Episode 232: New Migraine Research: GLP-1s, Breastfeeding Safety, and NDPH

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

Tim Smith, MD:
Doing well. Thanks for having me on again.

Lindsay Weitzel, PhD:
Thanks for being here. Dr. Smith is a regular on our show due to his extensive experience in migraine and clinical trials as the CEO of StudyMetrix Research. Dr. Smith is also a board member of the National Headache Foundation. We are going to discuss some of the recent, most interesting studies published related to headache medicine.

There has been a lot of talk recently about GLP-1 inhibitors, that a pilot study was just published in *Headache* a few weeks ago on the GLP-1 inhibitor Victoza [liraglutide][1] and migraine in patients with obesity.[2] What did they find?

Tim Smith, MD:
The researchers put patients on a drug called liraglutide, which is marketed under the brand name of Saxenda, and it's marketed for the indication of weight loss. It's a once-a-day injection as opposed to some of the more popular ones which are weekly. But this is the drug. And they studied patients with this as an intervention and then counted their migraine days basically. And they showed a substantial reduction in migraine days. And it was clinically relevant, and I wouldn't say surprising, but the effectiveness was as good or maybe even better than some of the FDA approved medications that are out there now.

And this was a small, open-label single treatment arm trial, so we don't have the good placebo-controlled numbers and all that kind of stuff. But better is better. And this is where we start. Lots of clinical programs start with the open-label trial of a small number of subjects. And that's what we have here, but with substantial results. And one of the interesting things that they showed was that the migraine reduction was not associated with weight loss. So, it's not just a weight loss reduction. We know that weight gain is one of the key associations with migraine chronification. So, it stands to reason that if you lose weight, you will have a reduction or less propensity to chronify your migraine attacks.

But this drug led to a reduction in migraine days without the corresponding weight loss. So that points to a different mechanism, and we think it may be inflammation related. Drugs are also shown to reduce expression of CGRP as well, and I have no idea how that works. It doesn't block receptors that are stimuli receptors for CGRP. So, it's just worked on the GLP-1 receptors and that's associated with appetite suppression and increased gastric emptying time so that it makes people feel full and not overeat. And they're less likely to snack in between meals. So that's how it works for weight loss. But there's probably another independent effect, and it may have something to do with inflammation.

Lindsay Weitzel, PhD:
I wanted to bring that study up because we had Dr. Betsy Grunch on recently who's a neurosurgeon and had brought up these medications and how they seem to be helping people with migraine. So, it is something that people are looking at and it is so interesting. So, thank you for explaining that to us.

Another study we were going to talk about today, I always like to bring up studies that are helpful for moms who are planning a family, etc. So, a few weeks ago a study was published in *Headache* that evaluated the safety of ubrogepant (Ubrelvy) in lactating mothers.[3] What exactly did they find? Now we have to say here that research and published research is not the same as FDA approval, but it can be promising if we find good news. So, what did they find?

Tim Smith, MD:
I'll say it's an open-label phase 1 study. So that means they had lactating women, less than six months out from their pregnancy, go and stay at a phase 1 center while they drew their blood for 24 hours. This is how you take a dose of medicine and then draw your blood every hour, every two hours, around the clock. So, getting people to do those kinds of studies can be a challenge. But anyway, it gives us very valuable information. And I'm going to just cut to the chase and say that this showed very negligible amounts of excreted Ubrelvy in the breast milk of lactating mothers.

In fact, they showed that only 2/100 of a milligram of a 100mg dose, only 2/100 of a milligram actually made it into the breast milk. So, I think we can feel good about that. And I think they may try and submit for some label update with the FDA for this. And that would be very convenient to have if we could get it. But the results sure are reassuring. And this comes on top of the fact that the rat studies when they did laboratory animal studies, if you looked at what happens in rats, the serum concentrations and the breast milk concentrations in rats doesn't really change. It's about the same. So, this is good. Obviously we know rats and humans are different. And this is just one more way and it's reassuring in my book, so we were happy to have that publication to look to.

Lindsay Weitzel, PhD:
Another study, this was a retrospective study, was published recently in *Headache*.[4] And this group conducted a chart review of adolescents with migraine who were prescribed a medication called memantine. Now, memantine is most often used in the setting of Alzheimer's disease, but they wanted to see if this would help with migraine prophylaxis in this group of adolescents. What did they find?

Tim Smith, MD:
They found that it does seem to work. It does reduce migraine days. And these were kids with a lot of headache days. And the average was 22 migraine days per month, and they shortened that to 15 days. 15 days is still a lot, but if you can take 7 migraine days out of the month, and just in this small subject population, I think that's a very good result. It's better than we see in a lot of FDA approved products. This medicine has been looked at in open-label series and case series and those kinds of things in the past in adults and did show some fairly successful results in those. And some headache clinic specialty clinics will sometimes utilize the drug. It's marketed under the brand name of Namenda. But it's been generic for a while, so it's very cost effective to do.

This drug inhibits glutamate receptors. We know, I don't want to get too esoteric here, but glutamate is one of those excitatory neurotransmitters. It's kind of a brain gas pedal that tends to escalate or be associated with escalation of migraine. And so, it makes sense if you can block it, then you can inhibit some of those migraine attacks. And that's what they saw. It is safe to use. Only a couple of the kids in this study developed a little bit of tired feelings from it, which is not bad for some of the drugs that we use. Beta blockers and tricyclics and things like that can be very sedating and zap your energy. This could have done a lot worse. Hopefully we'll get some good control studies, and we'll see where this goes. But certainly, we're always looking for options and answers. Some of our listenership and viewership are always interested in knowing more about things that could be a potential help. This doesn't guarantee it's going to help anybody, but it's good to have options.

Lindsay Weitzel, PhD:
This medication I like to talk about it. I like to bring up that study because I just love anything that can help kids that age, help families with kids that have that much migraine. It's a very difficult situation to be in. So, I hope that that was helpful to somebody.

The next one we're going to discuss is the randomized clinical trial called the UNITE study published in *JAMA Neurology*.[5] And they looked at Ajovy [fremanezumab] in patients who had both migraine and comorbid major depressive disorder. What happened when these patients with both migraine and major depressive disorder were treated with Ajovy?

Tim Smith, MD:
Well, they got better and they got better on both accounts. Their migraine days were reduced. Not a big surprise. That's what we use Ajovy for. And maybe it's not a huge surprise that if people have less migraine, they'll have better moods. But the patients were assessed using this Hamilton Depression score. We call it Ham-D scale in clinical trials. And they showed a substantial and clinically significant reduction in their depression scores. Interestingly, I think one of the really cool things to point out about this study is everybody that was in the study had the qualifying migraine diagnosis, and they also had qualifying major depression diagnosis as well.

This is unique because sometimes we wind up with patients with depression in clinical trials. But for the most part, most of the sponsored clinical trials, they exclude those patients just for safety risks and those kinds of things. So here we have a great study that actually proactively recruited patients with both diagnoses. You had to have at least a year of a depression episode that they were struggling with. So these were not people who had a history of depression, were on medicine and they were fine. We

see a lot of people like that, but these were people who were still having struggles with their depressed moods despite being diagnosed and plugged into the healthcare system and being treated. And that was great.

To our knowledge, this is the first study that has actually gone out and intentionally, prospectively done a clinical trial. Most of the work that we've seen done before is observational studies or cohort studies where patients just happened to fall into a database where we can look at outcomes. And those are helpful too, but nothing satisfies the scientific standards better than a prospective, controlled study. So, kudos to the researchers of Richard Lipton and some of his collaborators. We have seen them so many times in the literature with good studies, so we know that we usually give them the stamp of approval because they do a good job of designing these things. So, tip of the hat to them.

Lindsay Weitzel, PhD:
And it was a very interesting study. I like that one. The next one we're going to talk about was a group in the UK in the *Journal of Headache and Pain*, and they looked at the efficacy of Aimovig on people with NDPH (new daily persistent headache).[6] And I always like to report these types of studies because there's just not as many people studying NDPH as there is migraine etc., and we know we have a lot of friends in our audience that have NDPH. So how effective was Aimovig in treating NDPH?

Tim Smith, MD:
So this was an interesting study. They designed the study to have three comparison groups, and what they did is, we know that chronic migraine, especially daily chronic migraine, can appear to be very similar to new daily persistent headache. The primary distinguishing feature is that the NPDH (new daily persistent headache) is just like that. It starts suddenly and most of our chronic migraine people start with intermittent episodic migraine and will evolve into or transform into a chronic migraine condition, and some of the more severely impacted of those folks will progress onto a daily chronic migraine. So, there's a little difference between the daily, every single unremitting day, and chronic migraine.

And so, what they did in the study is they recruited a population of NDPH patients. They had daily chronic migraine patients, which are phenotypically identical, but they have a different start to their syndrome. And then the third was patients with chronic migraine, but not daily chronic migraine. So, they treated them all with [the CGRP monoclonal antibodies erenumab (aimovig) or galcanezumab (emgality).] And they looked at their monthly migraine days and headache days at the end of 12 weeks, which is kind of the standard first endpoint that we look at in clinical trials. And basically, they showed that the [CGRP monoclonal antibodies] worked for the chronic migraine populations.

It worked better for the non-daily chronic migraine population. Something like 80% of those patients had a reduction. Although I quibble with them a little bit on their endpoints. So, what they did is, they said they were looking at the proportion of patients that had a 30% reduction in their migraine days. We usually in migraine, or headache days I should call it, not migraine, but we usually look at 50% as sort of the measure of improvement that we're trying to get. That's what the pivotal trials have looked at in all the studies. In this they kind of lowered the bar a little bit because NDPH is so hard to treat. And what they showed was that the chronic migraine population that's not daily, I think the result was something like 86% of the population achieved that 30% reduction in their monthly migraine days or headache days.

And then the NDPH group, it was only 23%. So, it's less than 1 in 4 got this kind of lower bar that they managed to achieve. So, on one hand it's sort of discouraging that it looks like we can't count on the CGRP blockers very well for NDPH, but on the other hand, there is 1 out of 4 that kind of did have an improvement. And a lot of our folks out there would love to have a 30% reduction in their monthly headache days. So yeah, I wouldn't blow it off. But it does point out that there's something fundamentally different about NDPH from chronic migraine. And the CGRP may be part of that scenario but certainly blockade of CGRP with one of the best drugs we have doesn't get the job done for the majority of people.

So, it's helpful to know that there's a handful of folks who would benefit. And I would say in the clinic, I would certainly give it a try. It's worth trying. I wouldn't let the study or others like this kind of dissuade you from doing it, because there are some that will respond, at least partially. So it's worth a try. But from a scientific standpoint least, it means we've still got a long way to go on this, unfortunately.

Lindsay Weitzel, PhD:
Right. I think it's helpful for people with NDPH or people who know them just to hear these types of things just so they know they're not the only one who the medications are not helping them. And we do have a long way to go, as you said. So, I always like to bring up those studies.

Last, we have sort of a fun, interesting study that I like. It's a study that was just published.[7] It literally just came across my desk about the cycle of the moon and migraine attacks. This really is kind of fun. Can you tell us what this is about? And I also found this interesting because I have a friend who's an OB who swears that more babies are born on a full moon. So, I keep hearing from doctors that the moon matters. So tell us what this study found about migraine and the moon.

Tim Smith, MD:
From the results of this study, it looks like the moon matters with migraine too. But it doesn't track with the full moon. Interestingly it tracks the new moon. So, it's like the last day before the first day of the new moon seems to be like the worst period of the month for migraine attacks. And it was about 35% more migraine liability at that time point in the lunar cycle as compared to the full moon cycle. So, I don't know if that has anything to do with having babies. And maybe if people feel better on a full moon and have their worse migraines on a new moon that, like nine months later there's going to be more babies born. I shouldn't have gone there, sorry.

But this was actually from a methodology standpoint, I think this was a great study. They tracked this population of patients just prospectively. And they captured all kinds of variables. And patients did like diary entries twice a day in terms of their health and their headaches and what they were doing. They tracked their menstrual cycles. A lot of people will look at it and say, well, you have menstrual cycles, maybe this population, it was it was their menstrual cycles just happened to jive together. And it did not. So, this had nothing to do with their menstrual patterns. It had nothing to do to with any other activities that they were tracking.

They had these patients wear activity monitors like Fitbits and things like that so they could track some of their vital signs and how active they were, how much they were sleeping, how physically active they were. And there was no corresponding association with any of those endpoints. But there was for the

lunar cycle. Very interesting. This circalunar cycle is recognized in many animals and insects and other species of living beings on the planet. And some of those are known to be genetically driven that there are genes that express, lead to the expression of proteins or other molecules that tend to be associated or expressed or have their effect with respect to the lunar cycle.

So this makes you wonder if there's some kind of primordial thing that lives in the migraine brain that is something in your lizard brain, some of my patients call it. Some evolutionary thing that's just stuck with us over the millennia that may be associated with the expression of some inflammatory proteins or something else or has some effect on these neurogenic or neuronal pores that allow chemicals to flux in the brain and be associated with migraine physiology.

There's a bit of a leap between what we know and what we can hypothesize. But it's fun to think about it. And I thought that was a fun little article and it's well done. And I think it'll open up the doors to a lot of thinking about this. And I guess from a practical standpoint, our patients would, if you find that there's something to this, and everyone will have to do their own litmus test on it to see if it applies to them personally, but you might want to make sure you got your abortive medicine refilled before, having it handy. You don't want to get caught in a in a new moon without your abortive handy. Anyway, I don't know.

Lindsay Weitzel, PhD:
Very, very good point. Good advice. So yeah, thank you for that. And glad we got a fun study. We can end with laughter. So, thank you for being here, Dr. Smith. And thank you everyone for joining us on this episode of HeadWise. Please join us again. See you soon. Bye bye.

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[1] Saxenda and Victoza are both injectable medications that contain liraglutide. They have the same active ingredient, but they're approved for different uses. Saxenda is FDA approved for chronic weight management in people ages 12 and older. Victoza is approved to treat Type 2 diabetes in people ages 10 and older. It can also help lower the risk of major adverse cardiovascular events in adults with diabetes and heart disease. Saxenda and Victoza are both injected once a day.

[2] Effectiveness and tolerability of liraglutide as add-on treatment in patients with obesity and high-frequency or chronic migraine: A prospective pilot study. *Headache* https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/head.14991

[3] Milk and plasma pharmacokinetics of single-dose ubrogepant in healthy lactating women. *Headache* https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14960

[4] Memantine as a migraine prophylactic agent in adolescents: A retrospective analysis. *Headache* https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14979

[5] Fremanezumab for the Treatment of Patients With Migraine and Comorbid Major Depressive Disorder: The UNITE Randomized Clinical Trial. *JAMA Neurology* https://pubmed.ncbi.nlm.nih.gov/40323613/

[6] Calcitonin gene-related peptide monoclonal antibody treatment for new daily persistent headache. *Journal of Headache and Pain*
https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-025-02111-2

[7] Waning light, waxing pain: The lunar cycle's association with migraine headache occurrence. *Headache*
https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.15035