Episode 225: Allodynia, Central Sensitization, and the Progression of Migraine

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 Migraine Nation, and I have a history of chronic and daily migraine that began at the age of four. I'm honored to be here today with Dr. Richard Lipton. Hi, Dr. Lipton, how are you today?

Richard Lipton, MD:
Hi. Nice to see you.

Lindsay Weitzel, PhD:
Nice to see you, too. Thank you for being here. Dr. Lipton is a professor of neurology at the Einstein School of Medicine and the director of the Montefiore Headache Center. I'm very glad he's here today because he's widely published and is a familiar face to many of the people who spend time in the headache arena. Our topic today is allodynia, central sensitization, and migraine and other types of head pain.

Some people refer to central sensitization as nociplastic pain. We're going to talk about it as central sensitization today. Dr. Lipton is a published author in this area, and I can't wait to hear what he has to say. It is such an interesting topic. Dr. Lipton, let's start with what is allodynia and is it related to central sensitization. So, let's just go ahead and define what it is.

Richard Lipton, MD:
Sure. Allodynia is the experience of ordinarily non-painful stimuli as painful. And many people with migraine over the course of the attack develop allodynia. And they may have complaints like when I take a hot shower the hot water hurts on the side of my head pain or I can't put my head on a pillow, or I can't wear earrings. Men sometimes complain that it's painful to shave their faces. Some people can't wear a necklace because just the neck itself becomes sensitive.

Allodynia is the experience of ordinarily non-painful stimuli as painful. And we believe the mechanism of allodynia is both peripheral and central sensitization. And those are fancy terms, but the concept is actually very easy. The idea is that whatever the brain does over and over again, it gets better at. So, my tennis game is still improving from its pathetic level, and that is a manifestation of plasticity, the fact that the brain adapts to experience. And of course, on the tennis court, getting better with practice is a good thing. When what you're practicing against your will is being in pain, that's very much a bad thing.

But what happens when peripheral sensitization develops is that the peripheral nerves become more sensitive to pain. And for migraine, the most important one is the trigeminal nerve. And then the trigeminal nerve has connections inside the brain. There's a three-nerve cell pathway that goes from the periphery to structures in the brain stem, from the brain stem to a structure called the thalamus, which is a kind of sensory relay nucleus, a switchboard if you will. And then that sends pain signals to the cortex, to the part of the brain that's responsible for conscious experience. And what happens in central sensitization is that the nerve cells inside the brain become increasingly sensitive to pain, and

that leads to the experience of things that usually wouldn't hurt as painful. In summary then, allodynia is the experience of ordinarily non-painful stimuli as painful, and peripheral and central sensitization is the mechanism that gives rise to that phenomenon.

Lindsay Weitzel, PhD:
This is so interesting. I want to ask a few questions based on how you answered that. I'm curious when you say normally non-painful stimuli, do people with allodynia only feel the pain when there's stimuli, like when they touch their face or their head? Or is it painful all the time?

Richard Lipton, MD:
Allodynia refers to the experience of a stimulus that ordinarily wouldn't be painful as painful. Now, it may occur during a migraine attack in the setting of spontaneous head pain. So, somebody may have pain in the temple, and then if they put on a hat or put on their glasses, the pain may get worse. But particularly in people with chronic migraine, there's a phenomenon called interictal allodynia, allodynia between attacks.

And for interictal allodynia, you may not be in pain until you put on your tight hat, and then the pressure of the hat may induce pain that you weren't previously experiencing. So, the answer to your question is that during a headache, allodynia makes pain worse between headaches. If you're not in pain, allodynia can induce pain.

And there is a closely related phenomenon called hyperalgesia, and that's when a stimulus that would ordinarily be painful becomes more painful. But that's not what we're talking about here. I should say that allodynia is an incredibly common phenomenon. So, in our population surveys where we're studying people with migraine in the general population, not people who have terrible, frequent, disabling migraine, but a broad cross-section of people living with migraine. Two-thirds of them have allodynia. And allodynia becomes more common in people with more frequent or more disabling migraine attacks.

Lindsay Weitzel, PhD:
Why is it important for someone to know if they have allodynia?

Richard Lipton, MD:
Well, it's important for a number of reasons. For one thing, allodynia is actually a risk factor for headache progression. So, what happens to many people with migraine is that they begin with episodic migraine. They may have a headache once a month, once a week, twice a week, but it's a very intermittent phenomenon. But over time, some people progress from episodic to chronic migraine.

Allodynia is a risk factor for migraine progressing. So, in people with allodynia, it's particularly important to manage migraine in an effort to keep it from getting worse. We traditionally think of the goals of treatment as preventing headache through the preventive medications or relieving pain and associated symptoms and restoring function for the acute treatments that we give.

But a goal that I think about every day is identifying people who don't have chronic migraine, migraine on 15 or more days a month, and treating people in a way that keeps it from progressing. Now we also know that people who treat during allodynia are much less likely to respond to acute treatments than people who treat earlier while pain is still mild.

So, it's important to know about allodynia immediately on a short-term basis, because people sometimes frame this as acute treatment as a race against allodynia. You get a headache, you want to do an intervention before allodynia develops, and there's a short-term and a long reason to do that. The short-term reason is your treatment will work better. The long-term reason is that it may well make your headaches less likely to progress.

So, we did a large study where we measured how well acute treatment works for people. And we showed that people who get really good results from their acute treatment are much less likely to progress than people who don't get good results from their acute treatment.

And my belief is that if you don't get a good result from your acute treatment, the brain mechanism that underlies allodynia, central sensitization, comes into play. And if you practice being in pain, it becomes easier and easier to provoke pain. And so, people with bad migraine, most of the people who I see clinically have undergone that process of progression and come in with 15, 20, sometimes more headache days a month. But people who treat early, and oftentimes that's primary care doctors, have an opportunity to prevent that process from happening. And allodynia is an important clue that the process is happening.

Lindsay Weitzel, PhD:
Are there specific medications that are helpful for allodynia or that possibly make it worse?

Richard Lipton, MD:
Yeah. So well, first, the medications that make allodynia worse and make a substantial contribution to headache progression are opioids, narcotics, and barbiturate combination products. So, there's still a number of barbiturate combination products that are sold in the United States under brand names like Fiorinol, Fioricet, Esgic. And the 'Fior' in Fiorinol is [from] Montefiore, because it was developed at my headache center.

But that is not a source of pride for me. I mean, these drugs have been removed from the market in Germany and in some other European countries because there is pretty compelling evidence that they make people worse. And there's good evidence, both from human observational studies that my group has done, but also even in experimental animals, that these medications induce allodynia and on a long-term basis make headache worse.

There's also some evidence that if you take triptans too often, and too often might be ten times a month or more or if you have very frequent headache, that even non-steroidal anti-inflammatory agents may make people worse.

Now, the best treatment strategy if you're early in the experience of allodynia, is to just treat your headaches early. And if you don't treat too often, that can be a helpful strategy. And of course, early is a matter of not just when you take your medication, but when you absorb your medication, when it gets

into your body at an effective dose that can relieve your pain. And part of the reason non-oral medications are so important is that they achieve their maximal concentrations in the body more quickly.

So, the reason injectable sumatriptan is more effective than oral sumatriptan, the reason rapidly absorbed nasal sprays including gepant nasal sprays like zavegepant are more effective than oral gepants, essentially is because the drugs get in quicker. And we don't really know if it's the rapidity of the rising phase or when the drug gets to maximum concentration. We don't know which of those things drives efficacy, but non-oral therapy is one important strategy to relieve the headache before allodynia develops.

Lindsay Weitzel, PhD:
So, getting early treatment in the phase of migraine, and getting that migraine aborted before the allodynia can be a problem is one of the tricks to preventing this. This might sound silly to some people because if they're sitting at home and they're going, yeah, it hurts. I know I have allodynia. But this is an important question, and people will see why in a minute. How can someone tell if they have allodynia?

Richard Lipton, MD:
The way I determine if someone has allodynia is using a measure that my group developed called the allodynia symptom checklist. It's easy to download online.
[https://headaches.org/resources/headache-tests]

You can put it on an NHF website, if it's not on an NHF website already. It's 12 simple questions that asks things like, how often do you get pain during headache when you comb your hair, how often you get pain when you pull your head back in a ponytail. For men, how often do you get pain when you shave your face.

Basically, you answer the questions, you add up the score, and based on your score, you can determine if you have allodynia or not. And the questionnaire is free. We make it available to absolutely anybody who wants to use it as an individual, as a practitioner, and to pharma companies who have now included the measure in many, many studies.

But that's a simple, easy way to tell if you have allodynia. And if you do, that means you are at increased risk for worsening headache. If your headaches are very infrequent, it means you should try to treat early while pain is mild before allodynia develops in a particular attack. And if you have frequent headaches, that may be a very good reason to seriously consider preventive medications in discussion with your doctor.

It may be worth saying that the class of acute medications that do not contribute to headache worsening over time are the gepants. There's three FDA approved acute gepants for migraine: ubrogepant, rimegepant, and zavegepant. Two of them are oral tablets. One of them, zavegepant, is a nasal spray.

And for all of them, we have evidence that if you take the drug more quickly, it prevents your headache. It doesn't increase your headache frequency. And the opposite is true, particularly for opioids and barbiturate containing combination products, but also true if you use triptans too often. It

may also be worth mentioning, and this is based on work that my friend and colleague Rami Burstein has done, and he's been a clear leader in calling allodynia to our attention. Dr. Burstein has shown that fast acting, non-steroidal anti-inflammatory agents are also particularly beneficial in patients with allodynia. And he's taught the community the mechanism for that.

So triptans are very good at turning off the trigeminal nerve, that first-order neuron in the pathway that I described. But NSAIDs also turn off that second-order neuron. For some people, a combination of an NSAID and a triptan may be particularly effective. Some people really need non-oral medications if allodynia develops relatively quickly or if they have allodynia all the time, because that may make acute treatment less effective.

Lindsay Weitzel, PhD:
Let me ask another question here. When people get allodynia, is it always in the same place as their migraine pain? For example, if their migraine is on the right side and it's unilateral, is that where their allodynia is? And if their migraine is bilateral, is it all over their head?

Richard Lipton, MD:
Yes. So, allodynia usually begins in the same distribution as the spontaneous pain. And when allodynia occurs in the distribution of spontaneous pain, that may be from peripheral sensitization. That may be from increased sensitivity just in the trigeminal nerve and not in the brain structures that give rise to pain. As the headache progresses, it is very common for the experience of allodynia to spread to other parts of the head.

It can actually spread to other parts of the body as well. So, some people with migraine may get allodynia in their hands, may get allodynia in their feet. And when you get allodynia outside the head, that's because central sensitization can occur at multiple levels in the nervous system. The trigeminal nerve can be sensitized, and you get allodynia in the region of spontaneous pain. The brain stem structures can be sensitized and then the allodynia is usually confined to the head. But if the nerve cells in the thalamus, that central relay nucleus, gets sensitized, then you can experience whole-body allodynia.

And that can be more difficult to treat. Honestly, very early in my career, when people told me about whole-body pain with their migraine, I was not aware that allodynia and central sensitization could occur in the thalamus. And I thought they were elaborating. I didn't believe them. But advancing science has taught me to adhere to a principle I always adhere to now, which is, I believe what people are telling me. Maybe I'm not smart enough to understand what they're telling me, but people have experiences, and they report them.

And the truth is, the way clinicians learn is by listening to their patients. And I'm ashamed that I dismissed complaints whose mechanism I didn't understand. But discovering the mechanisms of that whole-body pain has first of all made me more humble. And second of all made me a better doctor because I can do something about it.

Lindsay Weitzel, PhD:
Well, when this occurs and it goes to other parts of the body, does it stay? We hear the phrase cutaneous allodynia. Does allodynia always stay as pain on the skin as the word cutaneous might make us think? Or does it sometimes hurt on a deeper level, like deeper pain?

Richard Lipton, MD:
Yeah. Allodynia can develop in other areas of the body. The phenomenon that is very common and really quite characteristic of migraine is cutaneous allodynia, which is increased sensitivity on the skin. But if someone has a source of visceral pain, pain coming from the liver or pain coming from the ovaries, allodynia can develop in deep structures, not just in the in the skin. But that is often not a phenomenon of migraine.

So incidentally, there is this incredibly interesting phenomena of pain disorders clustering together. So, people with migraine are more likely to have fibromyalgia. People with migraine are more likely to have vulvodynia, pain in the vaginal area. People with migraine are more likely to have osteoarthritis pain. And the presumed mechanism for that is that there is convergent input from pain structures at the level of the thalamus.

So, if you're migraine pain sensitizes your thalamus, you're more prone to the pain not just in the head but in other body bodily regions. So, migraine and fibromyalgia are very frequent comorbidities. And we've also shown in longitudinal studies that if you have migraine and other areas of pain, the more areas of pain you have, the more likely you are to progress. The more likely you are to worsen over time.

And we've shown that if you have chronic migraine, migraine on 15 or more days a month, and you have other areas of pain, your chronic migraine is less likely to remit. And that's why in headache centers, and of course chronic pain of all kinds also travels with depression, and depression and allodynia are fellow travelers.

But I think all of these things have a biological basis. So, when people have migraine and other pain disorders, I will often address the pain disorders myself. But if they need anesthesia procedures like blocks, if they need treatments that I can't offer, then I refer them to a pain center to someone who can manage their other forms of pain. And in many people with chronic migraine, pain in the head is not their only pain by any means. And the key to getting people better is to turn off all of the pain disorders.

My friend Fred Shefftel, who is no longer with us, used to have an image of a firecracker, and the firecracker was labeled migraine. But coming out of the firecracker were multiple fuses and one of the fuses was migraine triggers. But one of the fuses was fibromyalgia. One of the fuses was osteoarthritis and that slide conveys the notion that if you have a vulnerability to migraine, attacks can be triggered by migraine specific triggers, but they can also be triggered by things that trigger pain in other parts of the body.

And for people with really bad migraine and pain in other bodily regions, it's very important to understand that. And the truth is that I believe allodynia and central sensitization is a mechanism that

underlies the co-occurrence of many types of pain, and the fact that each pain disorder can make the other one worse, harder to treat, more likely to progress, less likely to remit.

Lindsay Weitzel, PhD:
Do other types of headache, for example NDPH or cluster or tension headache, also cause allodynia or is it mostly migraine?

Richard Lipton, MD:
Well, so all of them can cause allodynia. Allodynia is most common in migraine. And one possibility is migraine is worse than tension headaches, so maybe it's the severity of the pain, the frequency of pain, the amount of time you're in the pain that drives the development of allodynia. Cluster headaches are very short, 30 to 90 or maybe 120 minutes. But cluster headaches can be associated with allodynia as well. Though we know much less about the prognostic significance of allodynia in cluster headache.

But allodynia is a feature of the way the brain processes pain. It's the principle, whatever you practice, you get better at. And unfortunately, it's good to practice my tennis serve, and believe me, it needs a lot of work, but it's not good to practice being in pain. You want to get out of pain so you can manage it better.

Lindsay Weitzel, PhD:
My last question for you is, if central sensitization is the cause of allodynia, is central sensitization reversible?

Richard Lipton, MD:
Yes. My goal when I see patients with chronic migraine and allodynia, is to get them out of a state where it's very easy to trigger migraine attacks and into a state where it's harder to trigger migraine attacks, where they no longer have allodynia. And there is evidence, even from clinical trials, that some of our CGRP targeted therapies not only reduce monthly headache day frequency, not only reduce headache related disability, but also reduce allodynia as measured by the allodynia symptom checklist.

So, one way of using the allodynia symptom checklist is to see where you are right now, to see how bad your allodynia is right now, and then after you embark on a course of treatment as you improve, you can look at reduction in monthly headache day frequency. You can look at how effective your acute treatments are. You can look at reduction in disability, but you can also look at reduction in allodynia. And from my perspective, for the person with allodynia, a goal of treatment or at least a marker of treatment improving is that their allodynia burden reduces as well.

And it's kind of an iterative process. When people get worse, because you develop chronic daily headache at an early age, this might not be true for you. But when people get worse, they get more headaches. They get more allodynia. The increase in allodynia makes it easier to trigger the next headache.

And that produces a cycle of allodynia often with taking the wrong medications, often with more attacks and more pain. But there are also virtuous cycles where headache frequency goes down,

disability goes down, pain goes down. Acute treatment becomes more effective. Allodynia goes down and it gets harder and harder to trigger headaches.

So, when we graph trajectories of people with chronic migraine in the general population, we get this phenomenon that I call the migraine roller coaster, where people get worse and worse and worse, reach a peak, something changes, they get better, better, better, better. And then something happens, and they start getting worse again. And my belief is that that migraine roller coaster phenomenon is a result of cycles of worsening along the lines I just described and then cycles of improvement. So, the goal is to get into a cycle of improvement and then find ways of staying there. And that can take a while.

So, monthly headache days and disability may get better more quickly than allodynia, may get better more quickly than comorbid depression and anxiety. And so, there is a case to make for when you go on treatment and it makes your headache better, you want to stay on treatment long enough to be sure you're in a virtuous cycle and you're now living at a much lower monthly headache day frequency.

Lindsay Weitzel, PhD:
There's this phrase that I tell people, the better your pain gets, the better your pain gets. And it's just so true. Once you find something that gets you better, you just got to try and stay better and better and better, because pain causes pain. And it's just a simplistic way of saying it, but that is what you were kind of getting at.

Richard Lipton, MD:
It's exactly the idea I was trying to express. And so, I often tell people who present with intractable headache, there are two goals here. The first goal is to break the cycle of intractable pain. And the second goal is to keep you from going back. And honestly, we're better at breaking the cycle than at preventing relapse. But we're getting better and better at preventing relapse as well. And those are often separate goals in terms of the way we work to achieve them.

Lindsay Weitzel, PhD:
Well, that's a great way to come to an end. Is there anything else that you would like to add to this conversation that we did not cover?

Richard Lipton, MD:
Only one thing, and that is, I see many people who are very discouraged by virtue of their long-standing disease. Many people who feel stigmatized, who feel disrespected by the healthcare professionals they consult. And I think most people with migraine can be appropriately managed in primary care settings. But for the people whose headaches are worsening, for people who experience very frequent attacks, for people who are experiencing a lot of allodynia, those are people who should probably try to see someone with some expertise in their condition, because our treatment has never been better. And it's important to maintain hope and to take control of whatever medical condition you're suffering from. And that certainly includes migraine.

Lindsay Weitzel, PhD:
Well, thank you so much. This was an awesome episode. I loved it. I hope everyone gleaned something from it. Thank you for being here. And thank you everyone for listening in. Please join us again for the next episode of HeadWise. Bye-bye.

Richard Lipton, MD:
Thank you.