MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

WHAT TO DO IF YOUR CGRP TREATMENT DOESN'T HELP

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Introduction (00:06): If you don't respond to the anti-CGRP drugs, which work for a lot of people, one of the things I do now in my clinic is I just segue a moment, and I question the diagnosis. Because you know, for migraine, we don't have a blood test, we don't have an MRI scan; it's a clinical diagnosis. Now, I think the vast majority of people who were told by their doctors they have migraine actually do. I mean it's just, it's frightfully common, isn't it? But sometimes I say, "Well, you didn't respond to the CGRP drugs, but looking through your chart, you didn't respond to 10 other meds. Tell me again about your headaches." And, you know, you just hear it the third, fourth, fifth time: There are mimickers of migraine.

Elizabeth DeStefano (00:51): Introduction of the CGRP-related medications to the migraine landscape brought much excitement and, importantly, long-awaited relief for many people living with migraine. Unfortunately, we know migraine is far from a one-size-fits-all condition, and the relief welcomed by some has not been realized by all. Here to discuss what to do when CGRP-targeted medications aren't the answer is Dr. Peter McAllister. Dr. McAllister, welcome back to the Migraine World Summit.

Dr. McAllister (01:21): Thank you. It's a pleasure to be back.

Elizabeth DeStefano (01:25): To frame this discussion, can you please first just summarize what CGRP is and how it relates to migraine?

Dr. McAllister (01:33): So, it's interesting. Although the chemical entity CGRP — we've known about it since the 1980s. We really never talked about it until about seven or eight years ago, and now we can't shut up. I mean, you can't read a medical journal, a neurological journal, without hearing about calcitonin gene-related peptide. So, what is it really? It is a neuropeptide, and it turns out it's the inflammatory pain bad guy, not the only, but the primary one that propagates the pain signal of migraine. So, when one has a migraine, the nerves around the head, around the eyes, in the sinuses, the upper teeth, the upper neck: They begin to secrete CGRP. And once released, it binds to a receptor on the next nerve and propagates the signal in. So what we figured out was if we can block CGRP, we can block the pain transmission of migraine. And it turned out that's exactly what we did.

Elizabeth DeStefano (02:35): What classes of medications that act upon the CGRP pathway are available now to treat migraine, and how do they differ?

Dr. McAllister (02:42): So, there are two broad classes of anti-CGRP medications. The first ones are the monoclonal antibodies, and the second ones are small molecules — that is, pills. Now the monoclonal antibody looks like the letter Y if you looked under a microscope, and at the top of that Y, in the V section — we call that the business end — you can put anything you want in there. In the case of the CGRP monoclonal antibodies, we put something in which goes and finds CGRP or its receptor. If you wanted to, say, kill a lymphoma cell, you'd put something in there directing it to a lymphoma cell. Here, they're very specific for blocking either the CGRP receptor or the CGRP molecule itself. Later, after we came out with the monoclonal antibodies, we came out with the pills, and there are three of them, and they block the CGRP receptor itself.

Elizabeth DeStefano (03:38): So how successful have CGRP-related medications been in the treatment of migraine in the real world, now that we have some years of experience to observe this under our belts?

Dr. McAllister (03:48): It's really been a game changer. It's been really fun since April of 2018. We can almost divide the headache world — headache medicine — into pre-April 2018 and post-April 2018. That was when the first one, erenumab, or brand name Aimovig, came out. And it really changed the entire landscape for a number of reasons. First of all, the CGRP drugs, be they monoclonal antibodies or the pills, are the first migraine drugs directed against known migraine pathophysiology itself. Remember, all the other migraine preventives that we had were stumbled upon serendipitously when they were invented for something else, and we said, "Oh, by the way, they seemed to work on migraines." That was the beta blocker class; that was the anti-seizure class. Even Botox for chronic migraine originally came out for movement disorders, and then it was discovered to work for cosmetics, and by working on cosmetics we learned that it also works to knock out migraines.

Dr. McAllister (04:51): So, these drugs are just for migraine sufferers, just for persons with migraine disease, which I think is fantastic. Secondly, they couple really good efficacy, i.e., they work pretty well most of the time, with a very nice safety and tolerability. For example, topiramate — old branded Topamax — it's a drug that we still use in headache medicine, and it's really quite effective, but it's got a lot of potential side effects. And in fact, in the studies of Topamax for chronic — for migraine prevention — about 45% of the people dropped out of the study. That means something was wrong there.

Dr. McAllister (05:33): With these monoclonal antibody studies — and I've been a principal investigator on all of them — the dropout rates were in about the 1 to 4% range. So again, game changer when you have something that works for migraines specifically, that works really well most of the time in most people and has a very benign safety and tolerability, that's a really nice combination. And yet, there's more, because unlike the old migraine preventives, these new anti-CGRP drugs? They work fast. We've never had fast before. So, for migraine prevention, the old medications would take every bit of four, six, eight weeks to start working. These drugs work in a few days to a week; some take as many as four weeks. So we've got some really powerful new tools in our armamentarium now.

Elizabeth DeStefano (06:25): And one of the appealing things about these medications, or any promising new migraine treatments, of course, is the ability to help patients for whom previous treatments have failed. And you actually published research showing just that with the monoclonal antibodies. Can you summarize your findings on this?

Dr. McAllister (06:44): Yeah, I mean I think it applies across the board. We looked at a certain monoclonal antibody, fremanezumab, and we looked at people who had failed several classes of the, what we call the older migraine preventive drugs. Now, you would think — it seems to make intuitive sense, right? That if you failed those drugs — and really when I say that, I mean those drugs failed you — that you may be just a lost cause. Maybe things are not going to work. But we were very happy to find that in this trial, patients who didn't respond to those old drugs? They did respond to this monoclonal antibody. It was very encouraging.

Elizabeth DeStefano (07:22): But they don't work for everyone, right?

Dr. McAllister (07:25): No, sadly, no medicine works for everybody all the time.

Elizabeth DeStefano (07:30): And what really are those numbers that you're seeing in studies and then in the real world with patient populations?

Dr. McAllister (07:38): So, in the trials — remember the trials are a bit artificial by nature, right? We put people in, they're kind of pre-selected, they're fairly healthy, but they also know — because they sign a consent form to be in the trial — they know there's a chance they're going to be getting the placebo, right? So if it's a monoclonal antibody trial, it's a placebo shot. That is, it could be water. And if it's one of the pill studies, they could get what we call a sugar pill, an inert pill. That tends to pull down how well they respond to the medications. The human brain is endlessly fascinating, and if you have a chance that you're not getting the real stuff, it tends to dampen the full thing. That said, we saw pretty spectacular responses.

Dr. McAllister (08:24): So, if I had to generalize across the board, and individual trials varied a little bit, but we had — in episodic and chronic migraine, if I lumped them together — we had a good chunk of people getting at least a 50% reduction — more than 50% of them. We had up to a third to 40% of people getting a 75% reduction in their monthly migraine days. We even had, variably, a small handful but a good chunk, that had a 100% reduction in their migraine days. So, you know, again, very encouraging kind of paradigm-shifting, disruptive stuff. And it almost makes you wonder, as I said earlier: [If] CGRP is the main inflammatory pain bad guy in the migraine cascade, it kind of begs the question, doesn't it: Why isn't everybody getting better?

Dr. McAllister (09:17): There are a couple of theories there. First of all, when I said it's the biggie in most of us all the time, we do think there's a subset of persons with migraine disease who don't drive their headaches using this particular neuropeptide, CGRP. In fact, we're studying a cousin of CGRP. It has funny initials too — P-A-C-A-P, or PAY-CAP — and maybe a small percentage of the world needs a PACAP drug. Right now, there are none on the market. We're studying them. Maybe next year when you have me back, I will tell you about PACAP.

Dr. McAllister (09:50): But you know, it gets more interesting. When I say that this CGRP is the main bad guy along the pain nerve, it kind of implies there's only one pain nerve for migraine. There are actually two different types, and they have the names C fibers and A-delta fibers. Well, it turns out that the CGRP meds work at the A-delta fibers. But just like everything in life, it seems to get more complicated the more you study it. We thought there was only one particular A-delta fiber. Turns out there are like six different types, and some have more ability to respond to CGRP drugs than others, so it may be that genetics — the same things that determine your eye color and your hair color — maybe you got a bad bunch of A-delta nerve fibers, and the CGRP drugs may not be all that responsive to you.

Elizabeth DeStefano (10:43): So, are these theories — about whether CGRP or PACAP are the main driver in the headache or migraine disorder — the main belief about why nonresponders to CGRP medications don't have this relief? Is that the prevailing theory at this point?

Dr. McAllister (11:04): Yeah, that is the prevailing theory. Of course, one needs to take a step back, and if you don't respond to the anti-CGRP drugs, which work for a lot of people, one of the things I do now in my clinic is I just segue a moment, and I question the diagnosis. Because, you know, for migraine, we don't have a blood test, we don't have an MRI scan; it's a clinical diagnosis. Now, I think the vast majority of people who were told by their doctors they have migraine actually do. I mean it's just, it's frightfully common, isn't it? But sometimes I say, "Well, you didn't respond to the CGRP drugs, but looking through your chart, you didn't respond to 10 other meds. Tell me again about your headaches." And, you know, you just hear at the third, fourth, fifth time: There are mimickers of migraine — things, names like, new daily persistent headache, spontaneous intracranial hypotension, hemicrania continua — and sometimes these

conditions are occurring in that patient who's nonresponsive to a migraine med because they never had migraine.

Elizabeth DeStefano (12:15): So, you mentioned that one of the appealing things about these medications is the rapidity of onset and that we've not experienced that, really, before them, often. And I believe you mentioned that they could take days or maybe up to four weeks. How long do you give CGRP treatments to work in a patient before trying something else?

Dr. McAllister (12:38): It's a great question, because even though I said that, and I've got plenty of data to back it up, life is a bell-shaped curve, right? If we say the average male in the U.S. is 5-feet-10, it doesn't mean every male's 5-feet-10. There are 5-feet-2 males and 6-foot-8 males. So, you know, in that bell-shaped curve is a variable time to respond. That said, I'll usually give them two or three months, but not much more than that, because you pretty much know.

Dr. McAllister (13:07): I'll tell you a quick story. One of them, called eptinezumab, brand name Vyepti: That's the one that's intravenous. Very, very powerful medication. And when we did that trial as a migraine prevention drug, we looked at the data and said, "My goodness, this thing is working 24 hours after it's infused." And that was fascinating. And we wondered what it would be doing an hour or two hours after it was infused. But we didn't look. It didn't occur to us to look that early, so we didn't have that data.

Dr. McAllister (13:38): So, here's what we did. We asked our patients in a different study: “Come in when you have your migraine.” So, they're in the throes of their migraine, they've got nausea, pain, light sensitivity. We brought them into the clinic, we put the IV in, and we gave them this migraine-prevention drug. And guess what? It worked just like an acute medicine. It's like they were taking sumatriptan or something: They got better acutely. So talk about, again, disruptive and paradigm-shifting. This particular CGRP works not only prevention — and mind you, it works for three months in those in whom it works — but it can work on that day's headache. And we've never had that before in the migraine world.

Elizabeth DeStefano (14:21): So, can these medications help initially and then wane in effectiveness over time? We hear that sort of thing often in chatter from our community.

Dr. McAllister (14:32): It's a great question, and I'll start by saying: We don't have any really great data to support that. But I listen to patients, too, and I've got some patients I've known for many years, and I believe them when they say it. So it probably is real, but I would think it's in a small minority. Here's another thing, we go back to placebo. I was telling you about the placebo trials, right? Well, outside of a study, if I give someone a medicine and I say, "This is an amazing new migraine treatment; I was one of the principal investigators; I think it's going to be perfect for you." I've built up in them anticipation, haven't I? And I've built up a potential placebo effect. Now outside of trials, the placebo effect is fine. I don't care how you get better; I just want you to get better.

Dr. McAllister (15:18): And what happens is, if someone takes their first shot of one of the drugs and says, "My gosh, my headaches were terrific," and it never happens again with subsequent shots, they were a placebo responder. Reasonable brains want to get better, and they can be temporarily tricked, but the brain figures it out soon enough. I think that's the main reason why some people say the first one or two are great, but it stopped working. Now the monoclonal antibodies are indeed antibodies — they're protein. So there is a theoretical risk that just like a shot, say a COVID vaccine, you could potentially build up antibodies to that shot. Well, it turns

out in the studies, in all the trials I've been part of, we looked in the blood for antibodies to these, and occasionally we found them, but it didn't inactivate the power of the drug. So, I don't think that — even though it's a biologic and a protein — I don't think building antibodies against it is part of that.

Elizabeth DeStefano (16:21): So as someone living with a chronic condition like migraine, when you hear about something like these CGRP medications coming and having profound impacts, positively, on others, it can bring a lot of hope. And that can be devastating for those for whom any new medication or treatment doesn't work. A member of our Migraine World Summit team, Brian, has asked if he could be an outlier, noting that CGRP-related medications just have not been terribly effective for him. So, let's start with prevention: Where do you go next?

Dr. McAllister (16:54): Again, in a center like mine, I see patients like Brian all the time. So, I kind of divide them up as I hear their story and I review their records. There are some people, I think, who didn't give the CGRPs a good enough go. They may have tried one shot and one gepant or something; they may not have done it long enough. Not saying it's their fault; their clinician may not have directed them properly. So in those, I will revisit the CGRPs. I think that there are — of the CGRP monoclonal antibodies, three of them work against CGRP itself and one binds the receptor. If someone's only been on a receptor one, I'm going to switch them over to a nonreceptor one, and vice versa. And then we have some evidence to believe that the IV infusion is probably not only the fastest, but it's possibly the most powerful one.

Dr. McAllister (17:46): So, if they failed the subcutaneous autoinjectors, I will often try at least one or two goes with the intravenous version of the monoclonal antibodies. And mind you, when you mentioned gepants — that's the pills that we're talking about that block the CGRP receptor — they are a little bit different. So you can't say, "Oh, I tried 'a CGRP drug'" without having tried at least one gepant. The main difference is the size: that it can get in a lot deeper to other CGRP receptors that were not seen by that monoclonal antibody. I then take a step back and do something that not all doctors do.

Dr. McAllister (18:27): And I will preface this by saying — there's no studies on this, and you should check with your healthcare professional. But again, I've been involved in these studies for 10 years; I've helped design some of these trials; and what the FDA wants when we make up a trial, is they want the minimally effective dose in the trial that works for the most people, most of the time, with the least amount of side effects. That's a good trial dose. Now I mentioned the bell-shaped curve of life, right? Different heights, etc. So, one of my options in the right setting, if CGRP doesn't work, is to use more CGRP. Now, there are some theoretical reasons why you could run into problems there — and again, check with your healthcare professional — but I've really not seen them in my selected groups. Brian could be either a complete nonresponder, or Brian's particular makeup genetically is such, he needs a higher dose. So, we are already looking at the IV formulation in a 400-mg dose. We're looking at ubrogepant, the acute drug Ubrelvy, in a 200-mg dose. We're pushing these doses up, and we may find that we get more people in who are responders. And I think those studies are absolutely necessary.

Elizabeth DeStefano (19:51): So, you're looking here at dosing — frequency of dosing — to potentially reach those higher doses. Of course, also bringing in challenges, as you said: If you can get your hands on it, around insurance coverage, and cost, and those sorts of things. So, this is certainly, I'm sure, a complicated issue, but one that further points to "one size does not fit all" when it comes to migraine treatment.

Dr. McAllister (20:13): Absolutely. And then, we can do the, sort of, the finesse of headache medicine after really carefully listening to the patient. We can use medicines that have different mechanisms of action. So, remember when I mentioned those pain pathways, and I said one was a C fiber, then one was an A-delta fiber. Well, it may be that you're working on your A-delta fiber, but the C fiber is now going crazy transmitting pain information. In those individuals — now how do I know? I don't, we don't have a test for that — so we will sometimes add a medicine that works on the C fibers. So if it's chronic migraine, Botox happens to be a C-fiber drug, so that's where Botox works. So sometimes shutting down A-delta with a monoclonal antibody or a gepant CGRP blocker and using Botox to knock out those C-pain fibers, can completely wipe out the headache.

Dr. McAllister (21:12): Now, we are accumulating evidence on that; right now, it's just at the level of say, retrospective chart reviews. Someone can look at 500 patients in his or her practice — this has been published both on the left coast and the right coast — and found that if someone's headaches — let's say you're on Botox and you went from 28 headaches to 14 — well, that's a 50% reduction. You could say, "Job well done." But not really, right? They still have 14 bloody headaches in a month. So now we add on a CGRP, and with any luck we drop them another 50%, down to seven. And you could do the same thing with someone who's not terribly responsive to a CGRP — you can then add Botox. You can certainly add older medications as well, and I do that — just knowing that, you know, you bring in more potential side effects.

Elizabeth DeStefano (22:08): So, a number of approaches here in your practice, if someone comes in and indicates that they're not responding to prevention from CGRP-related medications. You're looking at diagnosis; you are assessing dosage and frequency, potentially, of dosage in assessing dose; you are looking at adding in something else to compliment that CGRP-related medication; and when need be, you're looking back at earlier older drugs for prevention.

Dr. McAllister (22:39): Correct. What we also do with someone who's really failed just about everything, including the CGRPs — and I'm convinced … I might have gone up on the dose, I may have added other products — we're then looking at newer molecules that have not been rigorously studied yet, such as intravenous ketamine, intravenous lidocaine. And then, only available in research right now, and very scant research, would be things like psilocybin, which is the stuff of magic mushrooms, and LSD. Most of those studies are being done outside the United States, particularly in Switzerland and in Austria and in Denmark.

Dr. McAllister (23:16): But we hope to get some really useful information because, you know, it can be really difficult as someone who has waited for this class of drugs forever, has been terribly excited about it, has done a good course of it with a good clinician working in tandem with them, only to have it not work. It's rather heartbreaking. And I always want to have something else to offer them, even if it's coming in the future. This molecule PACAP that I mentioned earlier — not available yet except in studies but we're hoping that those studies will be positive, and we'll have something else.

Elizabeth DeStefano (23:49): Now what about your approach for acute treatment if a CGRP-related medication does not seem to be the answer for one of your patients?

Dr. McAllister (23:58): As an investigator on all those trials, I was and still am, amazingly impressed by how safe and tolerable they are. I mean, they have side-effect profiles that are virtually placebo-like, and there's a lot to like there. In the trials, we had pain-freedom rates at about 21% and pain reduction in the 50, 60% [range]. So, with the acute drugs, there seems to

be a little bit bigger group who doesn't respond to them. The way I look at those gepants used acutely — Ubrelvy and Nurtec being the two available — is, when they work, there's nothing better because they're so benign. You can operate heavy machinery, you can work a full day, etc. When they don't work — again, this is off-label, check with your clinician — I'll have them sometimes double the dose, because, again, going back to my argument before, some brains just need more than what the studies were designed to show.

Dr. McAllister (24:59): And you know, we now have a ditan medicine out there. We still have the triptans — which were, again, back in the 90s, the revolutionary disruptive agents that really changed the landscape back then. We've got nonsteroidal anti-inflammatories, which have a lot of data in acute treatment. The problem with nonsteroidals is, in a pill form, they're too slow, right? Migraine is a race against time: Time is brain, and the quicker you put out the fire, the less likely you are to go onto a full-blown migraine with what we call central sensitization. The newer drugs, there is a liquid celecoxib. Celecoxib is old Celebrex, used for osteoarthritis and other things, which would be way too slow for a migraine in the pill form. We've now made it into a little liquid form in a wee little bottle about 2 inches tall, and at the onset of migraine, if you drink this — it's microemulsion is absorbed very, very quickly.

Dr. McAllister (25:58): We've also found novel ways to deliver — going back to the triptan class — delivered into the nose, for example, there is something called Intravail. If you mix that with a sumatriptan nasal spray, it opens up the cells in the nose and allows much more of it to get in. Fascinating. There's also a very old drug called dihydroergotamine. I mean, it came out after World War II in an IV form. There was a nasal spray form in the 90s, but it was very poorly absorbed. We came out with a new nasal spray of DHE called Trudhesa, which is sprayed way up to the top of the nose. It's a very small membrane separating nose from brain, and it just shoots right up there. You don't swallow it; it doesn't go through the stomach or the liver. So, you know, we have new things out in the acute-treatment landscape for those who fail the oral gepants.

Elizabeth DeStefano (26:58): So, Dr. McAllister, how would you advise patients to respond when their doctor tells them, "I've tried everything. I've done everything I can to help you."

Dr. McAllister (27:08): I would say rather dismissively, "Seek another healthcare professional." And maybe that is the case, but I don't know. I don't mind being gently challenged. I don't mind a patient saying, if I say to them, "Boy, you really have been on everything," they say, "Well, work with me. What else can we do?" There are novel combinations of layering on medications. We also have to take a step back. You know, these new medicines, these CGRP drugs in particular, are just so darn effective that we've almost gotten away a bit from all the other hallmarks of treating migraine: What's your lifestyle look like? Are you getting no sleep? Have you processed the trauma that occurred in your childhood? That's a — having traumatic life experiences is a big predictor for chronic migraine and a poor response to medications.

Dr. McAllister (28:00): So, at our center we have trauma therapists, and PhD psychologists; we do biofeedback. So sometimes you gotta get back to the essentials, back when we needed these tools because the medicines weren't so good. Now that the meds have gotten better, we need to kind of return to those type of things and really make sure we're really pushing that and reviewing that in detail with the patient. And then with all the new research out — I mentioned LSD and psilocybin and ketamine and all that — I always think there's stuff coming. And if you accept something for now, that doesn't mean there's not going to be something groundbreaking in six months or two years.

Elizabeth DeStefano (28:42): Well, and hope certainly is an important and powerful thing to offer.

Dr. McAllister (28:47): Absolutely.

Elizabeth DeStefano (28:47): Are there any final thoughts you'd like to leave with our audience, Dr. McAllister?

Dr. McAllister (28:53): Yeah, I think understanding that migraine is a disabling medical condition, and making sure that your healthcare provider understands that as well. I have found some people who are neurologists who might be very good at Parkinson's disease or Alzheimer's or MS, who really don't know headache medicine. Seek out the proper individual. And if you're gently pushing or challenging your doctor and not getting what you want, move on. You deserve to find someone who is going to listen loudly to you and give you options and give you hope and keep it alive.

Elizabeth DeStefano (29:28): Where can we learn more about you and the work that you are doing, Dr. McAllister?

Dr. McAllister (29:33): So, it's New England Institute for Neurology and Headache. The website is neinh.com and my email — feel free to reach out — is Peter@neinh.com.

Elizabeth DeStefano (29:46): Thank you for that. Are there any resources that you'd like to recommend on this topic, or related to migraine, to our audience?

Dr. McAllister (29:54): Well, a fun one is headachedocs on Instagram. We have an informative and lively Instagram, so please do go on and check us out and "like" us. I think the American Headache Society does a good job with some of their patient-related things, and I always try to keep up to date and give those to patients. We just wrote a book, and the two main authors are Robert Kaniecki and Mark Green. And my chapter's on clinical research in migraine. But what it is, is it's a textbook for patients and it's written in a question, like, "I have an ice pick headache, you know, in my eye, what is that?" Or, "How do I get into a research study?" So, if you look up Roberti Kaniecki and Mark Green and take a look at their brand new headache book, it answers an awful lot of questions.

Elizabeth DeStefano (30:46): Excellent. Thank you so much, Dr. McAllister, for being here with us.

Dr. McAllister (30:50): Thank you, Elizabeth. It was a lot of fun. I appreciate it.