A New Era of Migraine Management

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Dr. Dodick: Tonight's symposium is entitled "A New Era of Migraine Management." A lot of times these titles are hyperbole, right? They promise more than what they really deliver, but I think this is a new era of migraine management. I mean, we have neuromodulation. We have biologics. We have new small molecules. We have new targets. We are finally entering the era of precision medicine in headache where we have disease- and mechanism-specific therapies for our patients. I really do think it is a new era and I could not be more excited about it.

And tonight, we are lucky enough to have with us Dr. Andrew Charles, and Dr. Deb Friedman. Two superb speakers. Two superb clinicians who I think you will enjoy. Importantly, I am very grateful and I think we all should be very honored that we have a patient here with us tonight because after all, this is all about the patient. It always is and it always will be about the patient. You can listen to talking heads, but it is better to actually listen to the patient. It is better to listen to their journey. I know you are clinicians and I know you hear this, but it is nice to contextualize what we say with the patient. We have a patient here tonight, Lynn, who is going to share with us her story, her migraine journey, the treatments that she has tried before, and her experience on one of the new monoclonal antibodies.

I am David Dodick. I should have introduced myself. I am the chair for tonight's session. I am a Neurologist at the Mayo Clinic, and I have introduced Dr. Charles who is an Endowed Professor of Neurology and runs the Headache Program at UCLA, and Dr. Deb Friedman who is a Professor at UT Southwestern in Dallas.

I want to introduce the most important speaker tonight, and I truly mean that, Lynn. Lynn has come here tonight to share with you her story, which I think is a fascinating story, and one which has a lot of relevance to our discussion here tonight. So Lynn, thank you very much for being here. The floor is yours.

Lynn: Thank you. I never thought I would grow up to be a migraine advocate, to my surprise. It is way too hard for me to remember everything I have ever tried, so I am just going to go ahead and read the speech that I wrote:

"I remember my first headache. I was 12 years old and my family had just moved to California. Everyone said it was the smog. I had headaches all through high school and college. I got through with handfuls of Tylenol (acetaminophen). I planned a career in politics, but years of migraines whittled away at my ambitions. Law school was hard, but so much harder with headaches. I remember crying on exam days. I could not think straight. Overhead lights made me nauseous, and I was constantly moving away from anyone wearing perfume. Migraine disease is complicated. It messed with every area of my life.

"It's not right to complain too much about a headache. It's just a headache. It isn't life threatening. I wasn't sick, but I really wasn't well. I vacillated between feeling sorry for myself and feeling guilty. Every few years I convinced myself that I had a brain tumor. I had five CAT scans, so at least I was sure that it wasn't anything serious. With a migraine, my whole body was affected. I had flu-like symptoms, my jaw hurt, my nose felt frozen, I was dizzy, nauseous, and had balance issues. My head felt like a cement block. Vision was blurry and my hearing was off. Strong smells like perfume or ethnic food made me gag. My husband said on a regular basis that I was born on the wrong planet. That's how I felt. A day on migraine meds was not the same as a day without a migraine. About two hours after taking meds I couldn't keep my head up. I felt as though I was in a poppy field. I fell asleep at my desk more than once. I spent the rest of the days counting the hours until I could go to sleep. I had a good life despite the headaches. I've had a good life. I married, I have two kids and a law practice. In my late 30s, I decided to tackle those darn headaches. I saw my first neurologist and was identified for the first time as a 'migraineur.' I should point out that I had been to chiropractors and acupuncturists, and I've never heard the word *migraine* to describe myself. I just had these nasty headaches.

"My search for a cure for my migraines began. Every practitioner had a different theory. Here we go. I spent years and thousands and thousands of dollars. I endured painful, poisonous Botox injections. I rented a costly oxygen tank for two months. I suffered multiple trigger point injections. I wore a mouthguard. I had two sleep studies. I was told that a breast reduction was the answer. I'm still grateful for that.

"I saw Chinese acupuncturists and chiropractors. I cut gluten, alcohol, cheese, artificial sweeteners, and soy sauce from my diet for an entire year. For a few years, I convinced myself it was all sinus problems. I checked out different climates and we considered moving to the desert or the ocean. I was sad and frustrated. I missed work, I missed social engagements, and you can imagine how challenging the travel was. I couldn't go to a movie theater between the noise and the possibility that someone nearby was wearing perfume. I just gave up. I kept regular sleep times. By now, I'm certain that you understand that impact that these little headaches had on my life. This is very tragic — I can't believe I'm going to tell you this. I told my husband on a regular basis that if I was

ever in a coma — it was my greatest fear — he should feed me migraine meds every few days because my greatest fear is that I would be lying there with a migraine and no one would know. How sad is that?

“My life was controlled by my headaches. Eventually it became clear that there was actually no cure for migraines. I worried that I couldn’t go on like that for another 40 or 50 years. I never felt like the neurologist really *got it.* I realized that I was their least sick patient and without saying so, I was reminded of that regularly by the Parkinson's and MS pamphlets in their lobbies, never anything about migraines. I felt like a hypochondriac — after all, they treated Parkinson's and epilepsy. All I had was a headache. There was no hope. Several years ago, a doctor friend actually referred me to a migraine specialist. I don’t know how I missed this for so many years. I sat in his office, and I cried. I told him that he was my last hope. I would never see another doctor. He spent about an hour with me. We discussed every possible remedy. We went through everything, and lo and behold, I had tried them, every single one of them. I remember that day well. It was my eighth or ninth day of a continuous migraine.

“After a few months, he asked me to participate in a CGRP clinical trial. I told him I would pay him. I will always be grateful for that life-changing invitation. I felt better immediately. I went from 14 to 17 migraines a month down to 3 or 4 that first month. Eventually I was migraine free. I still don’t believe it. Since my last injection in mid-November, I have had five single-day migraines and taken prescription meds only twice. Unfortunately, many of the other symptoms have not disappeared since November. I am still overly sensitive to sounds and smells. I'd give anything to turn this light off right here, and I often have neck and shoulder pain that generally accompanied a migraine. I just don’t feel great. While on the CGRP inhibitor, I felt terrific; 90% of my symptoms disappeared. I never actually remember feeling better. I recently returned from a two-week trip through Italy. Miraculously, I got off the plane after a 14-hour flight headache-free. Sleep schedules were off. No migraine. I ate bread, pasta, and I drank wine. I had one bad headache. It was the day after the wine.

“It is very difficult to explain the absence of pain. Imagine having the flu, the kind where your ears and your teeth hurt, and then you get better. That's what's it like to live a migraine-free life. I wake up in the morning without fear that my day will be ruined by a constant headache. I work under all kinds of lighting now. I travel and I don’t worry about my sleep schedule. I eat and drink almost everything — still iffy about the wine, and I don’t count the hours until I can go to sleep. I no longer envy my friends who wake up in the morning pain-free, and I am so grateful.”

Dr. Dodick: There's a lot in that onion to unpack, and we are going to try to unpack some of that. So, we’ve heard about the social, the personal, the professional, the family impact, and Dr. Deb Friedman is going to talk to us a bit about impact. We have heard about some interesting aspects about onset of action, the fact that she became migraine-free, the fact that most of her symptoms disappeared while on antibody, and the fact that now off antibody she has had five single-day migraine attacks, but now all the other symptoms are back. It would be nice to sort of understand that or begin to try

to understand that from the pathophysiological perspective, and that's where Dr. Charles is going to help us. And then at the end, I am going to bounce something off you. Everyone is interested in who's eligible? Who should be eligible to be able to get to these new monoclonal antibodies? What are the starting rules and what are the stopping rules? I would like to bounce some ideas about starting rules and stopping rules off of you because that is an issue that we as clinicians are going to face every day in clinical practice.

We will start with Dr. Deb Friedman who is going to give us a presentation on burden, impact.

Dr. Friedman: Does anybody have any questions for Lynn? I can't actually see anything either. I'm either going to have a suntan or I'm going to get a migraine. Okay. Back of the room?

Dr. Dodick: The question is why did you stop in November?

Lynn: Oh, the clinical trial was over. I would have gone on forever.

Dr. Friedman: Okay. So we know, and I think this audience knows very well — don't you hate that when people say this audience knows very well, and then they go ahead and they tell you what's on the slide? Too bad. Okay. This actually is from a new publication that came out this year by Rebecca Burch and her colleagues, and I recommend that you read it. It's really very informative. They did a study looking at US Claims Data and various database data, and report that the three-month self-reported prevalence of migraine in adults is about one in six Americans, which is a lot higher number than usually floats around, including one in four women, and when looking at children and adolescents, it's about 8% or 9% overall, a little more prominent in girls than boys.

The prevalence of migraine or severe headache is actually highest in probably the least well-served populations in our country. This really struck me when I read about it, so American Indians and Alaskan Natives, the lowest prevalence is in Asian-Americans. The highest burden is in young people between ages 18 and 44, in unemployed persons, in those who have low family income, and in the elderly and disabled. Migraine is also the third leading cause of Emergency Department visits in reproductive age women.

Not only highly prevalent, but it is also highly disabling. These data come from the Global Burden of Disease Study. Headache is the second leading cause of years lived with disability (which they call YLDs) worldwide, and headache disorders are the cause of more than three-quarters of all neurological YLDs. The only thing that causes more disability in the neurology world is stroke. Migraine is the third leading cause of disability among people ages 15 to 49, and the second cause of disability in both sexes in all ages, number one being low back pain. It is the first cause of disability in people under age 50. I think these numbers are striking, and as you all know, migraine — the Rodney Dangerfield of neurology — gets no respect. With numbers like these, it should be getting a lot of respect. Most people with migraine and more than half of those who have

at least four migraine headache days a month believe that they have missed opportunities in their career. I think Lynn can speak to this, right?

Lynn: Yes, very much so.

Dr. Friedman: You would have been an incredible senator.

Lynn: No comment.

Dr. Friedman: Especially in California.

Migraine impacts work productivity for 68% of people who have it, and the pie charts on the bottom are the percentage of people who agreed with the statements below them — so, missed out on opportunities at work such as promotion, about 40%, and of those who had at least four migraine days a month, 52%. Missed out on additional earning potential at work, again, close to 40% overall, a little over 53% in those who had at least four migraine days a month. And we know that four migraine days a month is sort of the cut-off where disability really starts to take off; 32% chose to turn down opportunities at work because they felt they couldn't handle them because of their migraines, and 29% actually changed jobs to reduce the likelihood of getting a migraine. And Lynn talked a little bit about perfume phobia, and this is a huge problem for our patients in the workplace — the fluorescent lights, the perfume, the noise, the crowds — it all creates a really oppressive work environment if you have migraine.

The CaMEO Study was a large population study which looked at chronic migraine in the United States, and as part of the CaMEO Study, they assessed family burden of migraine, both for episodic as well as chronic migraine patients. There were over 13,000 respondents with a very good response rate, and there were about 4000 migraine and spouse pairs, including about half of them who also had children. Most of these people had episodic migraine. About half or a little over half of these pairs reported that migraine reduced their participation in family activities at least once a month. Many people perceived that their spouse or partner did not believe the severity or the impact of their migraine. We hear this frequently in clinic, and many times I think our patients come in with their partners and they are reluctant to say it in front of them, but I think that a lot of people really, given the opportunity, would express that they don't think that they're being taken seriously. About a third of people in the study worried about their family's long-term financial security because of their migraines. Many felt that they would be better parents, and I don't know about you, but I hear this a lot. Many people think that they're just not being good parents because of their migraines, and their spouses agreed with them but to a lesser extent. Then they looked at the adolescents. They had the parents that were paired with the adolescents, and they surveyed the adolescents about what they thought of their parents' migraine.

The responses that were highly statistically significant included loss of parental support or reverse caregiving. The teenager had to do the cooking or the cleaning or take care of their parent. The emotional experiences, fighting with their parent, being angry at their

parent for having migraine, feeling like the parent was needy or like they would just get along a lot better with their parent if their parent did not have migraine. Interference with school because parents can't participate like other parents do because of their migraines.

Missing group activities and social activities as well as major events. They looked at anxiety and depression rates among these teenagers, and they did not compare them with non-migraine family affected teenagers, but they compared them with each other. The episodic migraine children are in the darker color and the chronic migraine, the parents had chronic migraine, are in the lighter color. And you can see that among people who had parents with chronic migraine, the children were statistically significantly more likely to have depression and anxiety than those whose parents had a lesser burden of migraine.

So, you know, you never thought that you had migraine. Have you ever diagnosed yourself with migraine?

Lynn: I didn't have the word until I was about 36 or 37.

Dr. Friedman: What did you think you had?

Lynn: Headaches.

Dr. Friedman: Just headaches?

Lynn: That maybe they were sinus headaches or maybe I slept wrong. Somehow it was always my fault. Seriously. Something I did wrong. I ate the wrong food. I slept badly. Do you know how many times I went to the dentist? It must be dental.

Dr. Friedman: Yes. This is not uncommon, and the rate of self-awareness among patients with migraine is quite low.

It was a German study that interviewed patients with migraine. They had been screened for severe headaches in the 12 months prior to doing the study, and they found that there was a 60% prevalence of patients with severe headaches who actually turned out to have migraine that were diagnosed using what was then in vogue, which was the ICHD-2 criteria. The 12-month prevalence was a little higher in women than in men, as you would expect. They asked these patients, "*Do you believe that your headaches were, at least in part, due to migraine?* " 70% of them actually did. Only 41% had consulted a physician for their migraines in the past 12 months, and of those, 65% received a diagnosis of migraine. So sadly, not only is self-awareness a problem, but physician awareness is still a problem.

The most common misdiagnoses by physicians by far and away was tension-type headaches, followed by sinus headache, or then something else — stress, need a breast reduction — we know, we name it. The factors that predicted a higher self-awareness were people that had more severe headaches than more frequent headaches, those who

had typical associated symptoms of migraine, but the sex of the patient and having a medical consultation were not associated with a higher self-awareness. In a 2002 study in the United States, only 53% of patients correctly diagnosed their own headaches as migraine and the most common misdiagnoses were stress and sinus.

We know that in both the CaMEO Study as well as the AMPP Study that patients are not successfully traversing barriers to care. Richard Lipton and his colleagues defined these three tiers of hurdles that one needs to go through in order to get successful treatment. The first is consulting a physician, the second is getting a correct diagnosis, and the third is being prescribed an appropriate treatment. Now, Lynn when you were diagnosed, did they actually say you had chronic migraine?

Lynn: Never heard the word *chronic*.

Dr. Friedman: And did you? It sounded like you had chronic migraine.

Lynn: If chronic is half of my life.

Dr. Friedman: At least half days out of the month.

Lynn: 14 — 12 to 15 days a month.

Dr. Friedman: And all of your headaches were migraine, right?

Lynn: I now believe that all of my headaches were migraines. I've since had a headache. Like, oh, that's what a headache is. It's very different than a migraine. It's a little pain in my head.

Dr. Friedman: Okay. So even Lynn didn't really get an accurate diagnosis.

But we would almost settle for anything, right? Okay, so looking at patients who had episodic migraine, about 40% saw somebody. About 39%, this is the whole cohort, or 87% of those who had sought care, got a diagnosis. And then about two-thirds of those patients were prescribed in a very loose world of options what you might consider an appropriate treatment. Unfortunately, the chronic migraine story, as dismal as that is, is even worse. So again, about 40% go to the doctor or whoever they saw. Only 10% of the entire cohort gets an accurate diagnosis, so a quarter of the people that went to see a health professional are accurately diagnosed. And then slightly less than half of those get appropriate treatment. Only 4.5% of the entire cohort traverses all three barriers.

We asked the question about adherence to medication, and we know that adherence to preventives is very poor. There had been several studies done on this. I'm just going to go through one of them. It was a retrospective cohort that used a research database. This is how most of these studies are done. They identified adults in the database with a diagnosis of migraine who initiated preventive treatment, which the called their Index Event, either with topiramate, with a beta-blocker, or with a tricyclic antidepressant

between the years of 2008 and 2011. Patients had to be enrolled in a healthcare plan 12 months before and 12 months after their index date and then they looked at the gaps in therapy where prescriptions were not being filled, treatment changes, and additions of other index medications or acute medications. You can see that about half of the patients were on topiramate, about 20% on a beta-blocker, and 30% on a tricyclic.

Well, they found that 81% had gaps of at least three months in their very first year of treatment. So patients were not getting their prescriptions filled, and the gaps tended to occur early in therapy. Within the first three months, people already gave up and stopped filling their prescription. Only 10% restarted preventive therapy after having a gap, and you think, *well, maybe they just changed to a different medication*, but that was not really the case at all. Switching medications only occurred in 13%. Going to another medication or adding another preventive medication only occurred in 5%, so that didn't account for the lapse in care. And after one year, 65% of the people that were prescribed the treatment were no longer getting their prescriptions filled; 81% were using acute treatments, however. Sadly, 53% were using opioids, at least half those patients had no other pain condition for which they would be taking an opioid, meaning they were taking it for headache. And then triptans were used by about half of people.

We know that both episodic and chronic migraine have a significant impact on patients' lives. The 'chronics' are in gold and the 'episodics' are in blue. Did that come out right? You can see that the patients who have chronic migraine, yes, they missed more things, but episodic migraine is not that far behind. And I think sometimes we tend to trivialize episodic migraine as headache specialists, but there is still a significant amount of disability for patients who have episodic migraine.

Lastly, moving onto the stigma of migraine. A study of both episodic and chronic migraines and patients with epilepsy was done by Bill Young. This was actually a while ago, but they used a standard scale of stigma for chronic illness. Chronic migraine patients reported more stigma than epilepsy, which is kind of amazing, right? I mean of all the neurologic disease, as you look back through history, people with epilepsy probably were stigmatized more than anybody else, right? They were possessed by demons and had to have bloodletting. I mean epilepsy has always carried a great social stigma. Chronic migraine patients felt they were more stigmatized than the patients with epilepsy did. Both episodic and chronic migraine patients had higher rates of internalized stigma than those with epilepsy. Stigma was correlated with the inability to work in all of the groups, and age, income, and education did not affect stigma.

How do neurologists perceive migraine? This is a study that was done in France, we know that neurologists have migraine. They are more likely to have migraine than actually any other subspecialty or specialty in medicine. Right? Doctors have more migraine than the general population. Neurologists more than doctors in general. Headache specialists more than neurologists, and believe it or not, neuro ophthalmologists higher than headache specialists. These are 368 French neurologists and half of them had migraine themselves. Most of them claim to be quite interested in migraine. Most of them — thank goodness — considered it was a real illness, and most

of them considered it very or quite disabling. Unfortunately, half of them considered it very challenging to treat because of unrealistic patient expectations — we want a cure. That it is so time-consuming. That patients frequently have co-existing conditions, such as anxiety and depression, that feed into the time commitment that it takes to treat this. And, I like this term, *medical nomadism*. We call it doctor shopping, right? Going from doctor to doctor to doctor to doctor to doctor. They did not like that. There was no difference between the French neurologists who had migraine and those who did not have migraine.

Well, we got a problem here, right? There is a major shortage of headache specialists. As of the most recent count, there are only 475 UCNS-certified headache medicine specialist in the US and Canada, though we know there are people treating migraine that are not UCNS certified. I think Kathleen Digre estimated 1400 members of the American Headache Society. That is not very many people to cover the US and Canada. There's one specialist for every 80,000 patients, and there is a marked geographic disparity in this country. The best ratio of patient to doctors is in Washington, DC, New Hampshire, New York, and New Brunswick.

In 2014, there were six states in this country that had no headache specialist at all. Most of our headache specialists are located in urban areas and with higher income. There is a long wait time for appointments, and our fellowship programs are largely unfilled.

So last slide. This is the breakdown state by state of UCNS-certified headache specialists, and so you can see that there are several gray ones on the map where there's nobody and a heck of a lot of light blue ones where there are fewer than 10, and we have a long way to go and a lot of patients who need our help.

Dr. Dodick: Take it away, Dr. Charles.

Dr. Charles: Okay. Actually I wanted to ask you a question. You talked about how you tried a variety of other medications and how they made you feel, whereas the antibody therapies just seemed more definitively effective. Was there ever any treatment that you tried, any preventive treatment that you felt like it was really just doing the job and definitively helpful for you, or were just sort of taking them and trying them and giving up pretty quickly?

Lynn: Oh, I didn’t give up quickly. I hung in there. I'm astounded that people wouldn’t take a medication or fill a prescription. Nothing ever prevented migraines. I have a cabinet full of medication that I took when I got a migraine. I tried lots of different things, but nothing ever prevented, nothing ever reduced the migraines, the number of migraines I had.

Dr. Charles: That's kind of a segue into a little bit of discussion of neuropharmacology. Without getting too deep into the weeds, I do want to talk about something that isn’t really talked about that much. As much as we are hearing about CGRP, really what is it and how is it different from the other neurotransmitters that are targeted by the overwhelming majority of treatments that you tried and didn’t work for you?

So a neuropeptide is like a little protein. It is a small chain of amino acids that can be released both by neurons and by glial cells to signal the other cells, and it has multiple properties that set them apart from the classical neurotransmitters. What I mean by the classical neurotransmitters are serotonin, glutamate, GABA, dopamine that are basically even smaller and usually based on a modification of a single amino acid.

Some examples of other neuropeptides other than CGRP: at the top there is PACAP (pituitary adenylate cyclase activating peptide) which we will hear about because that is becoming a new target as well. Things called orexins that are released by the hypothalamus. Some people have heard about Substance P, called that because it is thought to have a role in pain. But multiple other hormones that are released by the hypothalamus or pituitary are peptides. Then there are the endogenous opioids in the body. Endorphins and enkephalins are peptides, and some other ones that you may have heard about involved in inflammation like bradykinin. There is a huge number of these peptides, but if you look at that list, you can see that they are involved in a variety of different functions and have some different ways that they might be released, and then might act in different regions throughout the body.

This is a slide that basically just compares and contrasts normal, what we would call synaptic transmission, and things like glutamate or GABA or serotonin are primarily released at synapses which most people know about. It's just a very tight association between one nerve and another in order to allow for very fast and very precise communication. The differences are that the traditional amino acid transmitters are processed in these what are called clear vesicles. They are turned over very rapidly. They are released very quickly over a very short distance, they activate. One of the things that I think is very important that might actually explain some of the differences in efficacy is even if they have high affinity for the receptor, they are kind of on and off the receptor and competing with the ligand for the receptor, meaning competing with glutamate or GABA. You never get a perfect blockade, and if you did, it probably wouldn’t be a good thing. The amino acid, the normal transmitters are actually recycled by pumps that basically pump the vesicles, but also pump the transmitters quickly into the postsynaptic cell on the other side. And they also, again, do not take that much to release them. Neuropeptides are processed in a very different way. They are in these sort of more robust vesicles. It takes a lot more nerve firing to release them. You have to actually wind up a nerve and really stimulate it harder in order to get it to release a neuropeptide than a transmitter. Once they bind to the receptor, they bind much more tightly. Interestingly, they can diffuse away from the synapse or be released in areas of the nerve cell that aren’t at the synapse. The idea is basically they are acting much more diffusely. They are harder to release, but once they are released they can act at a greater distance and then they bind more tightly to the receptor. You can start to think about how this sort of processing is different and also, by the way, they are degraded by enzymes that are taking them out, so they are degraded slowly as well.

Think about those kinds of concepts when you think about why this is a different target than most of the other kinds of targets that we have been using other drugs for. This is

just a summary of what I just talked about. Again, more sustained effect and I will just make the point also that this is a case where it is particularly appealing to think about antibody therapies because antibodies also bind more tightly to the receptor or bind to the peptide in a way that can have a more sustained effect than traditional drugs can.

So CGRP, it is a 37 amino acid polypeptide. You will hear this said, I think there is actually something more to this that we might need to think about. Most of the effects in the nervous system are believed to be mediated by this form alpha-CGRP, whereas the beta sub-form is thought to be more active in the GI tract. There are some potential side effects, like constipation, of these medications where this difference might actually be important and it may be important to be thinking about going after specifically alpha-CGRP as compared to the receptor that one of the other products does. There may be other types of receptors besides the CGRP receptor that are also activated by this.

There is really, really solid evidence that CGRP plays a key role in migraine. Again, also most of the other targets where we borrow drugs from other indications. We borrow Botox from its initial use for spasticity and cosmetic. We borrow antiepileptics and antidepressants and beta-blockers and blood pressure medicines, but this is something where development of these treatments is based on a fundamental understanding. And just running through these quickly, CGRP is released during a migraine attack. If you give a migraine patient CGRP which they are quite happy to do in Scandinavia, they have all kinds of ways of inducing migraine there, and we do it a little bit here too, but not as much as they do. If you give a migraine patient CGRP, they will develop a migraine attack. It has been reported that CGRP levels are elevated chronically in a chronic migraine patient. The small molecule and CGRP receptor antagonists have been shown to abort migraine, they are now being investigated as you probably heard also as preventive treatments. Then initial troubles with some of the specific small molecule antagonists led to people to go to antibodies which are not metabolized by the liver or the kidney and, therefore, are appealing because of the lack of potential toxicity due to those sorts of pathways of metabolism.

I just want to make one other point. We talked about CGRP being released in migraine, but there are other neuropeptides like Substance P, neuropeptide Y, VIP that are not released during migraine attacks. This is not just like all of these peptides are being released as some sort inflammatory response. It is a very specific response that involves CGRP, and now it has been shown that it involves PACAP as well. The other important thing is that the levels normalize when patients are treated. If they are effectively treated with sumatriptan, the levels go down.

This is just a graphic from the Scandinavian group showing that interestingly if you give CGRP to a migraine patient, they do not get a migraine attack right away but after several hours, and it does not happen in people who do not have migraines. What is happening in that delay period between which the time you give it and the migraine attack occurs? We have no idea, but I think it is an extraordinarily interesting question.

These are the so-called "gepants." This is an old slide because it only contains some of them, and these were the small molecule drugs that basically really were quite effective, especially olcegepant, in aborting migraine. And the trouble came with telcagepant which was looking good as an acute therapy, but when they started to give it on a regular basis, then it was found that a small percentage of patients developed significant liver toxicity which led to pulling that one from the market. Again, there are now multiple iterations of other gepants: rimegepant, ubrogepant, atogepant, and one other one from Biohaven.

The idea is that it looks like the ones that were pulled — that the molecules can be safe even though the ones that were pulled specifically had issues. But still the concept here that is important is, again, that the antibody therapies are not metabolized by the liver, and so it sort of takes that out of the picture as a potential adverse effect.

What do the clinical trials tell us? And this is really an exciting time because we can take what we learn from patients like you and how you respond and then go back and try and apply that understanding to really figuring out the biology. First of all, the fact that an antibody to either CGRP or the CGRP receptor works just definitively proves that CGRP is involved in migraine as far as I am concerned. I mean because it's entirely specific.

These are big molecules which probably do not cross the blood-brain barrier, suggesting that they are working outside of the brain, although as I just talked about in the symposium that made me late to this one, the hypothalamus is part of the brain that may be outside of the blood-brain barrier, but still we can start to figure out about where CGRP is important by where we think these antibodies are binding.

And then individual patient responses, again, give us an opportunity that markedly increased our understanding of basic mechanisms. I was just interested to hear about you now saying that maybe you think your neck pain is coming back a bit, more so than the headache since you stopped taking it. Are you having episodic neck pain or is it sort of there more all the time?

Lynn: Not all the time, but I don’t know that I always had it all the time, but you know, as I'm sitting here my nose is cold and my hands are a little cold — these are what I call migraine symptoms. I don’t feel great. And when I was on the CGRP, I'm telling you, I felt great.

Dr. Charles: Right. This then kind of gets to the idea that the CGRP — the CGRP peptide and its receptors are not just in what we think about with migraine always, which is the trigeminal vascular system, but they are also present in neck nerves and it is also present in the trigeminal cervical complex, the region of the brain where the neck nerves converge on the trigeminal nerves.

Another presentation that just happened in this session was the idea that the neck nerves really might, without any kind of necessarily pathology, it is not like it's a compression or anything like that, but they may be transmitting pain. And one of the things that I always ask is kind of provocative — is that every paper you read about

migraine says it's a trigeminal vascular disorder. But if that is the case, why is the first pain symptom — that a good percentage of migraine patients have — neck pain, and why is your neck pain coming back as sort of the more potentially sensitive symptom after you have come off of these therapies? Personally, I really like the idea of thinking about CGRP in cervical nerve roots as potentially a mediator.

So we moved away from the vascular hypothesis. This is a study from the Scandinavian group showing — the Copenhagen group showing that during migraine attack, there is no extracranial artery dilation, a little bit of intracranial artery dilation, but if you treat migraine effectively with sumatriptan, it is not constricting intracranial blood vessels. This is something that we have a lot of trouble with because CGRP is a vasodilator.

How do you reconcile the fact that CGRP is a vasodilator if I am saying that the blood vessels are not having anything to do with headache? First of all, I am not saying the blood vessels do not have anything to do with headache, but what I am saying is that it is not the dilation of blood vessels that is causing pain, that is the fundamental tenet of the vascular hypothesis that dilation of blood vessels is what is causing pain. The way to then explain this is that CGRP is doing multiple things. On the one hand, it is dilating blood vessels. On the other hand, it is causing pain, but it is not dilation of blood vessels that is causing the pain. And so that is the kind of thing that we have to think, not just sort of in this linear way, but that there are multiple things happening in parallel related to CGRP that again may not follow a straight line.

So this is the last slide, just kind of thinking about a migraine attack as a funnel where at the top we have genes and environment and hormones and metabolism and drugs, then multiple regions of the brain becoming either activated or inactivating. Then eventually towards the bottom on the funnel, this release of CGRP, and then depending on the patient's state at the time and their genes, then they may have different manifestations of their attack, depending on the state that they hit once they get to the bottom of the funnel.

So as David was saying and Deb was alluding to, extremely complicated and heterogenous disorder and in very hard to put into a kind of single linear pathway, but I have grown to like this idea of this sort of funnel where different individuals may have different aspects at the top of the funnel, but what we are looking for is really the final common pathways, and I think the kind of definitive effect that someone like you has had from the therapy really does suggest that this target CGRP is pretty close to the bottom of the funnel.

Dr. Dodick: Excellent. Thank you, Andy. I am going to close, and I am going to actually abbreviate my talk so there is time for questions and answers here.

Obviously, we have a lot of new therapies that have entered or about to enter the marketplace. Tonight's conversation is around the biologics and specifically the CGRP monoclonal antibodies. You have all told us already that you are knowledgeable or very knowledgeable about the antibodies. I am not going to spend a lot of time on this, but

you do know that there are three antibodies that target the peptide and one antibody that targets the receptor.

Three antibodies that target the peptide are delivered as a subcutaneous injection once monthly, although fremanezumab demonstrated efficacy as a subcutaneous administered drug once per quarter. It is a single injection. Eptinezumab, which is an intravenously administered antibody, has shown efficacy when delivered once per quarter, so once every three months. All of them have shown efficacy in episodic and chronic migraine. It is staggering actually. When you think about it, we have come to accept it now, but there has not in a single small molecule or monoclonal antibody in a single study that has not been shown to be effective. It is remarkable, and there are over 20 studies now in episodic and chronic migraine, both acute and preventive, and all of them are positive. That is remarkable. We should remind ourselves of that.

The other important thing is that there are no serious treatment-related adverse events that have been shown in any of the monoclonal antibody studies, and that is also reassuring for us and mostly reassuring for patients. Of course you know that there is an antibody, erenumab, that was approved about six weeks ago. There are two, fremanezumab and galcanezumab, that are under FDA review and have been for several months now, and eptinezumab is completing their phase III trials.

As Chair of the American Migraine Foundation, I think one of the most important things that we could have done is to advocate for our patients, and one of the most important ways to advocate for patients is to make sure that patients get access to these therapies. We are all familiar with biologics that enter the space, not migraine, but for other diseases, and patients do not get access. They cannot be treated with the medication, so wouldn't that be miserable if all of these 30 years of work and all of this effort to produce biologics came into the space and our patients could not access them? Back in January, a couple of us met with five payors, four of the five were the largest payors in the United States, a pharmacy benefit manager, a big one, and two large employers. Collectively they covered 107 million lives and over 35,000 employees and what we wanted to do was begin a dialogue about access, and what kind of restrictions or barriers to access they were thinking of placing in front of those patients. It was a very good discussion we had in Washington, DC. We were there for about six hours, and we thought we had a constructive dialogue and sort of working through issues of access. I am going to cut to the chase. We all know about what kind of patients should be treated for preventive medications and so we all see already the rather restrictive measures that are being put in place that are going to make it difficult for patients to access these therapies. I think it is important for an authoritative body to come out with some guidelines and some parameters that begin to frame up the type of patient who should be eligible for these treatments. I want to present to you some thoughts really about who should be eligible for these therapies.

We believe, or some of us believe, that a licensed medical provider who is authorized to practice medicine should be able to prescribe these therapies, that they should not be restricted to a headache specialist. You have heard that there are less than 500 in the

United States for 40 million people. The math just does not add up. Very few of them get to us, and actually only a fraction get to neurologists. We believe a licensed medical provider should be able to prescribe these therapies. Now, these antibodies are likely to be approved for patients with 4 to 30 headache days per months. Right? Because they have been shown to be effective in episodic migraine and chronic migraine, and all of the trials have had a floor or a threshold of at least 4 migraine headache days per month some a little more, but anyway. We believe that patients 18 years of age or older who had 4 to 7 migraine headache days per month and who fulfill criteria A and B should be eligible for access. Criteria A is that patients have failed to tolerate or to respond to or there is a contraindication to the use of one of those therapies listed below, at least a 6-week trial. So topiramate, divalproex, one of the beta-blockers, one of the tricyclics, one of the serotonin norepinephrine reuptake inhibitors, or one of the medications that according to the American Academy of Neurology are graded as level A or level B, and for those with 4 to 7 migraine headache days per month, they should have at least moderate disability. Because we have to thread the needle, we have to be aware of cost and so the patient with 4 migraine headache days per month likely should have a bit more of a barrier to get access than the one with 30 days per month.

These are the level A/B drugs according to the Academy and I am not going to go over that, but most of them, you are very familiar with.

Initiating treatment with one of the monoclonal antibodies in patients with 8 to 14 migraine headache days per month, the high frequency episodic group. Again, patients should have had a 6-week trial of at least two of the following same criteria. What is missing there is the level of disability. We are just saying if a patient has failed to respond to or tolerate or there is a contraindication to the use of two or more of those, they should be eligible regardless of the level of disability.

And then finally for those patients with chronic migraine, they should eligible for access if they have had a 6-week trial of any of the two of the following or they failed to respond to onabotulinumtoxinA for at least two injection cycles.

I am putting this out there because I actually really, really want some feedback tonight on whether you think these are reasonable, patient-centered, yet at the same time being cognizant of the fact that not all 40 million people or 25 million people with more than 4 headache days per month are going to get access to this treatment.

Another practical consideration I am often asked is how are you going to use these? Patients are usually on prophylactic medications certainly when they come in to see us, so are you going to add the antibody or are you going to take them off and wash them out from these other antibodies before you start the antibody? Well, I am going to add the antibody. I am not going to wash people out of something that they might have been taking for 5 years, 10 years, or 20 years. And so I think it is practical, and the nice thing about the antibodies is that they do not interact with other drugs. There is no drug-drug interaction, so I do not even have to think about that, and they do not compete with binding sites for protein or binding sites in the liver. We can add these, see if the patient

gets a robust response and then begin to start to taper away and discontinue other prophylactic medications.

I think another practical consideration is we are going to have to track outcomes. Why are we going to have to track outcomes? Because it is the right thing to do to show the patient and to demonstrate to ourselves the patients are actually getting better, but it is probably going to be a requirement for payors that we track some kind of outcomes, because if they are going to continue to pay for this, we have to demonstrate that the patients are actually getting better. And there are a number instruments that many of us use in practice that I think are — some of them have actually been developed with FDA guidance like MPFID and AIM-D, but there are a number that like MIDAS that are used in clinical practice, but I think we are going to have to follow some metric, some outcome measure to demonstrate that these patients are getting better.

Those are the starting rules that I wanted to sort of run by you, and then what patients should continue to get access after they have had initial access? We would suggest that reauthorization after initial use should be approved if either A or B are met. Patients who have a 50% reduction in mean monthly migraine days or moderate-to-severe headache days relative to their pretreatment baseline should continue to get access. And by pretreatment baseline, how many patients come to you with meticulously filled out diaries on their first visit? Not many. Not many. It is going to be based on retrospective history and not necessarily requiring diary documentation. A 50% reduction or a clinically meaningful improvement in any of the following validated migraine-specific patient reported outcome measures. A reduction in MIDAS of 5 points (when the disability level is between 11 and 10), or a reduction of more than 30% (if the score is above 20), or a drop in MPFID or HIT-6 of more than 5 points.

At the bottom, there is a little footnote, *exceptions to these criteria may be made under circumstances when deemed medically indicated*. So a little wiggle room which is appropriate for clinicians to be able to continue a treatment that is benefiting their patients. I presented a patient last night who had continuous headache, continuous migraine, who got on a monoclonal antibody and the severity was dropped from 8 to 3, and he went to 5 migrainous exacerbations per week to 2 per month, and his life was just dramatically transformed, yet he would have been a treatment failure in a clinical trial. There should be a little wiggle room because it is the patient in clinical practice who is going to define for us whether or not they are responding, and so that is just a little built-in wiggle room there that allows the patient and clinician to make a decision on whether and when to continue.