? And early identification of a primary headache disorder becomes very, very important in separating this, which everybody's worried about, from a secondary headache. So that screening and diagnosis become key in deciding how to proceed.



For primary care providers, that kind of routine questioning is very important. Pharmacists should identify patients who frequently purchase nonprescription analgesics or who ask, "What is the best or strongest nonprescription analgesic for a headache?" That's often a telling sign that that particular person has chronic migraine. And pharmacists have the opportunity to provide education about the importance of identifying which type of headache disorder that person has and of referring that person or sending a note either to the primary care clinician or to a neurologist or a headache specialist, if they're worried about the overuse of those analgesics.

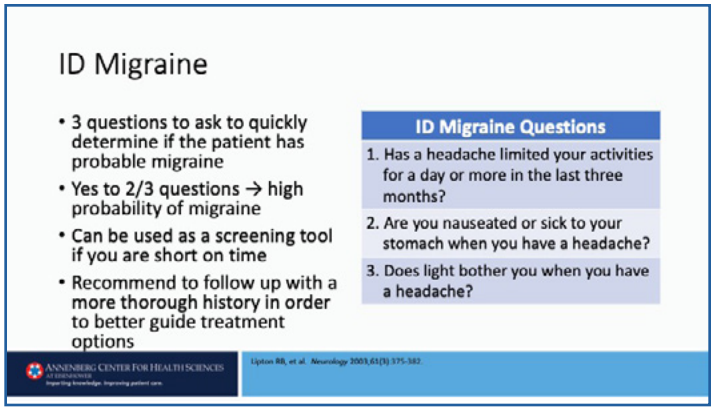
Jessica Ailani, MD

What is important to realize is making a diagnosis of a primary headache disorder really relies so much on the history, the details of the history, and a generally normal physical exam. So, these 2 components are all it takes to make the diagnosis. The details can separate a primary headache disorder from concerns that lead us to think about a secondary headache disorder. And we're going to talk a little bit about what these details are and how we can really gather that type of information.

Some of the first critical features we're looking at when we're talking to a patient about their headache, are what are their associated symptoms? Where is their pain located? What does it feel like? How long has it been there? Did something occur when it first started? Did you used to have headaches and then they got worse after something happened, like you started a new medication for depression, or you injured your head at a sporting event, or you are now starting to get your periods or going through perimenopause? Which are major life events that can definitely trigger change in headaches. These types of details are extremely important in understanding the pattern of headaches the patients are having and helping us make the diagnosis. The other important factor is that oftentimes the patient's coming in very anxious about the particular headache they're having and they might be losing their job, or they missed a major life event, but we want to understand their history.

When did you ever have a headache first? What was it like back then and how has it changed over time? So really taking a few moments and rewinding back the history and starting at the very first headache and really slowly moving it forward.

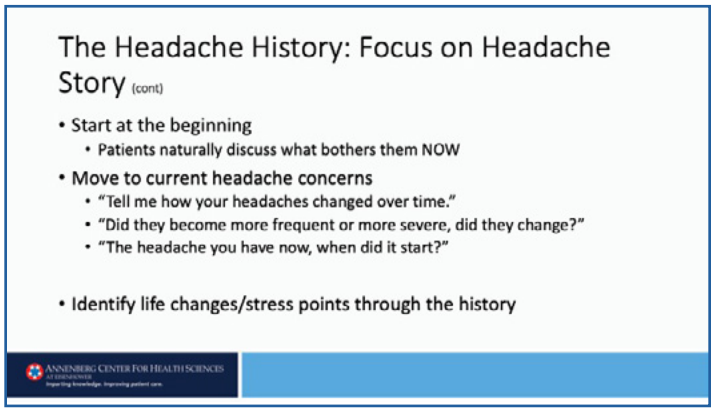
There's a great survey tool that's been validated called ID Migraine. It's 3 simple questions that you can ask the patient. And if they answer yes to 2 out of the 3 questions, there's a very high likelihood that the patient has migraine. And the questions are pretty easy to remember, or you can just print it out and hand it to the patient. You want to ask them if they've had a headache that's limited or stopped their activity sometime in the last 3 months. That's implying some limitation of physical activity because of the headache. You want to ask them if, with a headache, do



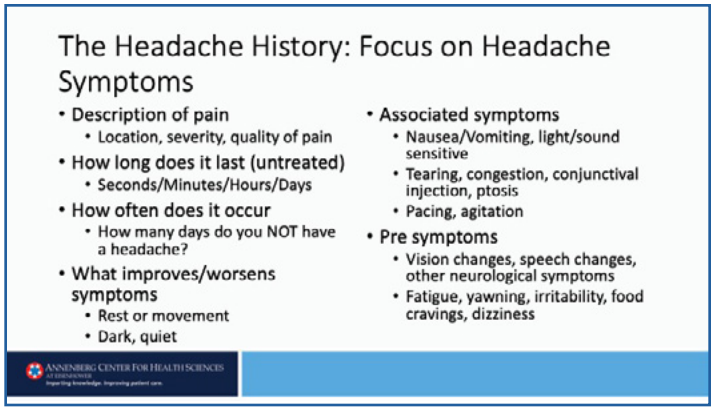
they get sick to their stomach or feel queasy or nauseous? You want to ask them if light bothers them more so with the headache than other times. And if they answer yes to 2 out of 3, like I said, there's a very good chance that they probably have migraine and you might want to sit down and have another conversation with them.

Let's talk a little bit about how we ask our patients the right questions so that we get that good story and we can get a better sense of what the diagnosis might be. As I said, the patients usually want to talk about right now. The headache I had yesterday, that's why I'm here today. Well, we want to ask them about headaches they've always had. And try to see if there was any sense of headaches when they were younger, even if they skipped a meal and they get a headache, or they ran around too much in the sun and they got a headache, that's still important information to know.

You can then ask them what kind of details they do recall. Not get too fixated on dates and times, but whatever details they remember can be very helpful. And the whole thing is that you're trying to build this story, is this a historical pattern that's always been there and has gotten worse in time because of some major event? Or is this a new type of headache they're having? And that might be a little bit more concerning.



You want to focus a little bit on the current headache they're having. How is it different if they've had headaches before? Is it more frequent? Is it more severe? Is the location different? Do they have new types of associated symptoms or is it the same, just more often? Tell me how your headaches have changed over time. Are they more frequent or severe? When do you think it started to get worse? What was going on in your life around that time? Sometimes headaches can get worse with major life stresses, that can really impact the brain and how the brain handles different things. So, anything happening around that time, did you move, did you have a change in your job? Anything going on in your life, good or bad?

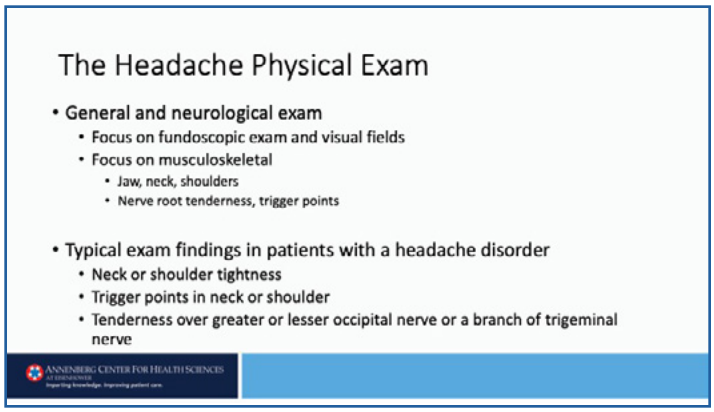


We can often ask them a list of different type of information, but a lot of times I just like to sit back and listen to their story. We actually have studies that show us just listening and asking open-ended questions will give us most of the history we need, rather than asking questions that are very brief and to the point. Through the questions, through their story, we really want to get a sense of the description, location of pain. Think about the words they're using to describe. We'll often hear things like, "A jackhammer to my head. Someone's pulling my eye out. There's a demon in there who's trying to get out." And these are all the words that patients are using in clinic to describe their headache types. And after a while, you'll notice that it's very similar, the stories sound very much the same.

We want to know how much their headache is impacting their life. There's a multitude of questionnaires that we can use, especially if we're rushed for time. These can be done before the patient even starts the visit. Examples of this is the HIT-6 or the MIDAS Scores.

We also want to understand what their goals and their fears are. Is this a patient who's like, "I'm here today because I want a cure? I never want to have another headache again." Is this a patient who just wants a better quality of life? Each of these goals are really important to address and the conversations we're going to have with a patient are very different based on the goals they have.

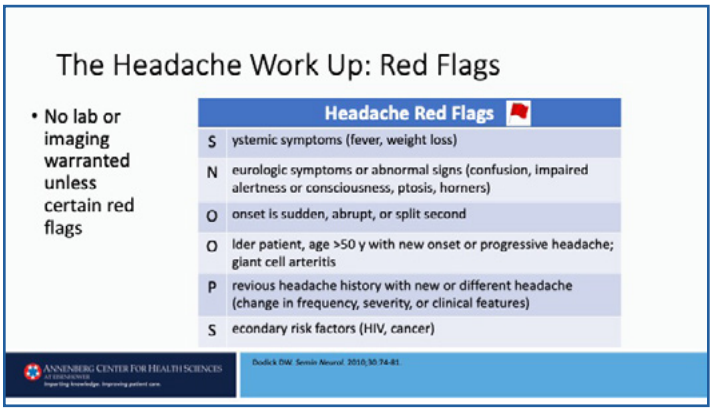
In headache disorders, especially for primary headache disorders, and most particularly in patients with migraine, patients with migraine tend to have other types of medical disorders that travel with migraine, like depression, anxiety, obesity, sleep disorders. Other pain disorders, like fibromyalgia, neck and back pain, gastrointestinal issues, cardiovascular issues like hypertension or a history of stroke, and sometimes endocrine disorders, also asthma and allergy disorders. It's important that we understand if they have any other medical problems, if they're taking other medications, and how that might impact decisions we make later on about treatment, but also how those medications might impact the headaches that they're having now.



There is a physical exam that's important we do on all of our patients. We like to do a nice general exam, making sure it's normal. A neurological exam with a focus on a funduscopic exam, making sure that they don't have papilledema. We also want to focus in on our musculoskeletal exam, feeling for neck and shoulder tenderness or trigger points. We feel the jaw to see if it's displaced or if there's any tightness in the masseter indicating that there might be some bruxism that can be contributing, not the reason they have migraine or a headache disorder, but contributing to their headache disorder. Is there any nerve root tenderness over the greater occipital nerve or the auriculotemporal supraorbital nerve?

Sometimes in a patient who says they're only having 1 migraine day a month or 1 headache day a month, you do a physical exam and you find them to have tender points, and they're telling you they're completely headache free. That's often the time when I start to probe a little bit more about how many days they're completely symptom-free and you start to hear a very different story. "Well, I have 1 that's very bad a month that puts me in bed, but I basically have a headache every day." So, that physical exam can also help cinch your diagnosis. So, it's very important.

There are sometimes cases where we hear something in the story, or we see something in their past medical history that's concerning. We call these headache red flags. These are things that we're looking for that indicate to us that perhaps this patient is going to need magnetic resonance imaging (MRI) of the brain to evaluate for a secondary headache disorder.



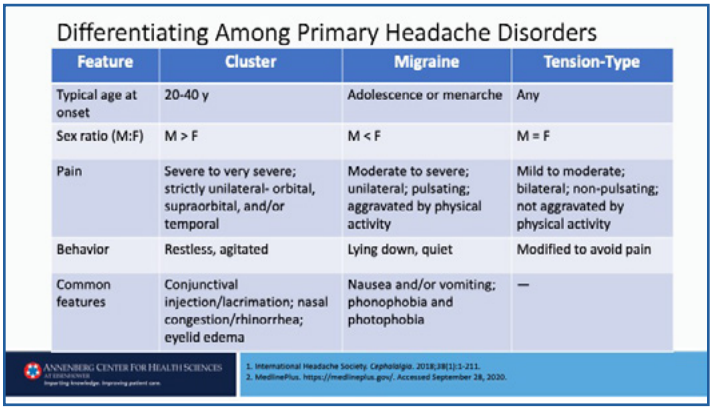
Stewart J. Tepper, MD

I think it's important to be very familiar with the primary headache disorders, at least the most common ones. And after considering the SNOOP mnemonic that Dr. Ailani showed you, where red flags for secondary headaches are eliminated, one is usually left with a primary headache disorder, which is 90% of all headache disorders. And remember, the primary headache disorders—although we know a lot about pathophysiology—are not secondary. Going back to what we talked about at the beginning, the International Classification of Headache Disorders, headaches are grouped into primary and secondary, and there are 4 categories of primary headache. And the classification itself uses the most commonly reported symptoms to create the criteria for diagnosis. They are very extensively validated and the first ICHD was published in 1988. So, we have years, decades of validation of the symptomatology and the association with a particular primary headache disorder.

Looking at the 4 big primary headache disorders, migraine, trigeminal autonomic cephalalgias, and then tension-type, and what are referred to as other primary headaches. Migraine has over 40 pages in the ICHD-3, because it can come in episodic and chronic forms, with and without aura, status migrainosus, menstrually-related migraine. It comes in a variety of types of aura. Learning about migraine becomes very important. Tension-type headache is generally not disabling and rarely do patients complain of true tension-type headache alone in the office. Trigeminal autonomic cephalalgias include cluster paroxysmal hemicrania, hemicrania continua, and short-lasting unilateral neuralgiform headache (SUNHA), the most common of which is cluster.

And then there are other primary headache disorders that are often missed, but which can be quite treatable, such as primary stabbing headache, primary cough headache, primary exercise, or primary headache associated with sexual activity. And then more difficult to treat other primary headaches such as new daily persistent headache or nummular headache.

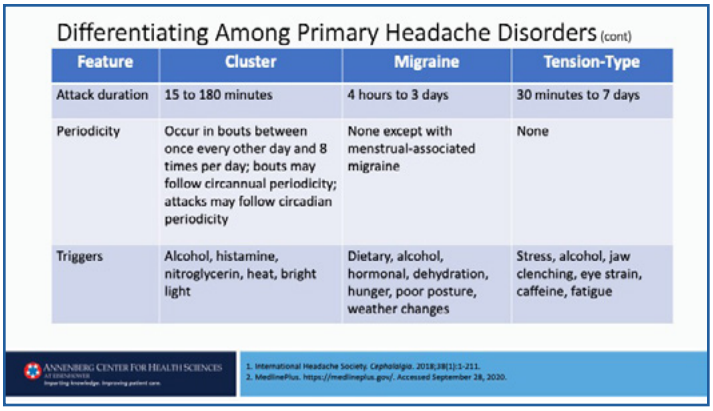
Differentiating migraine, cluster, and tension-type is very useful. Let's actually begin in the middle with migraine, which generally has an adolescent or menarche onset in terms of female patients. Male patients can get their migraines in childhood and have it go away in adolescence or it can come on in their 20s. But remember, migraine is a female predominant disorder, 18% vs 6% prevalence.



Migraine is moderate to severe, often unilateral, throbbing in quality, aggravated by routine physical activity, and the latter results in what Dr. Ailani talked about, the fact that a person with a migraine tends to lie down in a dark, quiet room. That's not true of cluster. The associated features of migraine are nausea or photophobia and phonophobia, both or all 3. Now, comparing that to tension-type headache, tension-type headache can come on at any time, is equally frequent in the genders, male and female, but tension-type headache is best diagnosed by being not migraine. It's not severe. It's not unilateral. It's not throbbing. It's not aggravated by routine physical activity. And behavior is rarely modified to avoid pain, and certainly they don't go to dark, quiet rooms.

Most of the time when somebody thinks they have tension-type headache, they actually have migraine and migraine can occur in lower intensities that make it disguised as tension headache, but then it turns out people have a spectrum of migraine. So, tension-type headache, while common in the general population, is rarely a cause of people coming into the office.

Cluster headache is completely different. Cluster headache is a male-predominant disorder. Onset is generally in middle-age. Severity is more severe than migraine. And as Dr. Ailani described, the patients are intensely restless and agitated due to the severity of the pain. A cluster attack is strictly unilateral, generally around the eye or temple, and is associated with cranial autonomic symptoms of a red eye, tearing eye, nasal congestion, rhinorrhea, eyelid edema, facial flushing, all on the



same side as the attack. Then the attack is generally 30 minutes to 2 hours, can be up to 3 hours. It's generally 45 minutes to an hour in duration, often at the same time of day. And as Dr. Ailani said, multiple times a day during a cluster period or cluster bout. Cluster does not look like migraine or tension type headache. I too have had cluster patients have an attack in the office and it is very, very upsetting as noted in that video.

Let's go through again, migraine duration, untreated, 4 hours to 3 days. Tension type, it's anything. It's short, it's long. Migraine periodicity is not really documented except menstrually-associated or menstrually-related migraine, although migraine attacks are more... At least 50% of migraine attacks do happen in the morning, but it's not exactly at the same time every day for a migraine patient. It's not like a cluster patient. No periodicity to tension headache. Remember, tension-type headache is not migraine.

Migraine has a variety of triggers: diet, alcohol, hormonal, dehydration, hunger, poor posture, weather change. Tension type headache, generally stress-related but also alcohol, jaw clenching, eye strain, caffeine which can also be a trigger for migraine, and fatigue which can also be a trigger for migraine. Cluster duration, generally 30 minutes to 2 hours. The range is 15 minutes to 3 hours, but usually about a 45-minute to 1-hour attack. So short, and in between the attacks, generally cluster patients are pain-free. Occasionally, they'll have a ghost-like pain on the side of the cluster.

There are 2 types of cluster. There are clusters that occur every day without ever remitting. That's chronic cluster. Then there are cluster patients that have bouts or periods of cluster in which the cluster attacks occur once every other day, 3 times a day, 8 times a day. These bouts or periods generally last 1–3 months. In between, the patient doesn't have cluster headaches and the bouts may follow circannual periodicity. As the bouts occur, for example, in spring and fall, so too the attacks that occur daily during the cluster periods may occur at the same time of day, each day.

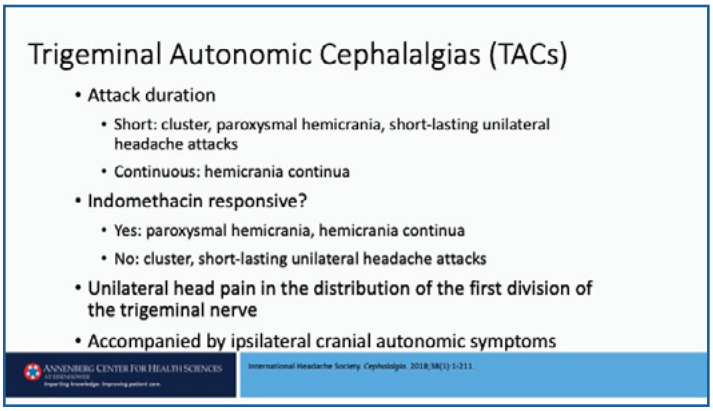
That's not like migraine. That's not like tension headache to have short attacks occurring at the same time of day, excruciating, associated with the cranial autonomic symptoms, and almost invariably triggered by alcohol. Cluster patients in cluster periods almost never drink.

Migraine can come in a variety of forms. As I said, there's over 40 pages of migraine types. Migraine without aura is the most common. The ICHD-3 criteria for migraine without aura require that the patient have had at least 5 attacks.

Migraine is divided, as I said at the beginning, between episodic and chronic. Episodic, which is not really an ICHD-3 term, but which is widely used, is characterized by discrete episodes of migraine, each one lasting 4-72 hours, but in which the total headache days occur less than 15 days a month. Chronic migraine is headache days now occur 15 or more days per month, for longer than 3 months. And on at least 8 days, the headaches reach a migraine level with or without aura, or the patient believes it's a migraine and they take a migraine-specific medicine such as a triptan, and that migraine is relieved by the migraine-specific medicine. So chronic migraine, headache at least 15 days a month, at least 8 days of which meet migraine criteria in one way or another, and this has been going on longer than 3 months.

Medication overuse headache is a secondary form of chronic migraine. Patients, therefore, have headaches on at least 15 days a month, as does everybody with chronic migraine, but the patient has a preexisting episodic migraine history. There's a link from the chronic migraine to a preexisting episodic migraine, and the patient is regularly overusing 1 or more drugs that can be taken for acute or symptomatic treatment of their headache, and that this has been going on for over 3 months.

The ICHD-3 sets the following hierarchy. If a patient is using triptans or combination of analgesics for at least 10 days a month, that's likely to be associated with medication overuse headache. If they're using NSAIDs or simple analgesics, such as acetaminophen, on 15 or more headache days per month, that's likely to be associated with medication overuse headache. And medication overuse headache, and chronic migraine occur together so frequently that treatment needs to address both. Going to the trigeminal autonomic cephalalgias, the TACs. Remember there are only 4. Cluster, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks or SUNHA, and one called hemicrania continua. The first 3 I mentioned are short attacks while hemicrania continua is continuous. The reason they're called trigeminal autonomic cephalalgias is the presence of these prominent cranial autonomic symptoms, the lacrimation, the rhinorrhea, the nasal stuffiness, all on the same side as the headache. Two of these are exquisitely indomethacin-responsive and diagnosis actually requires indomethacin to eliminate the headache, and as long as it's taken, a complete response to indomethacin. Those 2 are paroxysmal hemicrania and hemicrania continua. Paroxysmal hemicrania, which looks a bit like cluster, but is shorter and more frequent attacks during the day, and hemicrania continua, which is a continuous one-sided headache with cranial autonomic symptoms.



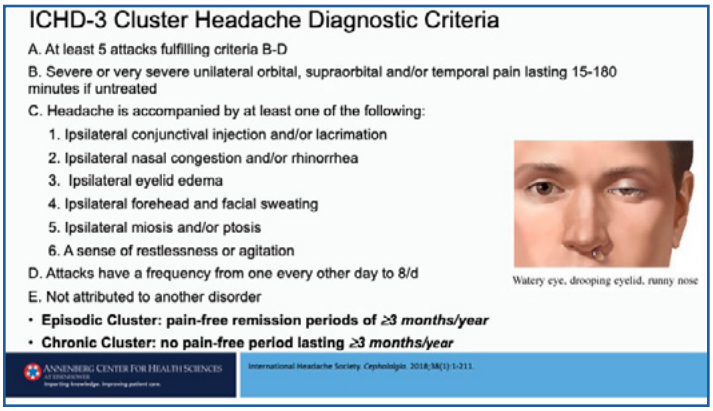
Cluster and short-lasting unilateral neuralgiform headache attacks, neither of those respond to indomethacin, but all of the TACs are associated with unilateral head pain in the first division of the trigeminal nerve. They are almost all at least partially orbital or temporal, and all of them are accompanied by ipsilateral cranial autonomic symptoms, although sometimes cluster is only accompanied by the severe agitation.

The 4 trigeminal autonomic cephalalgias are different, and because of the indomethacin responsiveness to 2 of them and because they have different kinds of treatment, it's worth at least being familiar with the fact that they exist and are differentiated in their clinical features.

Jessica Ailani, MD

It is important that when we take a look at patients who have trigeminal autonomic cephalalgias, we remember those headache red flags, where we think about those patients that have other neurological signs. As Dr. Tepper has talked to us about many of the signs and symptoms of trigeminal autonomic cephalalgias having these autonomic symptoms that come with the headache itself, these patients sometimes will have ptosis, miosis, can look like a Horner syndrome. It's important that we consider what other things can be on the differential diagnosis.

We've been talking a lot about the ICHD-3, our international classification system for headache, and here's our ICHD-3 criteria for cluster headache.



We've talked a bit about cluster headaches when you're having cluster attacks. That's when you're actually having the pain itself. This is often around the same time every day. The patients have a sense of, oh, it's around noon, and then again around 3:00, and then again around 8:00, as they get ready for bed. Many times, they will wake the patient from REM sleep. This can be at nighttime or sometimes even if they just lie down in the middle of the day to take a nap. So, it can be very disruptive to their sleep cycle.

A cluster bout, or a cycle or period, is the time that they're having these cluster attacks. It can usually last several weeks. Average length of time is between 2–12 weeks. It does tend to be seasonal. It can happen more often in the fall, sometimes in the spring. So, season change tends to be the time that you see it the most. Ninety percent of patients have, as I mentioned before, an episodic form of the disease and 10% have a chronic form.

What are the key takeaways from this section? We know that making the diagnosis is imperative in order to understand the type of disease the patient has, what is their headache disorder, to understand if it's a primary headache disorder or if more workup is needed to rule out a secondary headache disorder. As Dr. Tepper mentioned, most headache disorders that are going to come in to see us in clinic are a primary headache disorder. Key features in the history can really help us differentiate what type of headache disorder this person has, and making the diagnosis really helps us target in on what's the right type of treatment option for the patient.

It's important that we identify red flags, so we can think about that further workup, and looking at associated symptoms and how long the attacks are, can further help us make the diagnosis. In the end, the international classification system is extremely helpful in helping us make that diagnosis. These are available for all of us free, online, at their website. You can look at them anytime if you're kind of debating. Do I think it's cluster? Do I think it's migraine? I think Dr. Tepper's tools and tricks can be very useful when you're thinking about, does this seem like cluster? I think these attacks are too long, and they like to lie in bed in the dark. It's most likely migraine headaches.

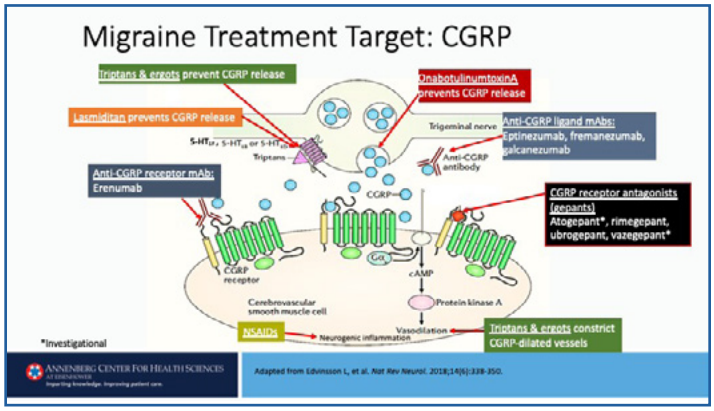
Acute Treatment/Migraine

Stewart J. Tepper, MD

Migraine probably starts centrally and there is evidence for changes in functional connectivity centrally in migraine across, for example, a month in the same patient who was imaged every single day with functional imaging. There were changes that occurred between the hypothalamus and the upper brainstem and the lower brainstem that were stereotypical and changed as the patient went into a migraine and then resolved somewhat in between, and then came back again.

Central change as central generator is probable in migraine, but migraine pain occurs peripherally. It occurs in the meninges, and for most patients, it's mediated by the relief of a single neuropeptide called calcitonin gene-related peptide or CGRP. When CGRP is released in the meninges, it causes intense vasodilation, and the release of neuroinflammatory peptides. The combination of vasodilation and inflammation around the vessels of the meninges is likely the source of the migraine pain, which in turn activates afferents that return to the central nervous system and are processed and patients then get photophobia, phonophobia, and nausea.

And of course, the example of translational research made real is that blocking or removing CGRP terminates migraine acutely and prevents migraine.



It turns out if one looks back at our older drugs, they often have relationship to taking out CGRP. This cartoon from Lars Edvinsson describes what can happen in a migraine. The blue spheres are CGRP being released from a trigeminal nerve and binding to a transmembrane CGRP receptor. In the center, the blue sphere is binding to that CGRP receptor, which when activated with a cyclic AMP mechanism, causes vasodilation and neurogenic inflammation postsynaptically. The question then becomes, how does one prevent or terminate that? Triptans are serotonin 1B/1D agonists. When they bind presynaptically, triptans prevent CGRP release. When they bind postsynaptically to the 1B receptor on blood vessels, they vasoconstrict. The 1D receptor is the presynaptic inhibitor of CGRP release. And the 1B receptor reverses the vasodilation associated with migraine.

Lasmiditan, a serotonin 1F agonist, works peripherally, also, to prevent CGRP release. OnabotulinumtoxinA prevents CGRP release, again, presynaptically. Now with the circulating CGRP needing to bind to the postsynaptic CGRP receptor, there is the possibility of taking out the CGRP effect by binding a monoclonal antibody to the receptor and the anti-CGRP receptor monoclonal antibody is erenumab. Or one can create a monoclonal antibody against the CGRP ligand. Three FDA approved monoclonal antibodies target the CGRP ligand: eptinezumab, fremanezumab, and galcanezumab.

Small molecules have been created that block the CGRP receptor. These are called gepants. Two of them are FDA-approved for the acute treatment of migraine: rimegepant and ubrogepant. One of them, atogepant, had a publication within the late 2020 range that showed that daily use prevented episodic migraine. Vazegepant has been renamed zavegepant in late 2020, and is a nasal gepant that can terminate migraine, but neither atogepant nor zavegepant are FDA-approved yet. Currently, we have rimegepant and ubrogepant as gepants that can terminate attacks as small molecules.

I mentioned that the triptans and ergots constrict the CGRP-dilated vessels postsynaptically with a 1B effect, serotonin-1B, and NSAIDs reverse the neurogenic inflammation that CGRP can trigger postsynaptically.

One can look at all of the medicines, new and old, that have been used acutely and preventively for migraine, and realize that the ones that work peripherally, all target CGRP in one way or another. The old-fashioned preventative medicines, tend to work centrally and interfere with the processing of migraine and are not CGRP targeting.

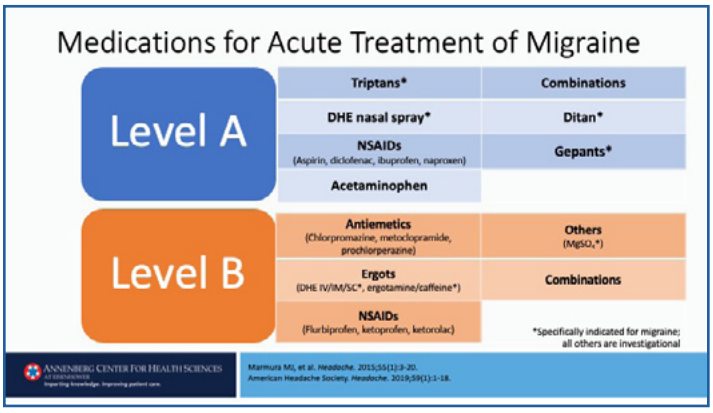
Lasmiditan actually, while it inhibits CGRP release peripherally with a 1F target, has most of its effect centrally. The serotonin-1F receptors are central, for the most part. And lasmiditan terminates migraine by interfering with the processing of migraine centrally. Because most of the action of lasmiditan is central, it does have central adverse events associated with its use. Lasmiditan has a little bit of triptan-like effect, in that it inhibits CGRP release peripherally, and a lot of central effect, which is quite unique in its action as an acute medication.

Jessica Ailani, MD

We're going to focus in now on acute treatment of migraine and really talking a bit about what the goals are and what types of treatments we can offer our patients. We mentioned earlier that patients are really interested—and who would blame them—in a medication that works quickly, that relieves their migraine attack, that has minimal side effects and reduces the use of rescue medication. That they know that they can rely on it. That if they take it, the migraine will go away. And that most of the time when they use it, the migraine is going to go away, it's not going to stop working.

They want minimum adverse events, as I said. And they want it to be cost-effective. What's also important to us in the healthcare system is that when a patient uses this acute treatment, they're not going to need to call us. They don't need to go to the emergency room. They don't need to go to urgent care and they don't need to come into the office for subsequent treatment. This really helps reduce healthcare use utilization, and also helps us reduce healthcare cost. This is also really important for a patient to have independence given back to them, especially with a disease like migraine, that can be so disabling and take so much away from our patients.

We have a number of different treatment options available to our patients.



Stewart J. Tepper, MD

I'd like to start by going back to the gepants. And remember from the pathophysiology diagram, gepants are small molecules that block the CGRP receptor. They can be taken intermittently to terminate migraine attacks and they can be taken daily or every other day for prevention, although they are not FDA- approved for that yet. Gepants prevent CGRP from causing vasodilation and neurogenic inflammation. But, gepants do not vasoconstrict. Theoretically they should be okay to use in patients with vascular disease. And there's no warning against using them in patients with vascular disease in the prescribing information. The 2 gepants that are FDA-approved for treatment of migraine have very similar efficacy. They are much more similar than different, and they are ubrogepant and rimegepant.

Ubrogepant was studied in 2 randomized control trials. And the 2 doses that appeared to be effective were 50 mg and 100 mg of ubrogepant. And those are the 2 doses that are FDA- approved for acute treatment of migraine, with a maximum dose of 200 mg in a day. All of the gepants work in creating about 20% of patients pain-free at 2 hours. They take a while to work. They don't work as fast as triptans, 20%, pain-free 2 hours. The FDA also requires that new acute treatment clear what patients say is their most bothersome symptom by 2 hours. And patients can select that from photophobia, phonophobia or nausea. And all of the gepants, as well as lasmiditan, successfully showed 2-hour pain freedom vs placebo and absence of most bothersome symptom at 2 hours. But, the take-home lesson in terms of efficacy for gepants, is 20%, pain-free 2 hours.

Rimegepant. Again, 20%, pain-free 2 hours. And it also clears most bothersome symptom at 2 hours. Rimegepant is only available as an orally dissolvable tablet or melt of 75 mg. And there has never been a study that looked at a second dose of rimegepant. So, 75 mg is it. Patient takes 1 dose. And because gepants are relatively slow in their onset, with the 20% pain-free 2 hours, it is worth telling patients they should treat early, in order to have a chance of getting to pain-free.

One of the great advantages of gepants is that they are incredibly well tolerated, remarkably well tolerated. And it is very rare to encounter a patient with a gepant tolerability side effect. They very rarely cause nausea. They almost never cause somnolence. And because they don't cause tolerability side effects, it's easy to say to a patient, "If you're going to use this gepant, take it early, you should not have side effects. And you won't know whether your migraine would have been a severe one or not because it should kick in over 2–4 hours, but you won't notice that you took it."

The gepants so far up here are very safe. They are metabolized in the liver by the cytochrome P450 3A4 system. Be aware about the potential

for CYP3A4 interactions. But you can see that there's a need for gepants in patients who either do not tolerate triptans, don't get adequate pain freedom from triptans, or who have vascular disease which precludes the use of the vasoconstrictive triptans. And gepants are appropriate for those patients. However, they may not be fast enough for someone with a quick time-to-peak intensity of an attack. And those patients might need to consider, especially if they have vascular disease, a different medication.

Jessica Ailani, MD

As we talked about earlier, lasmiditan is a 5- HT-1F agonist. It is focusing in on 1F, which is not located on blood vessels. Which does make it unique from the triptans. Because it's not located on blood vessels, there's no vasoconstriction. Similar to the gepants, we're not really concerned in using this medication in patients with cardiovascular risk factors. In fact, lasmitidan was studied in patients who had up to 2 cardiovascular risk factors. And I think that's an important thing for us to realize, when considering who would we prescribe this medication to.

Lasmiditan was studied in 2 pivotal trials, looking at treating a single migraine attack of moderate to severe intensity. And again, looking at rates of pain freedom in 2 hours, and freedom from most bothersome symptom. There were 3 doses that were studied. And all 3 doses compared to placebo, met its statistically significant endpoints of pain freedom and freedom from most bothersome symptom.

And here you can see for the 3 doses of lasmiditan that you have rates of around 30% to 35% pain freedom at 2 hours, compared to about 18% in placebo. And rates around 40% to 45% of freedom from most bothersome symptom, compared to 31%.

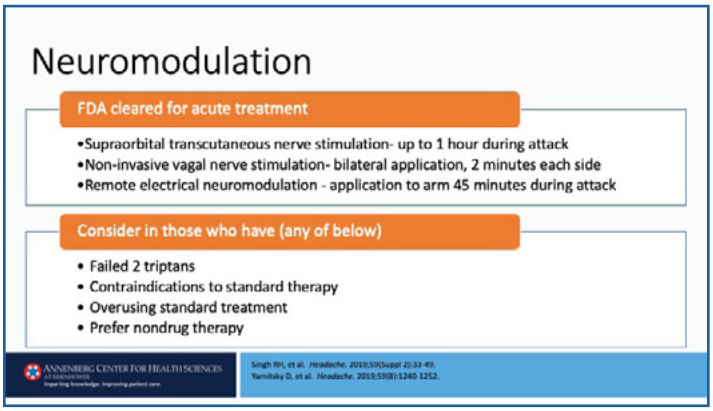
This shows us the uniqueness of lasmiditan, in that it does have some peripheral activity, but it possibly also works centrally, and is a little bit different than the triptans, and different from the gepants, and also unique in the sense that it doesn't cause that vasoconstriction. Because it might have that central activity though, we do have some differences when we're looking at side effects.

In these studies, the most common side effect noted for lasmiditan was dizziness, seen at rates up to 18% in those who were taking 200 mg in the trial. You could also see side effects that you see similarly in the triptans, the paresthesia, the sense of somnolence and fatigue. Generally, in the trials, these were reported as mild to moderate and transient. And patients said that they did like the medication and would choose to take it again. Because this medication does potentially work centrally, there was the need to do a driving safety study. This is a study that is required by the FDA in the United States. And this driving study was completed in healthy subjects who took the study when they didn't take lasmiditan and then were instructed to take lasmiditan and do the study again. And it showed that there was a change in driving. They didn't do so great on the driving study from a time period after taking lasmiditan to about 8 hours after. So, there is a driving restriction. That's very important that we discuss with patients, that they do not drive for 8 hours after use of lasmiditan.

Another important fact about lasmiditan, which is similar to many of our other central nervous system medications that are newer, is that it is a controlled substance in a class V category, similar to pregabalin and some of our other antiepileptic medications.

We have been talking about some of these new treatments. But, when do we think about using a new treatment option for the acute treatment of migraine? New treatment options really should be available to be prescribed by any licensed healthcare provider, in patients who meet the criteria, who have contraindications to triptan, like cardiovascular disease, uncontrolled hypertension, an MI or a stroke in the past. Someone who's tried standard therapy, but hasn't had a good response, or has had a lot of side effects. Particularly someone who's tried 2 oral triptans in the past.

If the healthcare provider has thought about patient-reported outcomes, questionnaires, and thinks this person has a good amount of disability and really would benefit from trying the new medications. And they have tried older medications, at least for 2 attacks and felt like it wasn't really a very helpful treatment.



Another option for our patients is the use of neuromodulation to treat migraine attacks. Neuromodulation is using an external device in the world of migraine, to treat headache attacks. And these are FDA-cleared for acute treatment in headache. We have 3 devices that are available. There's a supraorbital transcutaneous nerve stimulator, that can be applied for an hour during an acute migraine attack. There's a noninvasive vagal nerve stimulator, that's applied over the vagal nerve in the neck, 2 minutes on each side during a migraine attack.

And then there's a remote electrical neuromodulation device, I call this the band-aid. Actually, I think it kind of looks like a band-aid and it makes a lot of sense to patients. You put it on the upper arm and you turn the device on using your cell phone and you drive up the amplification of the device. And, it kind of feels like a little massage on the upper arm, kind of a funny vibration feeling. And you leave it on for 45 minutes during a migraine attack. Think about neuromodulation in a patient, again, similar to when you think about a new treatment option. Someone who's tried triptans and they have either not found them effective or have a lot of side effects. Someone who has contraindications to standard therapy. Someone who's overusing their standard medication options. I will often use neuromodulation in my patients who have chronic migraine who just don't have enough medication to treat all their acute attacks. This is a great option to treat their mild to moderate headaches and really make sure that they're functional for most of their days.

And especially think about it in a patient who comes in to see you, who really doesn't want to take any medications. We actually have options for these patients that can work really well for them, and they never have to put medication into their body. And I find that patients really appreciate that option. And it's important that we have that discussion with them. Some limitations for neuromodulation, though, is that they're not always covered by insurance. It is a conversation you need to have with them about potential cost.

All of these treatments together can get very overwhelming to go through and talk about and to discuss with the patient. How do we really pull this

all together? Well, it's important to realize that we don't throw everything all at once onto the patient at one visit. But that this is something we build over time. And what we're really working on with the patient, is building them a toolbox. We're trying to give them tools into their hand, that they can use together. That they can treat the different types of attacks they might have. Patients will tend to have some attacks they wake with, some attacks that happen later in the day.

And that's when you can layer all these different types of treatments together, and really help the patient to understand how the treatments work together. When to use these treatments, when to layer the treatments together, when to use an oral treatment, a nonoral treatment, and potentially when to add a neuromodulation. It's important that you write all this out for the patient, and then you adjust the plan at each follow-up visit, until you get it just right. This can take a long time. This might never reach just right. But, when it does happen, it's a good feeling for you and the patient, because then they can pretty much handle their migraine attacks independently. And again, we're trying to get that patient to gain that independence back, which this disease tends to strip so quickly from our patients.

Preventive Treatment/Migraine

Stewart J. Tepper, MD

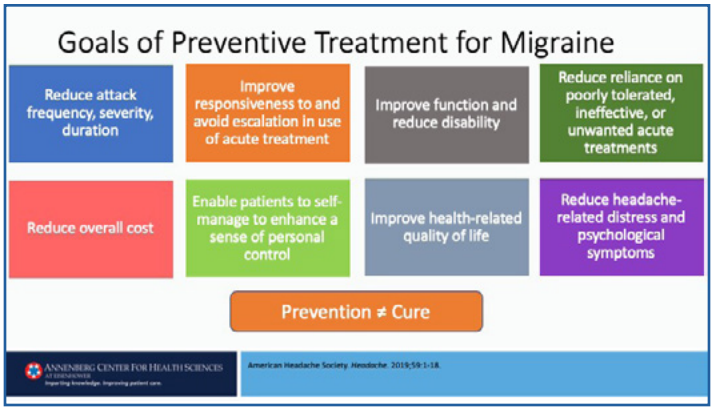
Patients with infrequent migraine can sometimes be treated with acute treatment alone. But sometimes the acute treatment is not perfect. Sometimes, it can't be matched perfectly. Sometimes the attacks continue to interfere with a patient's daily routine, despite all the work that one does with a patient in the therapeutic alliance to try to optimize the acute treatment.

Sometimes the attacks are so frequent the overuse of acute medication becomes a concern. It's not really holding the patient enough to restore their activities and prevent disability. And the point at which the attacks become frequent enough to consider prevention, is when a person's having at least 1 migraine a week. At that point, unless one can get the acute treatment reliably to a sustained pain-free response each time, without side effects, a discussion about preventive treatment becomes important.

Sometimes patients can't use the acute treatments. Sometimes they have vascular disease and they can't use triptans or ergots. We don't recommend opioids. We don't recommend barbiturates. And sometimes their insurance won't cover the new medications despite the fact that they appear to be good candidates for them. Sometimes the patients are overusing the older treatments. Overusing triptans at 10 or more days per month. Overusing combination analgesics at 10 or more days per month. Overusing NSAIDs at 15 or more days per month.

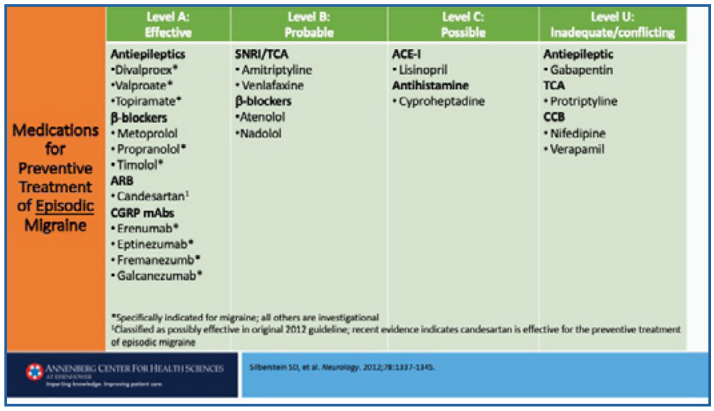
And they are transforming before your eyes, from episodic into chronic migraine. And from no medication overuse to acute medication overuse headache. And stepping in with prevention at that point can move a patient from right to left. Can move a patient from chronic migraine back to episodic migraine. Or from high-frequency episodic to low-frequency episodic. And reduce the disability and improve their quality of life. Some patients can't take any acute treatment. No matter what you give them, they have side effects. And some patients say, "Look, I want prevention. I do not want to have to wrestle with migraine attacks across my life, across a month." In all of those circumstances, you can offer prevention.

Some principles about preventive treatment. There is a difference between the old preventive oral medications, that we were used to using



prior to 2018, and the new monoclonal antibodies. The older treatments were designed for other therapeutic areas, and are often poorly tolerated. If you're going to use 1 of the traditional oral preventives, start low and go slow. It takes a month often to titrate up to an adequate dose. And then the patient will need an adequate trial of 2–3 months, once they are on the proper dose. So, for example, for topiramate, 25 mg increase a week up to 100 mg. And then 3 months of treatment to see if they get an adequate preventive response. During the use of the older medicines, we generally initiate a wean of the acute medicines, if they are being overused. And overuse of acute medicines can interfere with traditional oral prevention.

We use a calendar, a headache diary and help them taper those older acute medicines, while we're initiating the older preventative medicines. It's very important to talk to patients about adequate birth control with all of the preventive treatments, whether new or old.



Let's summarize where the preventive treatments sit. Level A evidence is available for valproate, topiramate, 3 beta-blockers, metoprolol, propranolol, and timolol, candesartan, and the 4 new anti-CGRP therapy monoclonal antibodies. Of these, valproate, topiramate, propranolol and timolol are the only FDA-approved oral preventives. And they only really were studied for the approval in episodic migraine. Level B drugs which are probably effective include amitriptyline, venlafaxine, and 2 other beta-blockers, atenolol and nadolol. And all of these medications were studied in episodic migraine.

Level C drugs, possibly effective, lisinopril and cyproheptadine. An inadequate or conflicting information is available for gabapentin, with the Cochrane meta-analysis that suggests it's ineffective in migraine prevention, although widely used. Protriptyline and verapamil.

Remember, then, when you're thinking about verapamil or gabapentin, there's really inadequate evidence that those are effective migraine

preventions. And remember that all of these were studied in episodic migraine. Now, the 4 monoclonal antibodies are approved for all migraine, episodic and chronic. Dr. Ailani will talk to you about that.

And onabotulinumtoxinA is only approved for chronic migraine. But, the traditional oral medications, all approved for preventive treatment of episodic migraine. And remember that when a payer is insisting that you write these for somebody with chronic migraine. They're unlikely to be effective. Patients are unlikely to adhere. And they are very likely to cause adverse events, other than the CGRP monoclonal antibodies and onabotulinumtoxinA for chronic migraine. I think that's a good place to stop and ask Dr. Ailani to take you through the evidence on these CGRP monoclonal antibodies. And where they stand. And why we think the paradigm may be shifting toward matching patient need to the use of the new preventive medications.

Jessica Ailani, MD

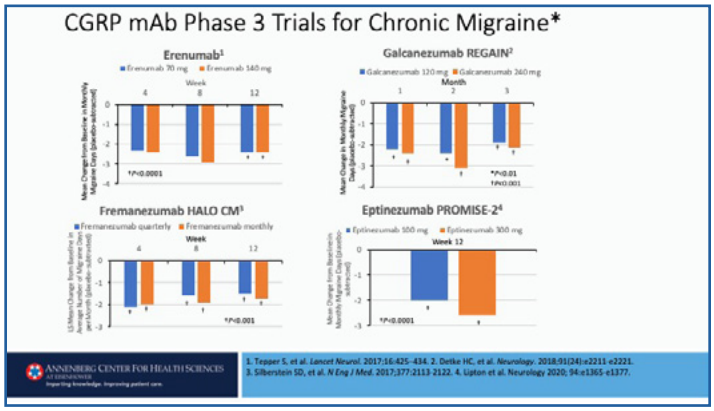
Currently, there are 4 CGRP monoclonal antibodies on the market. And they're more similar than different. Let's talk a little bit about their differences in a bit. Before that we have to market, erenumab, which came out first, is a CGRP monoclonal that binds to the CGRP receptor. Fremanezumab, galcanezumab and eptinezumab are all CGRP monoclonal antibodies that bind to the CGRP ligand. Erenumab, fremanezumab, and galcanezumab are all at-home, subcutaneous injections that can be done by the patient themselves or by a family member. Eptinezumab is an intravenous infusion that's given quarterly. Right now, at an infusion center, but potentially can be done as a home infusion with a nurse that comes to the house to give it to the patient.

We're going to take a look at the episodic migraine data. And these are the pivotal trials for each of the medications. And you'll notice something very particular about these medications. Now, you were hearing about the oral medications that are in use for migraine prevention, that they can take a little time for titration and that patients are on them for several months. For the monoclonal antibodies, we do usually recommend the patients try each. If they're going to time them on a full antibody, they stay on it for about 3, if not 6 months, to see the effect. But you'll notice right away when you're taking a look at the graphs here that for many of the studies there's a pretty significant drop in the first month after treatment is started in all of these trials, looking at episodic migraine. And here you can see the color bars are for the treatment groups and the gray is for placebo, and there's a statistically significant difference in reduction in the number of migraine days compared to placebo.

And about most of them have a 3–4 days less migraine days per month compared to about 1–2 less migraine days a month in the placebo arm.

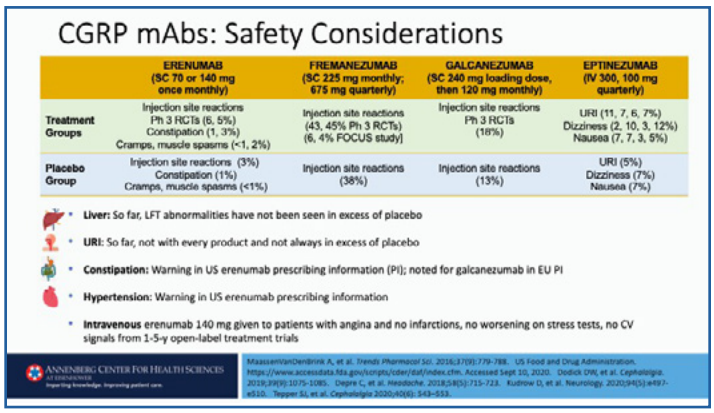
Erenumab is available in 2 dose options at 70 mg and 140 mg. Both were studied and both were FDA-approved for use. Eptinezumab also has 2 doses available, 100 mg and 300 mg. Both were studied and both are available for use. It is recommended that all patients first receive 100 mg and then the provider makes a decision if the patient should be elevated to 300 mg. Fremanezumab is unique in that it's been studied in either a monthly or quarterly injection, and the monthly and quarterly data looks very similar, in that patients do well either way. If it is given monthly, it's 1 injection of 225 mg per month. If it's done quarterly, it's 3 injections at 675 mg every 90 days. Galcanezumab was studied in a dose of 120 mg per month or 240 mg per month. Only the 120 mg is FDA-approved. There is a loading dose, however, where patients have to take 2 doses of 120 mg month 1, and then 120 mg every month thereafter. And it's considered a loading dose.

Let's take a look at the chronic migraine data. And this is looking at patients who have greater than 15 days a month of headache, with at least 8 of them being migraine in nature, either because the patient treated it as migraine or they feel it's going to be migraine, or they have migraine features. Again, all of these medications were also studied in patients with chronic migraine. These trials were of shorter duration. Episodic migraine trials for most of the medications were about 6 months, but for the chronic migraine, they were 3 months. Again, you're seeing that similar first month drop in reduction in migraine. But again, it's important that the patients do give it a proper time period of remaining on the medication at least 3 months to see if it's effective or not, because there are some patients that continue to improve over time.



It is important to see if they're going to get a full response. Here you can see that patients had about 4–6 days less per month of migraine attacks, over time, in the studies, compared to about 2–4 days less per month in placebo.

When we take a look at side effects, there's also a little bit of difference between the 4 monoclonal antibodies. Injection site reactions can happen with all of them, a little bit more common with the self-injecting subcutaneous auto-injectors. Constipation can be seen, potentially with all of them, in clinical trials. It was only seen in erenumab in clinical practice. We do hear a little bit of it with the other CGRP monoclonal antibodies. It is important to note that, after release, erenumab did have a label update showing potential serious constipation with hospitalization as a side effect that can occur. It is very important when we have patients who we're going to start erenumab on, that we actually do an intake about their GI history. I ask all of my patients about constipation. Many of the medications we actually use are very constipating. Allergy and asthma issues are very common comorbid disorders for patients with migraine, as is depression and anxiety, as is insomnia. And the medications used for insomnia, depression, and anxiety and allergies and asthma, all tend to be constipating. If I notice that my patient is on



multiple medications that cause constipation and I haven't asked about constipation and I put them on erenumab, there's a pretty good chance they're going to have some complications. I find that addressing this up front is very important. And considering this as a potential issue is also important when having that decision made with the patient about what's the right fit for them.

Another important factor to note is that there was another recent label update with erenumab, noting the potential for hypertension that could occur after a dose of erenumab, especially after the first dose, and particularly in patients who are on the cusp of hypertension. This was seen again, post-marketing, was not seen in the clinical trials, was not seen in the long-term safety trials as well, which were out to 4½ years. But again, an important factor that I will now look at in my patients in clinic, where you're taking a look at their blood pressure patterns, seeing if their blood pressure is under good control. In my patient who's borderline hypertensive, this is a conversation I'd be having with them. And I consider monitoring if we're going to choose to start them on erenumab. These are parts of the things that I consider when having a conversation about deciding which is the right fit for the patient.

Stewart J. Tepper, MD

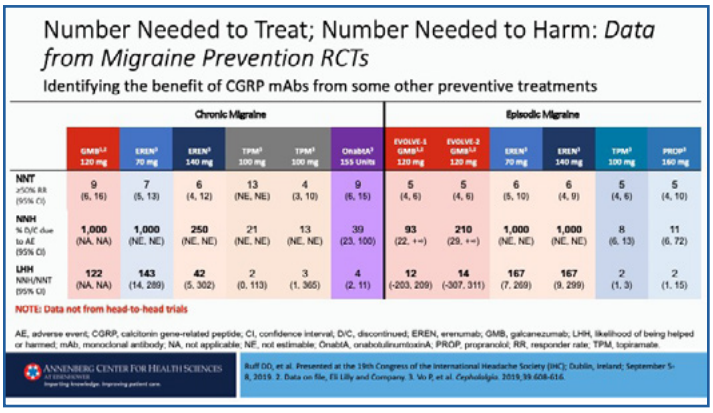
The question is, are they better? We've talked about, are they safer? Are they more tolerable than the previous treatments? And the monoclonal antibodies do appear to be more tolerable than most of our older treatments. And for the most part, they appear to have less adverse events associated with them than our traditional treatments. Very common to have adverse events associated with topiramate use, with valproate use, and sometimes with amitriptyline use. But the question is, how do you sort out whether these translational research derived anti-CGRP therapies represent a significant improvement over the older, more traditional and less expensive generic medications?

One way, is to look at therapeutic gain. Therapeutic gain is the active response minus the placebo response, in a randomized controlled trial. And this is often cited, so that if one looks at the mean, monthly migraine-day reduction with topiramate and compares it at 3 months to the mean, monthly migraine-day reduction with a monoclonal antibody, they may not look that different. But, remember that patients don't take placebo. And what really counts is the drop from baseline. Let's say, somebody has 17 or 18 migraine days a month, with chronic migraine, and drops by 6 days per month. That drop is what counts clinically. And the other problem with therapeutic gain is it doesn't really take into account the adverse events and whether there's better tolerability or safety. The British group Bombardier, worked out what happens if one looks at the reciprocal of therapeutic gain, which is referred to as number needed to treat or NNT. For NNT, the lower the value, the better. You do not want to have to treat a lot of patients before you see therapeutic benefit. You can calculate NNT, and that's a way of using therapeutic gain, that in which the placebo subtraction actually still gives you some useful clinical information. You want a low NNT.

Therapeutic harm is the active adverse events minus the placebo adverse events. And what you want when you do the reciprocal of that, that's called the number needed to harm.

For NNH, the number needed to harm, the higher the value, the better. You want to treat a ton of patients before you see a side effect. You want a high NNH and a low NNT. And if you're going to use placebo-subtracted analysis to evaluate the effectiveness of treatment, it's very useful to use these 2 calculations. And one can do a ratio of NNH to NNT, the likelihood of being harmed or helped, LLH. That ratio describes the value of your treatment as a benefit-risk analysis. It's actually a risk-benefit analysis because NNH is the numerator. For NNH to NNT, again, the higher the value, the better. So, you want a high NNH and a low NNT.

And we have enough randomized controlled trials to look at our old treatments and look at our new treatments and take into account the therapeutic response and the adverse events, and see whether there's a significant difference.



This table has been put together from a number of sources and shows you NNT, NNH, and the NNH to NNT ratio. And it's useful just to look at the bottom line. The NNH to NNT ratio, remember the higher the better. If one looks in chronic migraine, topiramate was studied in 2 chronic migraine studies, and you can see it in gray. And the NNH to NNT ratio was 2 or 3. OnabotulinumtoxinA, studied in chronic migraine, the NNH to NNT ratio was 4. On the left side, you see erenumab and galcanezumab, and their NNH to NNT ratios were 42 to 143. These are a lot, lot higher ratio numbers for these 2 monoclonal antibodies, compared to topiramate and onabotulinumtoxinA. Now, these are not head-to-head trials, but these analyses are placebo subtracted, and, therefore, very useful.

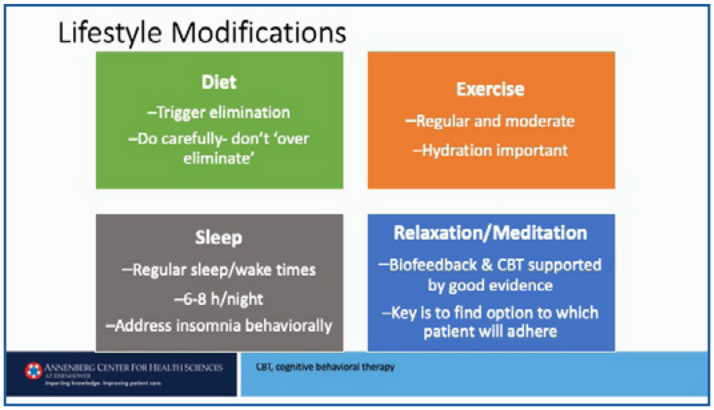
If one looks on the episodic migraine side, at the topiramate trial, the NNH to NNT ratio, again, was 2, propranolol was 2, and erenumab and galcanezumab range from 12 to 167. Again, these are huge differences in the NNH to NNT ratios. And they strongly suggest a paradigm shift. They strongly suggest that the new monoclonal antibodies are a tremendous improvement over our older treatments, when taking into account adverse events and efficacy.

Who should receive them? Well, again, the new treatments for prevention should be available to be prescribed by any licensed healthcare provider to patients who meet the following criteria that were evolved by the American Headache Society. If a person has low frequency episodic migraine, 4–7 headache days per month, and has had a lack of success with at least 2 of the older medicines, the anti-epilepsy drugs, valproate, topiramate, the tricyclics, the beta-blockers, the serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, or other level A or B migraine-preventive medicines, such as candesartan. If they've had a lack of success with 2 of those or more, and have documented at least moderate disability or impact by the migraines, those are good candidates for the newer treatments.

If they have high frequency, episodic migraine at 8–14 headache days per month, same requirements of lack of success, but you don't need to document the disability. They are clearly impacted. If, they have chronic migraine, 15 or more headache days per month, they either have to have had a lack of success with the 2 older drugs, in terms of categories, or onabotulinumtoxinA has failed.

And, if onabotulinumtoxinA has failed for chronic migraine, there's no need to do anything more. They've already gone through enough step

edits. There's no need to document their disability. They have chronic migraine, they're clearly impacted. Therefore, they are candidates for the newer treatments. There are a lot of patients who meet these criteria and it's really worth having a conversation with patients as to what they've tried and what they've abandoned, and whether they might consider the new treatments. Now, there are other ways of going at prevention and they involve non-medicines, including the neuromodulation that Dr. Ailani talked about, but also behavioral interventions.



Jessica Ailani, MD

It's important to have these conversations with patients. And it's also important to remember, to talk to them about how they're doing, but also how they're doing with their treatment plan. And the reason for this is because we find that our patients often don't always take the treatment as they should. And this isn't unique to migraine.

When we took a look at the studies itself, it was the CaMEO study, which is a very large longitudinal internet-based study, looking at over 13,000 patients with migraine. And these patients were asked numerous questions about migraines, and a part of the study focused on acute treatments. It looked at patients with migraine and showed about 36% of these patients had ever used an acute prescription medication for migraine and out of these patients, 36% of those stopped using acute treatment. And the reason is that many of them went to over-the-counter medications, and they were saying, "Well, I didn't think it was really very effective. I didn't really tolerate the medication very well." Some patients who stopped these medications, had migraines about 0–4 times a month. One in 5 patients said that they actually were able to function pretty well with a migraine, so they didn't really feel like they needed the prescription.

But 42% of them did have moderate disabilities. It was really still confusing why they chose to stop their prescription medication. Many of these patients stopped seeing a physician because of their migraines. They didn't go and continue to seek care, for greater than a year. They were really deprioritizing their migraine. And that might have been a reason they stopped prescription medication.

When we take a look at preventive, unfortunately the data for adherence is even worse.

What are some things we can do for our patients to try to improve that adherence rate? To try to help them be a little bit better about taking their medication and incorporating these lifestyle changes and really sticking with the plan, so they can get their disease under better control.

One thing we can help our patients with that is pretty easy, is helping them develop an organizational strategy. Anytime you're taking a medicine every day, how do you organize it so you remember to take it? Do you keep it at your bedside? Do you have a very hectic evening and need to take this medication around dinner time? And you're the one who cooks. Maybe having it right next to where the frying pans are kept, so you remember to take it as you're cooking dinner that night. Do you have a regimen before you go to bed, where you brush your teeth and you wash your face? Well then, have it right where you brush your teeth, so the medication's right there. Setting alerts on the phone is another great way to do it.

Every time the patient comes in, ask them about their treatment adherence. Remembering to do that can be a very simple way to make sure that they're taking their medicine. And if they're not, don't judge them, just ask them, how can you help them remember better? So that they can do better. They can keep a headache diary. On the diary, they can mark if they're taking their medicine or not. If they are religious about it, they're taking it every day. They can mark it every day, they can notice if they missed a day. They can also have some strategies in place to reduce treatment complexity. If you notice they're taking lots of different medicines and there's a way to simplify the medications by reducing ones that are unnecessary, clearing up some of the medications or supplements they're on that aren't needed. If there are other medications that can be combined together, because you know there's a combination. Well, these are ways that we can simplify their regimen, so they're taking less medicines and taking them less often and it can improve their adherence.

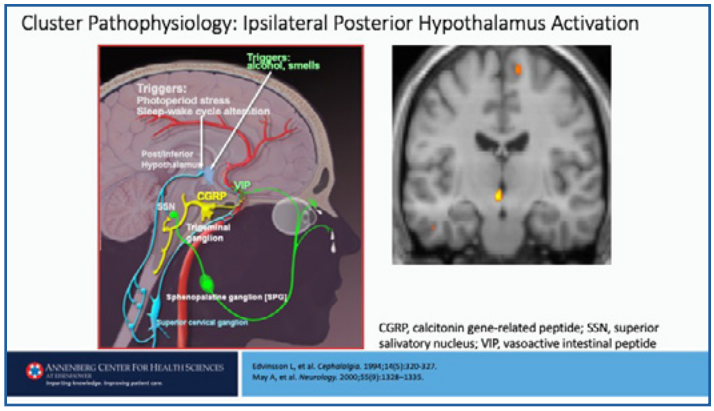
It's also important, our patients understand why they're on medicines. Oftentimes, they'll tell us, "I'm taking this. I don't really know for what." Well, if I didn't know why I was taking something, I probably would stop taking it. A lot of times, the only times we do, do something is because we realize it's important and we know the consequence for not doing it. Having that discussion is important as well.

You can also consider cognitive-behavioral therapy techniques. Like, think about what kinds of things that you're doing that are causing you not to take the medicine. What's the emotional distress that is causing this kind of adaptive behavior? You can have them see a therapist. And this is only if it's a serious ongoing problem that you've identified, that's really leading to them not being able to get better. And this is something I might bring up in a patient who is so anxious about their treatment plan, that they're really unable to past that anxiety and then we need to get to the source of what's making them so anxious. This is a big plan. Doing it all yourself is not always possible. If you have nursing staff that can be involved in educating the patients, if you've got a social worker in your office that can help out making phone calls to remind patients who are having a hard time remembering to take their meds. Just identifying people in the office and providing them key roles to reinforce and educate patients can be really helpful to improve adherence. And over time, as the patients get much better at this, they'll be able to do this on their own, and then you're not going to need to keep calling them, and they'll be better, which will be really great.

Cluster

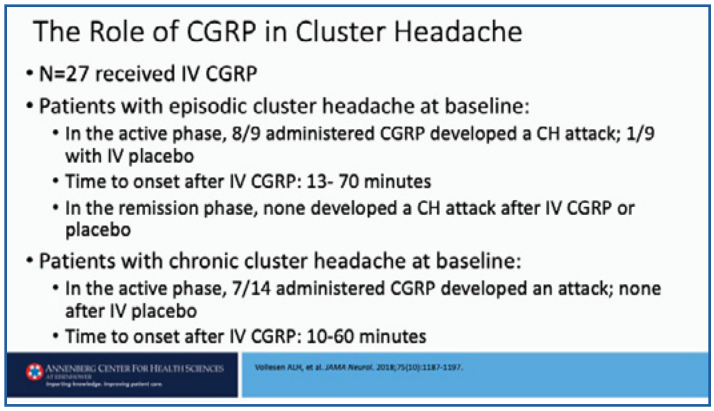
Stewart J. Tepper, MD

Cluster pathophysiology has also yielded important treatments. And in cluster, we actually know where the central generator is in the ipsilateral posterior hypothalamus, which is activated during cluster and seen in functional imaging. The outflow for cluster goes from the hypothalamus to the superior salivatory nucleus to the sphenopalatine ganglion to the target organs. And because autonomic fibers go out of the sphenopalatine ganglion that explains many of the autonomic



features of cluster. The parasympathetic autonomic features may be partially initiated by vasoactive intestinal peptide. However, it turns out that CGRP plays a role, at least in episodic cluster.

This is a study that was done in Copenhagen and 27 patients with cluster volunteered to receive infusions of CGRP, which was quite heroic. And in the patients with episodic cluster, almost all of them developed a cluster headache between 13 and 70 minutes after the IV CGRP during the active phase of a cluster period, when they were having daily attacks. The same patients were brought back in a remission phase when they were not in a cluster bout and they were given IV CGRP again, and not one developed a cluster headache attack. And this was placebo controlled as well. None of them developed after placebo.



In chronic cluster, however, it was much less clear. In chronic cluster, and it's always active, so it was an active phase when they studied the patients. Only half the patients who were given IV CGRP developed a cluster attack, and none after IV placebo. The time to the cluster attack after the IV CGRP was similar to episodic cluster. But one has to wonder whether chronic cluster has as much CGRP mediation as episodic cluster. And it turns out in research on cluster treatments that has proven to be a significant aspect.

I'm going to turn over to a patient again to describe the treatment experience with cluster, because it is so challenging and so important.

Jessica Ailani, MD

As in migraine, we have guidelines that help us understand better what the management cycles should be for treatment of cluster headache. We have established efficacy and FDA approval for certain medications for treatment of cluster. And 1 of these is oxygen for when a patient is having cluster attacks. Oxygen has been shown to be very useful and has level A evidence to treat those attacks. Also, having level A evidence is DHE, triptans, and particularly sumatriptan subcutaneous and zolmitriptan nasal. What's probably effective is sumatriptan nasal and zolmitriptan oral.

We also have had recently, in the last few years, the development of a neuromodulation device. A noninvasive vagal nerve stimulator, which we spoke about earlier in regard to migraine, was actually first discovered and investigated for the treatment of cluster attacks.

The noninvasive vagal nerve stimulator was looked at as an acute treatment for episodic cluster headache. And this device was looked at by giving 3 2-minute stimulations on the side of the cluster attack itself. And as you see the data here in this chart, you can see that patients with episodic cluster headache had a significant improvement compared to those that were treated with a sham device. Unfortunately, this didn't work as well in patients with chronic cluster headache, but overall patients with cluster headache had an improvement.

I'm going to turn it back to Dr. Tepper to talk to us a little bit more about transitional treatment for those with cluster headache.

Stewart J. Tepper, MD

Transitional treatment is a way to buy time. Cluster patients are very anxious and in great misery when they go into a cycle. And it may take time to get the prevention on board and reduce or stop cluster attacks. Cluster patients will be using a lot of acute treatment, whether that be oxygen or triptans or the noninvasive vagal nerve stimulator. But if they are having multiple attacks per day, sometimes the insurance companies won't allow enough of the acute treatment to provide a patient with cluster to treat each attack while the preventive treatment is being started. Transitional treatment is a way to ease the patient into prevention.

There are 2 main transitional treatments with good evidence. One is to treat a patient with high-dose oral steroids for 7–10 days while you get the preventive treatment in place. And the danger of that is the risk of avascular necrosis, the risk of steroid behavioral abnormalities, the risk of gastrointestinal upset with the steroids. But steroids at high dose will stop the cluster attacks temporarily when the prevention is being put on board.

Occipital nerve blocks with steroids works well, in addition. And this has to be a caine such as lidocaine with a steroid at the same time mixed together and then given as an occipital nerve block. Can't be just lidocaine or just a steroid. And sometimes, if one gets these blocks in early enough, one can actually terminate a cluster cycle with them. Some providers use high-dose melatonin to transitionally treat patients during the time of prophylaxis being started, but there's really no good evidence for that. I think if you're going to give a patient transitional treatment while you're getting prevention on board, it's either going to be high-dose steroids or nerve blocks or both.

Now, there are 2 cluster treatments that have been approved or cleared by the FDA for prophylaxis, and only 2. There's only 1 medication that is FDA-approved for prevention of cluster. And it's only for prevention of episodic cluster headache, and that's galcanezumab. Noninvasive vagal nerve stimulation, which as Dr. Ailani said, is effective and FDA cleared for acute treatment of episodic cluster, is approved as an adjunctive add-on for the prevention of both episodic and chronic cluster headache, for all cluster headache prevention. Those are the only 2 FDA- approved preventive treatments.

We use verapamil. We use anti-epilepsy drugs such as valproate and topiramate. We use lithium. We use long-acting ergot such as methylergonovine. Sometimes we use cyproheptadine. All for prevention,

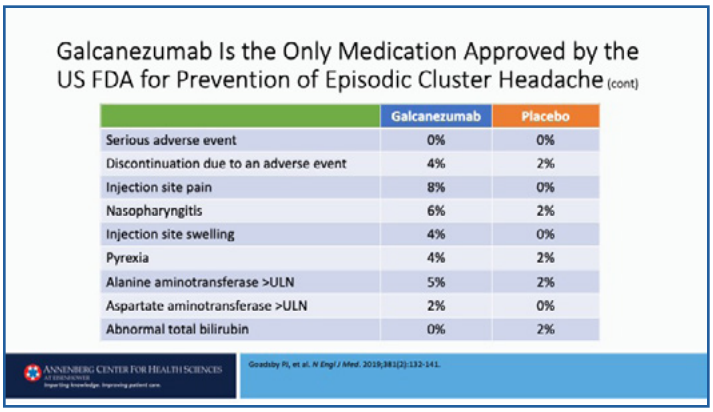
but not one of those is FDA-approved. And the only 2 are what you see above. But it was still a very important day for cluster patients when the FDA finally approved a medication to prevent episodic cluster headache, that is galcanezumab.

And the galcanezumab was approved for episodic cluster based on a randomized control trial of patients in episodic cluster cycles or periods or bouts. And when they were in cycle, in their baseline, they averaged more than 17 attacks per week. So at least 2–3 attacks of cluster per day, these were real episodic cluster patients, and they were randomized to receive galcanezumab 300 mg subcutaneously or placebo.

And the galcanezumab group dropped the number of attacks from above 17 to slightly above 9 attacks per week. And that was statistically different than the placebo. And it cut almost in half the number of attacks per week. The galcanezumab also dropped the number of cluster attacks by at least 50% in three-quarters of the patients.

This was a very encouraging study, hard to do, but encouraging. And the galcanezumab is administered as a subcutaneous injection of 100 mg, but 3 of them given across the abdomen. And I've not had a single cluster patient tell me that they're not willing to do that.

Fremanezumab was studied in the prevention of episodic cluster headache, and it was not effective, or at least the study failed. And both galcanezumab and fremanezumab were studied in the prevention of chronic cluster headache and both of those studies failed. One can understand why they may have failed in the chronic cluster patients because only half of the chronic cluster patients seem to have a CGRP biology for their attacks based on the infusion study. But why fremanezumab did not work in preventing episodic cluster may have been methodologic, but in any case, right now, the only FDA-approved drug, and the only medication with a real clear, significant, positive, randomized control trial for prevention of episodic cluster, is galcanezumab. And it's made a big difference for our episodic cluster patients. And we go right to it now at the beginning when they come in.



Adverse events, again, as in migraine were quite minimal with injection-site reaction being the most common. And injection- site reactions for the subcutaneous monoclonal antibodies can be redness. It can be a small hive. It can be a discoloration. It can be swelling. All of those account, in my book, as injection-site reactions. So, I do tell patients about those. There were a few patients that appeared to have allergic-type reactions, such as a fever or sinus-like symptoms, and a 2% over placebo did discontinue during an adverse event, but I've not seen any adverse events have consequence in my episodic cluster patients with galcanezumab. And as I say, I tend to go to it first now for my patients with episodic cluster headache when they go into cycle.

If they are veterans, the VA does cover the noninvasive vagal nerve stimulator. And I always try to get that for veterans. And it's hoped that there will be better commercial coverage for the noninvasive vagal nerve stimulator for cluster patients in the future. The noninvasive vagal nerve stimulator was, remember, only approved for the adjunctive preventive treatment of cluster headache. And the way the study was done in Europe was that standard of care, which in those days did not include galcanezumab, but which basically were verapamil plus or verapamil alone. Verapamil plus an anti-epilepsy drug, or verapamil plus lithium or verapamil alone as the standard of care was given to patients with cluster. And this was both episodic and chronic cluster, and then a second group received standard of care and the noninvasive vagal nerve stimulator was also administered in 3 2-minute stimulations twice daily. And attack frequency was reduced considerably more in the patients who were on standard of care plus the noninvasive vagal nerve stimulator, and as evidenced for the reduced attack frequency, there was reduced use of as-needed or acute sumatriptan and oxygen seen on the right.

And so, the FDA said, "Well, this is not a randomized controlled trial against placebo, so we will approve it or we will clear it." Which is the technical term that the FDA uses when they clear a noninvasive neuromodulation device. They cleared it for the add-on preventive treatment of cluster. And the big problem with the noninvasive vagal nerve stimulator is access. As I said, the VA covers it, and there's hope that commercial coverage will improve so that patients can use this device for both adjunctive prevention of cluster, both episodic and chronic, and acute treatment of cluster, as Dr. Ailani said, but episodic cluster only for the acute treatment.

But it's a hopeful time for cluster headache patients. We have a more clear way of diagnosing episodic cluster now, requiring at least 3 months of no attacks per year. We know now where the cluster headache generator is located, in the ipsilateral posterior hypothalamus. We have 2 new treatments for cluster, the noninvasive vagal nerve stimulation for acute treatment of episodic cluster and adjunctive preventive treatment of cluster.

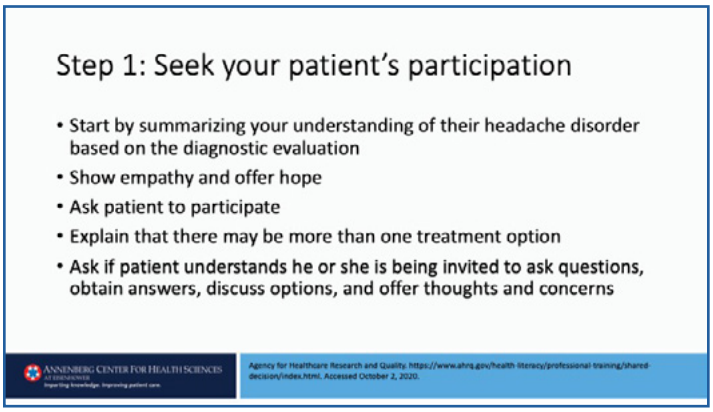
And just to remind you of the doses for acute treatment for episodic cluster, 3 2-minutes stimulations up to 24 stimulations in a day, and for preventive treatment adjunctively for chronic cluster and episodic cluster, 3 2-minute stimulations twice daily. And then we have galcanezumab for the preventive treatment of episodic cluster. And that one does not have an auto-injector. It's a prefilled subcutaneous syringe dosed 3 times. So, 3 100 mg doses across the abdomen monthly for the duration of the episodic cluster cycle and then discontinued when the patient goes out of cluster.

Shared Decision-Making

Jessica Ailani, MD

Let's talk a little bit about shared decision-making. What does that mean? Shared decision-making is when the healthcare provider and the patient work together to make a healthcare decision that's best for the patient. Now, this is something we all hope that we're doing, but it's a little bit more involved than just saying, "Hey, what do you think? This is all the options you have." It involves a lot of conversations about options, benefits, risk ratios, a lot of what Dr. Tepper was talking about earlier about you understanding all of this data that we've talked to you about and processing it into this understanding of how many you need to treat, how many needs to be harmed for you to understand which treatment

option might actually have the best evidence, and then distill all of that into English to explain to the patient that these are the options, these are the differences, this is maybe what might fit best into your lifestyle based on what things you have said to me. Let's take a closer look at all the steps that are involved in shared decision-making.



The very first step in shared decision-making is to seek your patient's participation. We want to start by summarizing the patient's understanding of their headache disorder based on the diagnostic evaluation. We want to show empathy and offer hope. This is extremely important in the conversation. A way we can do that is offer them a sentence like, "Having headaches as you described can make it really difficult to live the life that you really want to live. I want us to work together as I'm sure we can find a treatment that you're going to find very helpful for your headaches."

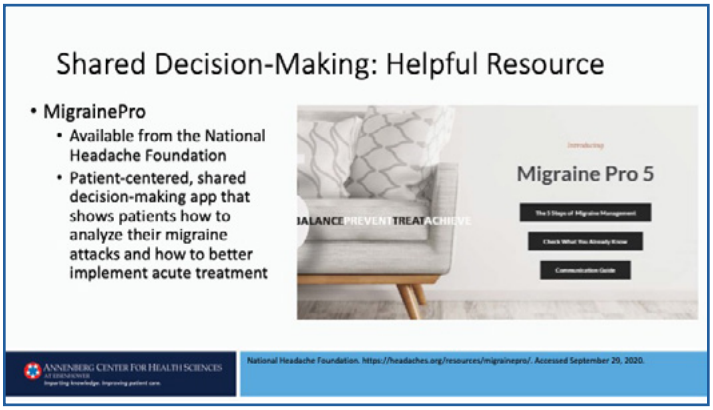
You want to ask the patient to participate in the care. You might say, "There's some new medications that might not have the same type of side effects that you experienced with the medications you've tried before for your migraines. Are you interested in hearing more about that? How would you feel about trying an option that had less side effects? How would you feel about injecting yourself if I told you it was only once a month and it came with a better chance of improvement?" Explain that there might be more than 1 treatment option and that you're going to work together to make a good decision for the patient. Ask if the patient understands that they're being asked to ask questions and to participate in their care, that this is a discussion, that this isn't going to be the type of visit where you're going to tell them what to do and they're just going to have to listen.

And sometimes this might be the first time that happens to the patient and they might really not know what to make of it. It's not an uncommon thing that I'm in a clinic visit doing this and the patient just looks at me and says, "Well, aren't you the doctor? Aren't you just going to tell me what to do?" But at the end of it, there's actually a much higher level of satisfaction. And the adherence rates go up because the patient is involved in making the decision. But they're involved in a way where they're better educated about the options that they're choosing and they feel more comfortable. And you're also engaging them the whole way, so they have a better understanding about why the options are being chosen. And so, again, there's a better chance they understand, so there's a better chance they're going to stick with the medication.

After we've discussed available treatment options with the patient, we've learned about their values and preferences. It's time to really reach the decision about treatment with the patient. We want to ask them if they're ready to make a treatment decision, "Are you ready to make a decision at this time or do you have some other questions that you want to go through? Do you need a little bit more time? Because it's really not a rush to have to make this decision today." Again, this is something they might never have heard.

And the first time I was in a clinic supervising a resident and I said this to the patient, the resident just stopped and looked at me like, "Are you kidding Dr. Ailani? Did you just give them more time?" Later, I explained to the resident that our goal is not to push the patient to make a decision quickly that later they were going to regret and call us and change their mind, not feel confident about. Our job was to give the patient a lot of information and if they look like they were uncomfortable to make the choice today, to bring them back in a week or 2 after they had time to think about it and then make the decision at that point. That making these kinds of steps early on in the relationship really not only secures a relationship between you and the patient, but really helps make the patient feel more secure to ask the right question and make better decisions for their healthcare.

In the end, you want to confirm the decision they made. "So, I'm understanding that you wish to start the new medication we discussed because it has less side effects and you really feel it's going to fit better into your lifestyle. Is that correct?" Make sure that you understand what they're saying to you and that you're both on the same page. That's a really important step in shared decision-making.



There are a lot of available tools that can be really helpful for your patient and for yourself when you're trying to use shared decision-making in clinical practice. It's a helpful process that facilitates collaboration. It doesn't take as much time as I'm making it seem. It actually becomes much easier to do the more you do it and it starts to become a natural part of your practice. The National Headache Foundation developed something called the MigrainePro, and it's a patient centered shared decision-making software application that shows patients how to analyze their migraine attacks and how to better implement acute treatment, and also provides them opportunities to assess what they know about migraine. It kind of is like a little mini quiz to make sure they really understand their disease and their treatment options. It also gives them some tips about how to better communicate with their healthcare team. This might be an option that you can give to your patients to use after their visits so they can practice some of the things that you would have talked to them about.

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