Episode 217: Headache & Migraine News: FDA Approvals, Treatment Updates & More | March 2025

Lindsay Weitzel, PhD:
Hello and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I'm the founder of Migraine Nation 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 today?

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

Lindsay Weitzel, PhD:
Thanks for being here. Dr. Smith is a regular on our show because of his extensive experience in migraine clinical trials as the CEO of StudyMetrix Research. Dr. Smith is also a board member of the National Headache Foundation and a headache specialist. We're extra excited whenever he is on, and he knows so much. So, let's see what we can learn about today.

We have a few newly published studies to discuss, and we even have a couple of new medications that have been approved by the FDA that I'm really excited to chat about. Let's dive right into the new medicines. Let's start with the one that's for migraine. There is a new migraine medication approval. It is not yet available in the pharmacy. We're going to have to wait another four months or so, but it's been approved by the FDA and it's from a company called Axsome. Can you talk to us about that Dr. Smith?

Tim Smith, MD:
Sure. It's exciting to have a new FDA approval for acute treatment of migraine and the brand name of this drug is called Symbravo. We're referring to it as a new drug. It's actually a combination of two drugs that we've had for quite a while. And those two drugs are rizatriptan, which we know is the brand name of Maxalt, and it's been around for a long time and many of our viewers undoubtedly may use a rizatriptan or drugs like it, and then the other component is something called meloxicam, which is a prescription anti-inflammatory medication.

And so what this Axsome group has done is combine the two ingredients together in a single tablet. And the meloxicam is marketed for treatment of arthritis or inflammatory conditions, and people take it basically once a day. And it's got this long half-life, and it kind of has the onset and duration that you would want from an arthritis medicine. But we know that these ibuprofen, super ibuprofen like medications can be good for migraine pain as well.

And this company put together meloxicam, it's a little higher dose than what you can get on the original brand name that's out there, but it's 20mg of meloxicam and 10mg of rizatriptan which is the standard dose that's in the Maxalt marketed tablets. The unique thing that they did is they formulated this tablet so that the meloxicam portion is released quickly. And instead of having a time to the maximum onset of three hours, it gets to maximum onset in less than an hour. So that, combined with the rizatriptan, which kicks in in less than an hour, gives you sort of that two mechanisms.

It's kind of like what they did with Treximet you may remember some years back with sumatriptan and naproxen. And so, this is kind of a follow on to that but trying to get the longer duration with meloxicam and get that more rapid onset with the special formulation. They've performed well in their clinical trials. About 20% of people were pain free at two hours, compared to less than 7% on the placebo arm. And the researchers did a good job of trying to minimize that placebo response in the study.

And interestingly, they did a second study where they treated the patients when the headache was mild.

Lindsay Weitzel, PhD:
So earlier.

Tim Smith, MD:
Yeah and their percent response for just a level one headache out of a one, two, three scale, the pain freedom rate was almost 33% compared to 16% on the placebo arm. So these were significant. The FDA reviewed. They've had a long and kind of rocky road getting this thing to the market. They started out in the pandemic debacle and their studies were stymied, and they had a lot of delays in that. And then the FDA had them do a lot of additional statistical analysis and different ways to report. And it's taken them a while, but they've finally gotten their FDA approval. And I think we'll have a lot of our folks that will want to try that.

Lindsay Weitzel, PhD:
We only have about four more months to wait. And Symbravo is what it's called. So be on the lookout for that. And as Dr. Smith said, we actually did report on that for the first time quite some time ago. We've been waiting a while for this medicine, and there are some people that are pretty excited.

We're going to move on to our next FDA approval, which is not specifically for migraine. In fact, it's for acute pain. It's a non-opioid that is a painkiller. But we do have a lot of people in our audience who get a lot of procedures, etc. So, we are going to talk about this medicine, and it could be relevant to us. It's called, I hope I'm saying it right, Dr. Smith. It's called Journavx. Why don't you talk to us about that.

Tim Smith, MD:
Yeah, I think it's Journavx. That's what it looks like. This is what they call a gated sodium channel blocker. And sodium channels are on peripheral nerves and the relay stations in the spinal cord that send pain signals to the brain. And they're basically the open the pore and the signal is transmitted. And so if you block it, you can block a pain signal. And that's what the researchers were able to show in these acute pain models. I think you pointed out this is a non-opioid and this is a first non-opioid acute pain treatment we've had in my career basically. And the medicines work peripherally so they don't have central nervous system side effects to speak of. This class of drugs, I think it will be, this is the first one. There could be others in the development pathways.

They studied these acutely post-operative patients. So you have surgery for, in the studies they did, was abdominoplasty kind of tummy tuck procedures, and then bunionectomy. It's a foot surgery to remove bunions. And these are painful surgeries. And the patients require analgesics, opioids in the post-op stage. And they substituted Journavx for the opioids. And basically the studies to cut to the chase, they showed similar results between the opioids and the Journavx. That's encouraging because we are trying to steer clear of opioids for obvious reasons. Diversion of use, misuse, and overdoses, those kinds of things are a problem with opioids.

And we know for our migraine patients they are problem with inducing this opioid induced hyperalgesia. Presumably these sodium channel blockers won't have those kinds of issues and rebound and or medication overuse problems. It's not specifically for migraine. They study this differently than we do migraine. They use different endpoints. But I could see patients who frequently have to rescue with analgesics, this might be something that would be a preferable substitute for some of the opioid medicines that some people have to use for a rescue out there or sometimes do.

Lindsay Weitzel, PhD:
I was going to ask, what's the next step? Is there a reason that it's not indicated for chronic pain or specifically for headache yet? Or do you think that they'll start testing it in these populations or using it in these populations?

Tim Smith, MD:
The company is already sponsoring chronic pain studies, so for like diabetic neuropathy or other chronic daily pain issues. And those results are still pending. The studies are ongoing, but they did get their approval for acute pain. I'm not aware of any migraine work going on anywhere. Perhaps they will study a migraine population or sponsor a study that some of our research friends could perform. I think that would be a great project to pull off.

Lindsay Weitzel, PhD:
Or any of our other headache disorders, NDPH, or anything. It sounds like it would be interesting to know if it helps anyone in our community. Our next study is a meta-analysis that was published this month. And it's on a medication that's normally prescribed to lower cholesterol. But it is thought that it may actually help improve migraine, which I find super interesting. What do you think of this work and why might this be true?

Tim Smith, MD:
Now, this is kind of a pooled analysis from some researchers that pulled together some observational data to look at this association. But we've known about or thought about this migraine preventive effect that apparently statin drugs may have. It still needs to be studied, but there looks to be like there's a connection. The authors of this paper point out that the statins are what we used to call them HMG-CoA reductase inhibitors, and now we call them statins I think for obvious reasons. That's a mouthful, but HMG-CoA reductase is the enzyme that's produced that is responsible for creation of LDL, bad cholesterol we call it. And the association between overexpression of this gene and increased headache has been described before. And then there have been some small observational studies that have looked at the association of migraine with the statin drugs.

To cut to the chase, patients who are treated with statins tend to have a reduction in their headaches. And their analysis, when they pulled this information together, it was about a three-day reduction in monthly migraine burden just from these small studies. And the other interesting thing is that it appeared to be extra effective in patients who had higher vitamin D levels. We're aware of a company that was trying to design a study a few years ago to look at the combination of statin drug with vitamin D as a supplementation as migraine headache preventive, but we never got to do that study. I don't know where it is, if they're seeking funding or whatever. But hopefully we'll get more information on that.

But it's sort of interesting. And I guess from my perspective, this doesn't give us reason to go out and start putting everyone on statin drugs. But especially if your general practice prescribers, internal medicine, family medicine, generalists who may be looking at a patient's overall health care, if there's an opportunity for kind of a what we call a therapeutic twofer, someone's cholesterol is high or even borderline high, and they have migraine, it certainly makes sense to me to try to get a statin on board and count some headache days and see if it's worth pursuing.

Lindsay Weitzel, PhD:
I guess what I'm curious about it, and I bet some people are wondering, do we know if there's any obvious risk factors to taking a statin if you don't have high cholesterol?

Tim Smith, MD:
Because I could imagine someone who's, well, my cholesterol is not high, could I take this anyway and look for the headache benefit potentially. And we don't know of the potential downside from taking a statin drug in the face of normal cholesterol. We know that some people who have heart attack and stroke and have normal cholesterol, they put them on statins anyway because the statin drugs have what we call endothelial stabilizing effects. And that means the inside lining of the blood vessels are stabilized so they're less likely to have another stroke or heart attack. Some people take that another step and say that may be related to why there might be a migraine prevention effect, but we don't know that for sure. But it's an interesting association.

There used to be a presumption that extremely low cholesterol was associated with cancer, but that came from patients who had cancer and had low cholesterol. It turns out those people were really sick and had been on chemotherapy and their cholesterol runs low because of their cancer and their treatments. And so it's not a cause and effect relationship. This would be something that individuals would need to talk with their doctor about whether or not it would be worthwhile. You say, I've got a strong family history of stroke, and my blood pressure runs a little bit high, but I don't have high cholesterol. But I do have these migraines. Would it be reasonable. You can think of scenarios where it might be considered.

Lindsay Weitzel, PhD:
I love this study. This is another surprising study. It looked at the use of proton pump inhibitors and migraine. And the reason this is interesting to me is I feel like we're always hearing about something negative related to proton pump inhibitors. And so many people with migraine take them, whether it's because we took indomethacin or some other NSAID, and we got ulcers or something wrong with our

stomach. It is interesting so I really wanted to report on this. What do you think of their findings that it might increase migraine?

Tim Smith, MD:
If you go and look at the package labels for Protonix and Prilosec and some of these, the omeprazole and other like molecules that are very, very common. You can get Prilosec without a prescription, and I think Nexium too these days or some brand of that. So, they're felt to be highly safe and very effective in preventing stomach ulcers or treating stomach ulcers or preventing acid reflux where they're commonly used a lot or treating the symptoms of that.

But if you go back and look at the original clinical trials on several of these proton pump inhibitors, the number one side effect in the clinical trials was headache. It occurred at something as often as 12% of the patients. And we think of with more modern medicines if they have side effects occurring more than, say, 2 to 5% of the time, that's considered a lot. And as many as 6 to 12% of patients on proton pump inhibitors had headaches. And these were in clinical trials for stomach acid reduction, so patients just report what they have. That's not to say that these people met the IHS criteria for migraine, the things that we say in clinical studies, but they did have significant headache. And it was during proton pump inhibitors use and did not occur to that extent in the placebo arms of those studies.

So, this is something we've been aware of for a while. We still don't understand exactly why. But what these folks did, is they did a PubMed review, and they wound up doing a narrative review looking at the few studies that have looked at this. Basically, the clinical trials had not been done to look at the association. But we do know there are people who metabolize the proton pump inhibitors very quickly. Rapid metabolizers we call them. And then there are people that are slow metabolizers. And in studies that were looking at the differences between those two, the patients who were the slow metabolizers and accumulated more of the drug in their bloodstream had a lot more headache days than the people who were the fast metabolizers.

So that is sort of more supportive information, just besides the placebo control's adverse events in the clinical trials for the drugs. Some have suggested that there may be a CGRP role in this, but the evidence is not great for that. So I don't want to get in that situation. What we know, we look for. What we look for, we find. I don't want to get into that business. But it's clear that proton pump inhibitors may be associated with increased headache. I think for our viewership, those of you that are taking proton pump inhibitors out there, I would suggest you talk to your doctors. I don't want you to just discontinue a drug because of this. If you wound up having bleeding ulcers or something as a result of discontinuing it unwisely, that wouldn't be good.

The take home message is be careful with this. In my career, I have had patients who've had refractory headaches that if they were on proton pump inhibitors, I would have them stop at least if it was medically feasible to do so. I'd have them stop and see what happens to their headache days. And more than once, we saw some people get some reduction in their migraine. So, this is kind of some more supportive data to really confirm that it's not just a casual observation, that this is really an association that we need to pay attention to. And hopefully we'll have some more research work done on it down the line.

Lindsay Weitzel, PhD:
I think the last study we're going to talk about today, it's interesting because it found a relationship between chronic migraine and pelvic pain in women. So why might that be?

Tim Smith, MD:
Well, I think the general way of thinking of this is that our patients with chronic migraine, we know that they have a fair amount of central nervous system sensitization. So, these higher pain centers get switched on and it just makes pain sensitivity go up. And so, we know that's a characteristic of chronic migraine. And we know that that's a shared feature with other comorbid pain disorders such as fibromyalgia and irritable bowel syndrome. It's also comorbid with mood disorders and things like that, sleep disturbances.

But I think what we're pointing out on this is that pelvic pain or pelvic floor pain, pelvic myalgias, dyspareunia, which is a fancy word for saying pain on intercourse, and they also included things like this chronic cystitis issues that some women have is associated with pelvic pain, and it's just this heightened pain sensitivity occurs at about two and a half times the rate of people who don't have migraine. So, this is sort of confirmation of information that we already know. And this was some research that was done out of Stanford. And they were looking at some large databases and saw this clear association with chronic pelvic pain and dyspareunia with people with migraine.

I think it's important to highlight this study today, because we commonly think of in our female patients who have migraine, we always talk about fibromyalgia. We talk about irritable bowel and mood disorders and sleep disturbances. But I think painful intercourse or pelvic pain is not something that you would necessarily go in and talk to your neurologist about, or maybe even your general physician. You might put that together. And I think this may be occurring at a much higher rate than we think, because claims databases are not going to be coded for these other pain syndromes very much. And we just want to highlight the fact that these two pain disorders do occur together. And there may be some common ways of treating as well, and it should be part of the conversation in managing migraine as well.

Lindsay Weitzel, PhD:
That is super interesting. And I think it's important that everyone understands why. Because I think sometimes when we are starting to accumulate multiple pain syndromes, multiple things that are wrong, sometimes we don't want to talk to the doctor about all of them because we feel like whiners. But the fact is that that's what is characteristic of being someone with chronic migraine because our nervous systems are just so heightened and the central sensitization that you spoke of. I was pretty excited to report on that study. I think people will find it interesting.

That is it for today. We will be back soon with another news episode. We try to do these as often as possible. Thank you so much for being here with us today, Dr. Smith. Thank you everyone for joining us on this episode of HeadWise News. Bye-bye.