Episode 249: April Migraine Research News: PACAP Treatments, Exercise & Cannabis Studies

Lindsay Weitzel, PhD:
Hello, everyone, and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I have a history of chronic and daily migraine that began at the age of four. Today we are here for our headache news episode with Dr. Tim Smith. Hello, Dr. Smith, how are you?

Tim Smith, MD:
I'm doing very well. Thanks for having me on again.

Lindsay Weitzel, PhD:
Well, thank you for being here. We love having Dr. Smith. He is a regular on our show due to his extensive experience in migraine clinical trials as the CEO of StudyMetrix Research. He is also a board member of the National Headache Foundation. He is awesome to talk to. I always learn so much when he's here and I get very excited, so I hope you are all ready.

We are going to start with a press release for a new medication that is in clinical trials. This announcement is something that most of you probably haven't heard about. But here on HeadWise, if you follow us, we have discussed how some new medications that are coming out are not targeting the CGRP pathway like so many of our medicines do, but instead are targeting a different pathway, the PACAP pathway or PACAP. It depends on how you say it. And so, Dr. Smith, why don't you tell us about this medication and what this new information coming out about it is.

Tim Smith, MD:
The medication obviously it doesn't have a brand name yet, but the chemical name or generic name, it's bocunebart. And I know that's how you pronounce it, because I got my AI program to explain it to me how you pronounce it. It's bocunebart. This has been in development for some time, and the pharmaceutical company Lundbeck has had this in clinical trials looking at a new alternative way of treating migraine. As you mentioned, it does not block the CGRP pathway. It blocks this PACAP pathway, PACAP-38 to be specific. And there's a long name. It's pituitary adenylate cyclase-activating polypeptide. And you can practice that when you're trying to fall asleep at night.

Lindsay Weitzel, PhD:
That's the reason God made acronyms.

Tim Smith, MD:
No better acronym than this one. Basically, it's a signaler for part of what we call the parasympathetic nervous system which is involved in migraine. It's the part of migraine that makes your eye turn red or you produce tears or get a stuffy nose or some of the other autonomic dysfunction kinds of things. And so, it's been an attractive model. Three different pharmaceutical companies have had candidate molecules in the pipeline. And today, Lundbeck is the only one that has positive results. And this came from this phase 2 study. Interestingly, it is using the medication in an IV route. So, this would be kind of similar to Vyepti, if people know what that is, administered intermittently via the IV pathway.

The press release doesn't give any numbers, but I looked up some study numbers from their results that they are starting to put into the medical literature and I expect will be presented at some of the scientific meetings this spring, show that 32% of people had a 50% reduction in their migraine attacks. And so, I don't know what the placebo response was, but the announcement says that it was statistically significant. And so, for a phase 2 study and for those people that know about the study results, phase 2, even if it doesn't achieve statistical significance and it's an area where there's a big unmet need, the pharma companies may go ahead and enter into phase 3. And that's where the real tale of the tape is going to be.

So, the upshot of this press release is that this drug looks like it's good enough to go on into phase 3. And if it does, they'll finish their phase 3, and if it continues to perform like this, it'll be FDA approved and available. It may be 2 or 3 years before we get there if it's positive. But I think that having this completely new route of treatment that doesn't track along with the serotonin pathways or with the CGRP pathways or others, or anti-inflammatory pathways of other sorts. This is a totally new mechanism. And this might be, to me, it would hold out hope to folks that don't respond to the usual treatments that we have out there. And we know that those people are still there and they're still looking and searching. So, my message is I hope this gives some people hope that at least we haven't given up yet, and somebody is still looking and trying new pathways. And there are some others in the in the pipeline too, and we can talk about those someday, some other molecular pathways are not this far along. But if there's new things coming, this one will be the next one if it does pass muster in phase 3 trials.

Lindsay Weitzel, PhD:
I was going to ask, for anyone who's listening who did not respond to any of the medications targeting the CGRP pathway, is there any reason to believe that they might be a responder to these medications targeting PACAP?

Tim Smith, MD:
I think it's very reasonable to expect that. Some scientists have posited that PACAP may be the most important non-CGRP pathway that we could be treating. So, I think a lot of the non-CGRP responders could do better. And just from my perspective, I would wonder if what if you used a combination, and you had two separate pathways that could be synergistic or at least additive in your results. And that might give a pretty fascinating result. So, hopefully we'll be able to do those trials. They'll have to confer with the FDA and get their plans together. But I would expect they'll probably be trying to start a phase 3 study within the next six months to a year. And so, I'll keep you posted on that. If we get to do the trials, we'll be very anxious to see how it works in people in the clinic here. So that's the fun part of my job.

Lindsay Weitzel, PhD:
Our next study is moving on to something a little more immediate and something we can do ourselves. It's on aerobic exercise. I always listen up on these. I'm one of those people who can notice right away with exercise the difference in my pain level. They looked at how much aerobic exercise is needed to reduce migraine. And they did it as a meta-analysis, meaning they looked at all sorts of studies pooled together. And they wanted to see if they could actually come up with an amount so that they could recommend it to people. What did they find? Could they give us an amount that's best for reducing frequency or severity of our migraine?

Tim Smith, MD:
Well, they did actually come up with some numbers. And to your point, I think the results have been sort of all over the place and recommendations have been all over the place. And in most migraine clinics, headache centers, and neurology clinics recommend patients exercise. And then if you ask how much they just gave you the standard whatever people need for weight management or cardiovascular health. And the question always been is the migraine need the same. Because we also know that there's such a thing as getting too much exercise. If you go out and do a long distance run and you get dehydrated and you get whatever other lactate buildup, other physiologic things that happen to you when you exercise vigorously for a longer period of time and that'll trigger a migraine for migraine patients. And it's been a big thing for me. And I've loved to run for many years, but I always have to be careful and realize that as much as I love running, I don't love having migraine. So, it's kind of trying to find that balance in between.

And so, what they found, they pulled the results from 15 studies, and they pulled the data from the individual analytics and made a big data set out of it. And what they saw is, if you look at the amount of aerobic exercise that people do, and this is aerobic exercise, this is not pumping iron, resistance training. It's aerobic, cardiovascular aerobic exercise, which we think is the best for migraine management. But if you look at the response, if you start with from zero exercise and then you go forward, your migraine frequency and intensity go down with increasing exercise. And then if you continue, the people who do more and more and more, that it starts going the other way.

So, it's kind of a U-shaped curve. And on the low end is sort of less than 200 or 300 minutes. And this happened to be in a 10-week to 11-week period. So, you had to get at least 200 or 300 minutes of exercise over that period of time to start seeing a significant benefit, and it maximized at about 900 to 950 [minutes]. That was your maximum benefit for both. Interesting to note, this is for both migraine intensity or severity and migraine frequency. The optimum zone for the pooled data from this study, and everybody's going to be different so it may not exactly pan out for individuals out there, but if you play the odds, that should according to this analysis, that should be the target. If you think about 10 weeks, 900 minutes, that's 30 minutes, 3 days a week as being the ideal spot. So going over that, you start running the risk of your migraine getting worse again in terms of frequency and intensity. And if you do less, they'll get more. And so, it's trying to be structured in that range. Nobody has that perfectly structured of life. But if you can kind of use that as target numbers, according to this analysis, this would be the optimum initial target, is to try to build to that amount.

Lindsay Weitzel, PhD:
So, three times a week, 30 minutes sounds like it was the best for most of the people in that group. So, we finally have a bit of a recommendation, so that sounds good.

Let's move on to our next study. A group of researchers published on something that I almost find a little funny because we've heard when it comes of the CGRP medications with regard to nonresponders. We've heard of super-responders. I thought we'd heard of all the responders. But this group named something called false nonresponders to the anti-CGRP therapies. And these were people who were treated with the monoclonal antibodies but perhaps did not meet the usual endpoints that researchers looked for, for such reduction in headache frequency. However, they may have found other benefits to the medications. So, can you tell us what they found in this group of people and why it's interesting medically and research wise?

Tim Smith, MD:
I think this has some clinical relevance and also relevance as it pertains to insurance coverage for example. And so basically, the 50% reduction in migraine days is the primary outcome for migraine preventive studies. And as it turns out, insurance plans have sort of arbitrarily picked six months and said if you haven't reduced your migraines by 50%, your migraine days by 50% by that time, then you're really not a candidate. You're not benefiting enough from it to stay on the treatment. And it doesn't matter, patients may be very happy with a 25% reduction in migraine, especially the folks with the high end, 25% may be like a miracle drug to them. But then if the insurance company pulls the plug and they are left to spend their own cash on it, it's like a car payment. And so, it's very hard to keep up.

And what these folks did is they looked at people who were nonresponders. And then they got them access to drugs to be able to stay on it and followed them for another six months, so they got on out to 12 months. And what they showed was that, number one, for many people, the other surrogate markers for response are more important than or is equally important is migraine days. So, for instance, they looked at things like the HIT-6 score which is a measure of headache impact. And if patients who had reductions in that but still had migraine many more days of the month than not and didn't have a significant reduction in the number of migraine days but had a significant reduction in the impact that their migraine had on their quality of life, those people this study showed that it was not desirable for them to be taken off of their medication because they relapsed and their quality of life got worse etc.

And then the other thing they noticed from this was if they were able to have those people who were declared nonresponders at six months, if they were able to keep them on medication, by the time they got out to 12 months, about 20% more of them, they became true responders. And so, that's the population they're calling false nonresponders, so they were declared nonresponder too early is basically the deal. And so, the message is that we should advocate for patients to be able to get access to treatments even if they're having a partial response. If their severity may be down, but their migraine days are still high, and if their impact is lower, their quality of life is better, they're better able to do more things in their life, be it work better, more completely without as much absenteeism, presenteeism, then it's worthwhile to stay on it for another six months or more and see what goes on with that.

We know that these markers that we look at, we have to pick these endpoints to make sense of the clinical trials. But then taking just that endpoint and applying it to the real world is not always the

wisest thing to do. Those endpoints are designed to answer research questions, not to answer questions about drug coverage by insurance companies. I think I said that right.

Lindsay Weitzel, PhD:
I think that's a great study. I do think even just some of the people I know, it took them quite a while to respond and they really do need these medications. So, I think it's interesting that we have that in the data now.

And our last study, is from a group that looked at vaporized cannabis for the treatment of migraine. We are getting more and more studies now on cannabis and on THC. But the field is still fairly new. We don't have a ton of data. What did they find? Were they able to look at THC versus CBD, etc.? What was helpful?

Tim Smith, MD:
Yes, they looked at all that. Cannabis extracts are kind of like, it's a mix of a bunch of stuff, but we think that the principal effective ingredients have to do with some derivatives of THC and/or some derivatives of CBD or cannabidiol. These are basically marijuana or cannabis extracts that do have central nervous system effects. They attach to endocannabinoid receptors and elicit responses that can actually be pain reducing. And we've had anecdotes of this. Anybody who's managed migraine for any length of time has had patients who are, if you talk to people, I'm sure in your groups that you host you have people who discuss their responses to these.

I've done this for 30 years or more and in the early days, the cannabis products were kind of taboo, and they were illegal in all 50 states, and enforcement of the laws was more strict. And so, it was harder to get any research done on them. These cannabis derivatives were schedule I controlled substances, and there was only one place in the United States that could grow and use marijuana extracts for research. And that was my alma mater of Ole Miss. I went to Ole Miss pharmacy school. University of Mississippi had marijuana fields and a lab that studied the extracts of marijuana when I was in pharmacy school in the early 80s. But things have changed a lot since then. Now the majority of states have either medical marijuana or recreational marijuana availability.

And so, our anecdotes of people getting relief from things like migraine and other pain states as well has multiplied. But then it's always been the debate of what's the best way to take it? What's the best preparation to use? Is CBD the active ingredient? Is it THC? Is it something else? Is it a combination of things? And so, what these researchers did from California is they looked at vaporized or vaped cannabis products. And they looked at CBD, they looked at THC, and they looked at a combination of THC and CBD, and then they compared to placebo. It was in a blinded trial, and they used four puffs from a standardized vape device.

The results were sort of interesting. The CBD + THC combination was the most effective of the treatments and was statistically very significant versus placebo. The CBD alone did not separate from placebo significantly. But the THC + CBD combination did and had the best results. And the pain relief, migraine relief measure, which means going from moderate or severe migraine to mild or none, this used to be the measure we used for triptans studies many years ago. But if you looked at just that result, the result was 67% responder rate. And if you go back and look at all the old triptan trials, that's basically the best numbers we had from sumatriptan and from rizatriptan and all the different triptans

drugs had a result about that same level. And if you looked at the two-hour pain freedom measure, which is what we use nowadays, that's what the marker was for the CGRP drugs to get them approved. And the pain freedom at two hours response rate was 34.5%. Which actually, if you look across all the clinical trials that have used this as primary outcome is that's pretty darn good. So, in the placebo arm was 15%, so it was doubled that, so the therapeutic gain was about 15%, which for that endpoint in this population is a pretty good result as a research outcome. So, these kinds of results would get any drug approved as long as the safety data and all that was there. This was just a single-attack trial, so longer term use, I don't know. We haven't seen those study results published yet.

There are some companies that are looking at sort of more purified endocannabinoid agonists that would instead of using the THC or some recreational drug preparation, this would kind of refine it better. But the inhaled route was sort of the interesting approach on this study. And people would say, well, why can't you just take a pill or gummies or a shot of something or whatever? It turns out the inhaled route of delivery, pharmacologist and pharmaceutical experts will tell you that's one of the fastest ways to get a concentration of drug into the body. It's faster than an IV administration because you inhale it and there's all the surface area inside the lungs. And those molecules that pass across mucus membranes will get straight into the bloodstream. From the lungs it goes straight to the heart and straight to the brain, so there would hardly be a faster way of administering a pharmacotherapeutic agent too. If you're trying to elicit a change in the central nervous system, this would be an ideal way doing it

Lindsay Weitzel, PhD:
Is there any risk in inhaling it? With results that great, I would think that there's a lot of people that are like, wow, my triptan or my whatever hardly works, maybe I should try it. But is there any risk?

Tim Smith, MD:
Well, that's the unknown, because it is a single attack trial. The real risks would probably come from repeated use, unless somebody had an allergic reaction to whatever it's diluted in or something like that. I don't even know what other kind of preservatives and vehicles they put in there, but that would be the unknown. But people have been vaping marijuana derivatives for years. Just my side of it, I know that people have been smoking these derivatives for many more years than that. I did grow up in the 60s and 70s, and so it's been around for a while and widely, widely used. And obviously inhaling smoke into your lungs is not a good thing physiologically. These vape products, they get rid of the smoke, but do they have other things in there that might make it a problem long term. If somebody, some company was going to try to market this product as a migraine remedy, they would have to do those safety studies and submit that to the FDA to get FDA approved. So maybe that'll be in the future.

Those of us that work in our space, that do what we do, would love to see that get done. But with the availability of vaped THC and CBD products out there, a lot of patients may just take it on their own to go out there and try it. And it's certainly well within their prerogative to do so. But we don't endorse the use of something that hasn't been adequately proven. I think we got some pretty good efficacy results here in this small study. But what we need is longer term studies with better safety and adverse event outcomes looked at over time. And I think we'll see that. I think there's probably 150 or more studies on clinicaltrials.gov right now that's looking at cannabis derivatives for different kinds of pain, including migraine.

Just 10, 15 years ago, there was only like three or five, so there's really kind of a great interest in this and I think people want to know more. And it's become a lot more socially acceptable to use these as a medical intervention. Most state governments have approved it. It opens the door for people to consider it and decide what they want to do for themselves. But I think as a researcher, I would really like to see the next steps take place, and let's really get a good compendium of data to support the recommendation of this for our patients that suffer so much.

Lindsay Weitzel, PhD:
Right. And I think this is a good time. I think we can ask our viewers to drop a note if you have used vaporized cannabis and it worked for your migraine. You can let us know. I think it would be a great way for us to interact with our audience. Or if THC versus CBD, or if there's a combination that works, because this is an interesting thing to share. So go ahead and drop a note if you can.

That is the last study that we are going to report on today. And thank you so much, Dr. Smith, for being here with us. We always learn so much and thank you everyone for joining us. Please join us again on the next episode of HeadWise. Bye bye.

Resources:

1. Lundbeck corporate release: Lundbeck announces positive phase IIb top-line results with bocunebart (Lu AG09222; anti-PACAP mAb) in migraine prevention https://mb.cision.com/Main/18215/4307114/3933204.pdf

2. How much aerobic exercise is needed to reduce migraine? A dose–response meta-analysis of pain intensity and frequency https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.15070

3. False nonresponders to anti-calcitonin gene-related peptide monoclonal antibodies: A real-world analysis beyond migraine frequency reduction https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/head.70012

4. Vaporized cannabis versus placebo for acute migraine: A randomized, double-- blind, placebo-- controlled crossover trial https://pmc.ncbi.nlm.nih.gov/articles/PMC12872409/pdf/HEAD-66-365.pdf