HEAD Wise

**Episode 264: Headache News**

**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 the education and support group 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:**
I'm doing great, Lindsay.

**Lindsay Weitzel, PhD:**
Dr. Smith is a regular on our show because of his extensive experience in migraine clinical trials as the chief medical officer of Rovia Clinical Research Site Network. He is also a board member of the National Headache Foundation. Today we have lots of interesting studies to talk about.

Statisticians recently noticed an association between cluster headache and certain COVID vaccines. Can you please talk to us about this publication?

**Tim Smith, MD:**
Sure. There have been some case reports, primarily from tertiary headache centers, that have hit the literature over the last couple of years suggesting an association with some of the COVID vaccines and onset of cluster headache. And some researchers from France looked at the French pharmacovigilance database. And this is the post-market and other reporting database. It's a voluntary database that clinicians or patients can report things that happen to them after a new medicine or a vaccine or those kinds of things.

And so, these researchers looked at reporting frame of time appropriate and looking at the onset of cluster headache after receiving one of the COVID vaccines. And there was a definite association with those vaccine administrations and the onset of cluster headache attacks soon thereafter, within a few days, usually. And there was also an association with worsening of intensity or increased intensification or triggering a new cluster episode in patients who had previously diagnosed cluster headache that might have been going through a dormant period. One of the patients' headache had been dormant for seven years and then got this new onset of a cluster attack after having received a COVID vaccine.

So, this was in this French registry. And we see these associations in registries sometimes, and we look at them in the US as well. And what was interesting that these researchers did is they looked at the probabilities of patients having some other onset of a medical illness after a vaccine. And it was clear that this cluster headache association was real. It was more pronounced for certain brands of vaccines.

It looked like the one that is marketed in France, which is an attenuated viral vaccine, not the mRNA vaccines that were so popular in the US and elsewhere. But it seemed to be more associated with this live virus vaccine in France. But they all showed a signal, and it was anywhere from 14 to 20% increase to as much as three times increased in what they would have expected to have occurred.

The problem with studies like this is we don't know, there's all kinds of biases in the reporting, but when you do look at those probabilities, it does suggest that there's an association. And as we talk about all the time in this podcast, association does not mean causation necessarily. But there is a plausible sort of theory. We know that there's a lot of inflammatory, processes going on in cluster headache, and some have hypothesized that cluster headache is a chronic inflammatory condition that is marked by these episodes of almost near unbearable headache attacks. And we also know that vaccines stimulate the immune system, which is an inflammation reaction basically. And so that's about as close as we can get. Nobody knows why if there is an association, if there could be any causation, but it could be having something to do with activating some inflammatory mediators. But it's a leap. We don't know that, but it's a presumption. But it's worth more study. But it's certainly an interesting correlation and one worth mentioning.

**Lindsay Weitzel, PhD:**
I think that people listening to this, a couple of questions that I bet are going through their mind are, were all of these people in this study people who had previously had cluster headache, or are some of them patients who developed cluster headache?

**Tim Smith, MD:**
Some were new cluster headache. Some had never had a cluster headache attack before, and they started experiencing cluster headache attacks after receiving the vaccine. And this occurred at a higher rate than you would have expected just by chance alone. And it occurred at a higher rate than other conditions that could be seen at a similar rate just by random chance. So, there was a definite correlation.

I guess we probably should also, and you may have been heading in this direction, but this doesn't mean that people shouldn't take vaccines because of the fear of triggering headache syndromes. But it is just a curiosity that that shows up. And I'm sure they're going to be more reports that will come out about this and we'll see. It's sort of interesting that over time the data becomes less correlative. But there's sort of a reporting fatigue that happens over time as people have gotten more and more used to COVID being present in the world. There's less of a reporting initiative on the part of many. So, there's some of that in this too, and that kind of tends to make the data a little more difficult to understand.

**Lindsay Weitzel, PhD:**
Another question that might come to people's minds is does this study follow patients long enough to know if this trend went away? In other words, did these headaches resolve or did they not follow people long enough to know?

**Tim Smith, MD:**
And so, this was data that was mined from a reporting database, so they don't really have good longitudinal follow up. So, we don't really know what happened to these patients. Did they continue to have cluster headache attacks. And that that's a great question. And I'm sure everyone would love to know the answer that. We just don't have it here. Some headache clinics have reported out on some of the longevity of the attacks because those patients are followed there. But the jury's still out on whether this is going to be a long-term phenomenon.

**Lindsay Weitzel, PhD:**
Let's move on to our next study we're going to discuss. There's a study out recently that reported an interesting side effect of atogepant (Qulipta). What did they find?

**Tim Smith, MD:**
This was the results of a long-term open-label study that was tacked on to the end of placebo-controlled trials using atogepant for migraine prophylaxis. And they studied both episodic and chronic migraine prophylaxis. And they took the patients who completed both of those studies and put them into an open-label extension that went on for as long as 156 weeks total. And what they showed was there was this association with weight loss for the patients that were taking atogepant. The dose was 60mg, which is the standard sort of top dose for atogepant, which is marketed in the US under the brand name of Qulipta.

So, this was an interesting thing. This has been reported before. There's been an association from the double-blind portion of the study, which was very short. And this gives us some information about continued use and what happens basically. And what the researchers showed that they considered a 5% body weight loss to be clinically relevant body mass loss. And for the patients in this long-term open-label extension study, about 45% achieved that significant weight loss at some point, at any time during the study. And about 30% had that significant 5% or greater weight loss at week 52, so one year in.

So, this gives us that longer duration, what happens to these patients. If I'm not mistaken, I think the previous data releases had shown that people would lose 3 or 4kg for part of the study participants. But this gives us these patients over much longer. We want to know if this is this a persistent thing. Do people continue to lose weight. And those were the results that they found. So, it's interesting. I think compared to the weight loss products that are being marketed today, this is a very modest sort of weight loss. But given the fact that many migraine preventives can actually lead to weight gain, and having chronic migraine, for example is associated with weight gain as well.

And then we also know weight gain is associated with the propensity to transform into chronic migraine. So, we'll take what we can get on this. I think patients would be, if you've got 2 or 3 treatments to choose from and one of them could potentially help you lose 5% or more of your body weight and keep it off for a year, that would be a welcome addition, both just for body weight control for some people and then also for prevention of transformation of headache into chronic migraine, or worse.

**Lindsay Weitzel, PhD:**
And to just clarify, while this recent study seems to have found that there's weight loss associated with atogepant (Qulipta), that association hasn't necessarily been found for the other CGRP medications, has it?

**Tim Smith, MD:**
That's true. It's speculative to try to understand why, but this may have something to do, and this is just my opinion, I'll throw it out there for what it's worth, but a lot of the research that's going on in the weight loss world now is focusing on amylin receptor stimulation, and there may be some bleed over. The amylin receptor genetic code lives right next door to the CGRP DNA signal. And so there may be some bleed over to those receptors, since they come up from the same strand of DNA and there are some lookalike areas in those receptors, in those molecules, that it's perhaps Qulipta gives that desired effect on amylin as well. Again, that's just my made-up response. Someone who knows more about amylin receptors could probably comment better. But these are some things that we suspect. And we know that there could be a possible contribution from that.

**Lindsay Weitzel, PhD:**
That's pretty darn good for a made-up response if you ask me.

Hormone replacement therapy (HRT) has been in the news a lot lately for various reasons, and we do have a recent paper out on HRT, headache and migraine. What did this paper find?

**Tim Smith, MD:**
This was an interesting paper. The researchers that did this work went back to Women's Health Initiative study results, which was back from the 90s, actually. And our listeners may and viewers may recall that this was the study that sort of incriminated hormone replacement therapy with the incidence of breast cancer and endometrial cancer in women and led to a very stark reduction in the amount of hormone replacement therapy that were given to menopausal women. And we saw a corresponding drop in breast cancer rates as a result of that. But this database is still there, and it’s a treasure trove of data, because they looked at all aspects of life in these women who were taking menopausal hormone replacement therapy, so including things like headache severity and headache trajectory for migraine patients.

And what they looked at on this was the different forms and combinations of the hormone replacement therapy. And just to cut to the chase of what they found was that the women who were taking only estrogen postmenopausally for hormone replacement therapy reasons, did not really have a significant change in their headache intensity or their migraine intensity or trajectory. By trajectory, I mean worsening over time. But the women who were taking estrogen and progesterone combination therapy, and many have done that, that combination was associated with an increase in migraine intensity and a worsening trajectory for women. So, suffice it to say, nowadays, not as many women take a menopausal hormone replacement therapy and if they do, they don't for very long.

And incidentally, this study looked at one year's worth of data in women that were 64 turning 65. And they followed it for a year, just as a snapshot to look at what was happening to their migraine attacks

while on therapy. And I think there was something like 28,000 cases in the database, so this was a huge analysis that went on. So, for women who would benefit from menopausal hormone replacement therapy, there is ample evidence that an estrogen alone plan would be potentially less intrusive to their migraine attacks for our patients who suffer from migraine.

**Lindsay Weitzel, PhD:**
That's surprising because it's not necessarily what we've always heard to do, is take estrogen alone, but it's super interesting

There is a press release on Dysport which is a neurotoxin much like Botox. What did this press release say that might be interesting to people who have headache and migraine that are watching?

**Tim Smith, MD:**
Well, basically what it said is that they've completed studies looking at prevention of migraine. And interestingly, they looked at both chronic migraine and episodic migraine. Our readers and viewers know that this means less than 15 monthly days of migraine and headache. And we know that the previous neurotoxin studies have not shown a benefit in the episodic group. And this study using Dysport, there was a demonstrable improvement in the migraine attacks in this episodic group. And they also had good results in the chronic migraine group as well. Problem is this is just a high-level press release, and we don't really have the numbers. Everybody's going to want to know how many how many headache days were reduced, and that hasn't been released yet. I expect it will be at a scientific meeting or in a publication soon. But for right now, it's just a press release showing that they have positive study results. So, I think our viewers will want to know that and be on the lookout for what those numbers look like when they're published.

**Lindsay Weitzel, PhD:**
And then last but not least, there are some new guidelines about migraine care that have been released, and we're going to do an entire episode on them. But I was hoping you could just introduce the fact that they're out there so that our audience is aware.

**Tim Smith, MD:**
The American Headache Society and the American Academy of Neurology issued a jointly created set of guidelines. And there was another organization that had produced guidelines a year or two ago, and they weren't met with much approval, at least in the headache world. And by that, I mean headache clinicians and migraine patients, to be honest with you. But these guidelines are, as you said, they've just been published in the journal *Headache* recently. And a lot of organizations and patients have been digesting them. And the National Headache Foundation is going to have a commentary released about this. And I'm sure this will be discussed on a future episode with you.

But I think the reviewers who came up with these guidelines looked at evidence. They had a very strict methodology for making these guideline recommendations. But I think what's different about these recommendations, and I think they tried to do an honest job to take into account the patients' preferences. For example, for chronic migraine prevention, and by the way, this is all prevention, so different preventive medicines for preventing migraine attacks. The acute treatments are under a

different guideline. But this is the newest version of preventive guidelines, medication guidelines for migraine, chronic and episodic. And just for an example, for chronic migraine, you have a category that shows the most efficacious treatments that are out there. And then they also have a category of recommendations for patients who prioritize low risk of side effects.

So, it's not just the comparing, splitting hairs over minute differences and success rates in between studies where these agents weren't even compared head-to-head. This is sort of giving information that patients and clinicians care about. And I guess I'll leave it there and you guys can discuss it more in depth for your upcoming episode. These new guidelines are there. And I think we're spending some time getting used to the way they approach this. And so, it's causing a lot of discussion. And as I said, the National Headache Foundation is going to release a commentary on it. It won't be a new guideline per se, but what we think about the pros and cons of this new set of guidelines.

**Lindsay Weitzel, PhD:**
All right. Well, thank you so much. Thank you for being here, Dr. Smith. And thank you everyone for listening in. Please join us on our next episode of HeadWise.

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