INTERVIEW TRANSCRIPT

DISCUSSIONS WITH WORLD-LEADING EXPERTS

Beyond Pills: Your Guide to Drug-Free Neuromodulation for Migraine

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Introduction (00:05): Neuromodulation represents a key area of progress in migraine care, offering effective, drug-free options for both treating and preventing attacks. But with a growing number of devices with unique mechanisms and evidence bases, how do we make the best choices about whether to incorporate these into our treatment plans, and which to use?

Introduction (cont.) (00:28): Here to guide us is Dr. Stewart Tepper, a leading headache specialist who has been at the forefront of neuromodulation research, leading pivotal clinical trials and publishing key analyses that have shaped the field. With him, we'll compare the available devices, dive into the science behind the research, and discuss the practical realities of using these technologies to manage migraine. Dr. Tepper, welcome back to the Migraine World Summit.

Dr. Tepper (00:53): Thank you very much. Pleasure to be here.

Elizabeth DeStefano (00:56): So I'd like to start by discussing external neuromodulation — devices people can utilize outside of their bodies — and then later touch upon implantable approaches. So let's start with an even bigger picture than that. For a patient who is new to this concept of neuromodulation: What is it? And how would you broadly categorize available options?

Dr. Tepper (01:20): We'll start, as you said, with noninvasive neuromodulation because it's not clear that the implantable devices work yet. And we, in headache medicine, are not recommending them yet, prior to studies. The noninvasive neuromodulation devices are portable, and patients put them on their head or their arm or hold them in place. And when activated they modulate — they change brain function — and can stop migraine in progress or prevent migraine.

Dr. Tepper (01:59): Almost all of them — all of these devices have a U.S. FDA designation as nonsignificant risk, meaning that they really don't carry any significant side effects. And as you said, these offer the opportunity to treat migraine without medication. One way to think about them is that when we give medications, we are generally aiming at specific chemical targets — targets that we know about — such as calcitonin gene-related peptide, or CGRP, the big one currently.

Dr. Tepper (02:38): When we use noninvasive neuromodulation, we are affecting the brain as a whole or specific pathways in the brain, and we may be aiming at targets that we know about but also targets that we don't know about. And that offers hope for people for whom multiple medications have not worked or who want to avoid medication in general. Thus, the opportunity for people with noninvasive neuromodulation is really quite high. And where it fits into practice is not completely worked out, but in my practice, I integrate these devices pretty routinely.

Elizabeth DeStefano (03:21): That is fascinating. So you're talking about an option that instead of acting as medications do neurochemically, they act on the brain as a whole, addressing pathways. And parts of those pathways that we're familiar with, and maybe parts of those pathways that are relevant that we don't yet know but are still being acted upon by the device.

Dr. Tepper (03:45): That's correct.

Elizabeth DeStefano (03:48): So we can think about the available devices as those that could act preventively, acutely, and then some that can act both preventively and acutely. Is that correct?

Dr. Tepper (04:01): Well, actually, I think that all six FDA-cleared devices in the U.S. work both acutely and preventively. Some of them have only an FDA clearance for acute treatment, some only for preventive treatment, but I believe they all work both ways. Now we have treatment that works for both acute and preventive treatment, although there's not always FDA clearance for both indications. And I think it helps when thinking about these devices to be aware that they work both acutely and preventively, and that is an additional advantage for them in terms of how they can help people.

Elizabeth DeStefano (04:52): So when someone is using a neuromodulation device acutely to treat an attack that's in progress, you're saying that it may be that they're actually receiving, sort of, a dose of preventive therapy at the same time, regardless of whether that device may be cleared for that or not.

Dr. Tepper (05:10): That's correct. It probably has to do with the frequency of use. It may have to do with the certain ways that these devices are set — for how long they stay on and what kind of stimulation they're giving at a particular time. Because some of them — I was thinking about the external trigeminal stimulator, Cefaly — that one has a setting for acute treatment and a setting for preventive treatment.

Dr. Tepper (05:42): And the acute treatment setting is that it turns on with a particular stimulus for an hour — although we often have people take it for two hours — while for prevention, people use it for 20 minutes nightly with a different setting. Therefore, for some of the devices, there are very specific settings for acute and preventive. For others of these devices, I really think it's related to how often they're used.

Dr. Tepper (06:10): And for example, for the remote electrical neuromodulation device called Nerivio, it always turns on for 45 minutes. But when used at a point of every other day — turning it on every other day — it seems to have a preventive effect, or it definitely has a preventive effect. So with that device, the frequency of use, as people use it more acutely, they start to get prevention. The same thing with the single-pulse transcranial magnetic stimulator (sTMS) or SAVI Dual.

Dr. Tepper (06:43): We know that use of that at four doses, or four pulses, of the magnet twice a day over a period of time results in prevention. We also know that taking four pulses at the onset of a migraine can stop the migraine. And you can see how, as people use these devices acutely over time, frequency of headache goes down. They don't cause overuse headache. They don't cause rebound. They don't increase the frequency of attacks. There are no limits on the number of times they can be used in a day or across time.

Elizabeth DeStefano (07:19): You mentioned that when someone selects one setting for acute treatment or another setting for preventive treatment on certain devices, that different things happen from that device. What is the difference in what that device is delivering or doing between those settings?

Dr. Tepper (07:36): It depends on the device. And the engineers that create these devices experiment with how fast the stimulus is going, how long the stimulus is going, how intense the stimulus is. And then those aspects of the stimulation can be adjusted to optimize the treatment for a particular indication. That is, either to terminate a migraine in progress or to prevent migraine across time. But it varies with the device and with the kind of energy that the device is giving.

Dr. Tepper (08:17): Some of these devices work with vibration. Some work with magnets. Some are more electrical. So it really depends on the device and how those devices work in terms of those settings. Others, for example, in the combined front/back trigeminal-occipital stimulator Relivion, that device is only cleared for acute treatment. And the acute treatment is usually 45 minutes to 60 minutes.

Dr. Tepper (08:58): And the preventive treatment, again, as with some of the other treatments, we don't really know how many minutes they should apply it. But it's done, generally, daily or four out of seven days a week. And the patient selects how long to stimulate each time they're giving it preventively. Other devices require the person who's using it to set the intensity of the device and set a particular intensity and then use that across time. There's a lot of variability in terms of the devices and setting them up properly for people.

Elizabeth DeStefano (09:37): So before we get into some specifics around each of the six available devices, I'd like to just recap. You shared that neuromodulation externally, offers a number of fundamental advantages as a part of migraine care, including the fact, first, that they're portable; that they are very low risk with low risk of side effects; that they are treating the whole brain; that they can be used and have efficacy both preventively and acutely; and that they are fairly easy to use and don't run the risk — regardless of amount of frequency of use — they don't run the risk of medication overuse headache.

Elizabeth DeStefano (10:24): OK, so let's talk about the six neuromodulation devices that are currently available. Could you please discuss each of them, including: how or where they are applied on the body or used; whether they're cleared for prevention or acute use, despite what you shared about likely efficacy in both directions; their mechanism of action, you mentioned electrical versus magnetic; and their availability, geographically and financially?

Dr. Tepper (10:53): Well, let's start with availability before we even move forward. I have bad news. Almost none of them is covered by insurance — period, the end. There are a few exceptions. One is in the Veterans Administration — the VA covers all of them. And the VA has been at the forefront of access. And that is really entirely due to the neurologist who runs the national VA Headache Centers of Excellence, Dr. Jason Sico, who has read these data and has made these devices available for veterans.

Dr. Tepper (11:33): So if a patient is a veteran — it's the first question I ask — then they will be paid for. For everybody else, there's very limited or no access anywhere. So the cost of the device becomes really the next question. There is an exception: The remote electrical neuromodulation device, or Nerivio, was recently approved for reimbursement by one of the large pharmacy benefits managers, CVS Caremark.

Dr. Tepper (12:05): And there are, I think, 8 million people [130 million as of February 2026] that are therefore eligible for the use of Nerivio in the country, but that's 8 million out of 300 million. So it's a very small number, but at least it's the first crack. There are a few other small regional insurance companies that will cover. But I always warn people: Access is going to be a significant issue, cost will be the next issue. Now what we can do is then go on to the six devices, and I can cover them as we proceed through them.

Dr. Tepper (12:42): The first device that was approved — that was cleared by the FDA; these devices are not technically *approved*, they're *cleared* by a different section of the FDA than does medications — was the external trigeminal nerve stimulator (eTNS), Cefaly. Cefaly is one of two that is available without a prescription. So people can go online and simply order it. There's a lot of teaching that I do with people to explain how to use Cefaly, because if they try it without proper training, they probably won't tolerate it.

Dr. Tepper (13:23): But Cefaly is a device that goes on the forehead as a sticky pad, and then it's turned on. And it is turned on either, as we talked about, for the acute as-needed treatment of a migraine, in which it turns on for 45 minutes and buzzes the forehead and stimulates nerves in the forehead. And it turns on for an hour in that setting for acute treatment, although one large study suggested that two hours works better than one hour. Two hours of acute treatment is more likely to result in pain freedom than one hour.

Dr. Tepper (14:02): And the other treatment turns it on for 20 minutes to prevent migraine, and that's done every night for 20 minutes. And the FDA has cleared it in adults for the acute treatment of migraine and the preventive treatment of migraine. The device is rechargeable, and it costs — depending on which month you look online — about $400 for the device, so a $400 one-time price.

Dr. Tepper (14:29): But the sticky electrodes that go on the forehead have to be replaced, and they only last about a month. Three sticky electrodes costs $25, so every two or three months, people have to pay $25 to renew the electrodes. And if they hate the device, they can return it within 90 days to get their money back. So that is the Cefaly device. Works acutely and preventively, and it is available without a prescription. And a lot of people can access it for the $400.

Dr. Tepper (15:16): How do these trigeminal stimulators work? Well, there are two ways that I think that they work: One is there are nerves in the forehead that are part of the trigeminal nerve. The trigeminal nerve serves pain in the front of the head, and what the trigeminal stimulators or neuromodulation devices do is they send an inhibitory signal to the lower brain stem to try to turn off the migraine that way, and people will feel the stimulation on these nerves going up the forehead.

Dr. Tepper (15:50): But it's also been shown that these devices affect the brain functioning that has to do with pain — in what's called the pain matrix — and there are what are called functional imaging studies that show that with repetitive use of this device, the pain matrix starts to turn down. Therefore, I think these devices have both an acute effect on the pain pathways that integrate migraine, and a long-term effect on reducing brain activity that is associated with pain. That's how I think the two external trigeminal neurostimulators work.

Elizabeth DeStefano (16:35): So is that essentially a reduction of sensitization of the brain through that pathway?

Dr. Tepper (16:41): The second part where it affects the pain matrix, it probably is that. The first part is more direct. Interestingly, the FDA designates these devices as TENS [transcutaneous electrical nerve stimulation] units. I'm not convinced that that's an adequate evaluation of their upside. A TENS unit, the minute you take it off, it stops working, and that's not true here because if a person puts it on for an hour or two hours to stop a migraine and the migraine stops, that's not really like a TENS. A TENS, the minute you take it off, it stops working. Also, the long-term cortical and pain matrix effects I don't think, are consistent with the idea that these are TENS units. But for whatever reason, the government has classified them as TENS units.

Elizabeth DeStefano (17:39): If I can ask, Dr. Tepper, what are the main barriers you observe people experiencing, without training, that you mentioned about how to use the Cefaly device?

Dr. Tepper (17:56): It hurts. It hurts too much to tolerate. What happens is, for example, in the preventive setting when it's put on and turned on, it escalates the intensity of the stimulus — increases across the 20 minutes and then shuts off. And many, many people cannot tolerate how intense it feels as it escalates.

Dr. Tepper (18:03): Now, one can teach people how to get around that by having them escalate — let it accelerate for five minutes and then press a button and let it sit there. And do five minutes of acceleration a week, and then 10 minutes for a week, and then 15 minutes for a week. And then finally, after a month, they can get to the full stimulation. Doing it that way, most people can learn to tolerate the intensity of the treatment. That's one of the things that we teach in how to get used to it. But otherwise, you put it on and it hurts so much that people return it.

Elizabeth DeStefano (18:45): Great. So moving on to the second device, Dr. Tepper.

Dr. Tepper (18:50): Very similar to the first device, a knockoff. The second device also goes on the forehead and it's called HeadaTerm. It can be used acutely and preventively. The preventive dosage, again, similar to Cefaly, is 20 minutes daily. The acute treatment is not FDA-cleared.

Dr. Tepper (19:13): But actually, the only study ever done on this device was for acute treatment and it was for 20 minutes of acute treatment rather than an hour or two hours. But it can be turned back on

again. And unlike Cefaly, which gradually increases across the 20 minutes of prevention, HeadaTerm has five settings and people can set how intense the stimulation is and gradually work up by simply setting it at a higher and higher level.

Dr. Tepper (19:45): Again, HeadaTerm does not require a prescription, so people can simply go online and order it. Again, there is a HeadaTerm rechargeable device and the advantage of HeadaTerm is it's less expensive. It's $109 for the rechargeable device instead of $400. It's $24 for the three sticky electrodes instead of $25. So it has that advantage. It doesn't have, technically, the FDA clearance for both acute and prevention. And for acute treatment, people keep having to turn it on because it only stays on for 20 minutes at a time, but it should work the same way as Cefaly.

Elizabeth DeStefano (20:36): Now, the third device, Dr. Tepper.

Dr. Tepper (20:39): The third device — in terms of the order in which they were approved — is the single-pulse transcranial magnetic stimulator, which is called sTMS. The brand name is SAVI Dual. And this is a device that is about shoebox size. And it's plugged in and you turn it on and it boots up and then you put it on the back of the head and you press a button and it pulses a magnet that fast. Boom. And then you have to reboot it to pulse it again.

Dr. Tepper (21:10): And what this device does is send a magnetic pulse forward in the brain, about halfway forward, and the pulse does not go below the chin. And the initial FDA clearance was for acute treatment, that is, as-needed treatment. Initially, it was for three pulses. Now, people tend to use four pulses for acute treatment. And then there was a study that suggested that it worked preventively with four pulses applied in the morning and four pulses applied at night — over three months, it took to see the prevention.

Dr. Tepper (21:56): And the FDA cleared it for both acute and preventive treatment. There is not a maximal number of pulses per day for the sTMS device. And the sTMS device is approved not only for adults for acute and preventive treatment, but down to age 12, for adolescents. So it has an adolescent indication. It's the first of them that obtained that. And I was on some of these studies, I think it works quite well.

Dr. Tepper (22:34): How it works is: that there are, again, two ways that it probably works. One is that when people get migraine aura — and about a quarter of people get migraine aura — the magnet can actually stop the wave of the migraine aura at the beginning of the aura.

Dr. Tepper (23:57): For people without aura, or for the prevention: The switching site for pain in the brain — coming up from the bottom of the brain going up into the pain matrix and the cortex — is the thalamus. The thalamus is like your switching station for railroad tracks. And the magnetic pulse probably inhibits the thalamus. It turns off the ability of the thalamus to send the signal upstairs.

Dr. Tepper (23:30): The biggest problem with the sTMS device is that it's very expensive — very, very expensive. People have to pay $1,050 for the first three months, no money back guarantee. And then after that, it's $350 a month to rent. And you can't own it. And you have to get the SIM card recharged in order for it to go forward. So that is a problem with it.

Dr. Tepper (24:02): Now, one advantage of sTMS is that in the U.K., the National Health Service actually cleared it for use during pregnancy. And the reason for that is that the pulse of the magnet, as I said, goes halfway forward and no lower than the chin. And so it's not felt to do anything deleterious to a developing fetus. The U.S. has not weighed in on whether it's safe for use in pregnancy. But for those that can afford it, it would be, I think, an option during pregnancy.

Dr. Tepper (24:38): The next device is the noninvasive vagal nerve stimulator, nVNS, which is — the brand name is called gammaCore Sapphire. But there's an additional piece of information about it,

which I will let you know about at the end. And this is a device, it's like an old Norelco razor, and goop is applied to it, and then it's put on the neck, and it is activated for two minutes.

Dr. Tepper (25:03): And when it's activated, the side of the lip twitches. Some people get a sore throat or something in the throat when it's activated. And it is FDA-cleared for acute treatment of migraine, preventive treatment of migraine, and acute treatment of episodic cluster headache attacks, and on top of cluster treatment for prevention of cluster headache attacks. And it's also cleared for two of the more rare forms of headache that are called trigeminal autonomic cephalalgias: hemicrania continua, and paroxysmal hemicrania. And there are different numbers of times that the two-minute stimulations have to be applied, either three times a day, or twice a day, or as needed. And so it is variable depending on which kind of headache you're trying to treat and whether you're going to use it acutely or preventively or both.

Dr. Tepper (26:18): But it is flexible in terms of giving people the opportunity to treat all of these different kinds of headache disorders. In fact, there was a paper that was published within the last couple of months by Dr. Goadsby that evaluated its effectiveness in a large number of people with those rare kinds of headache disorders. And it really seemed to work both acutely and preventively in a large number of people with all of the trigeminal autonomic cephalalgias. So that was encouraging.

Dr. Tepper (26:50): The disadvantage of gammaCore, again, is that — and by the way, all of them except Cefaly and HeadaTerm require prescriptions. And the prescriptions always have to be sent into different places. So that's another obstacle in care. But the noninvasive vagal nerve stimulator, the gammaCore device, is $450 to try it for the first three months. Then it's $600 per three months — and that's $200 a month every month to use it. And it has to be recharged via the SIM card or some other thing that they do.

Dr. Tepper (27:29): So that really makes it not very attractive for most people outside the VA. But the same company makes another device that does exactly the same things called Truvaga Plus. And Truvaga Plus is not FDA-cleared for all of the headache disorders. It's cleared for rather nonspecific indications like, I think, sleep and feeling of wellness and things of that sort. And it turns out — that stress release, sleep, and mental clarity are the clearance for the Truvaga device. But it's rechargeable.

Dr. Tepper (28:20): And it does exactly the same thing. And it delivers two minutes of stimulation. It's made by the same company. And it costs $500 one time. And then you do have to access the goop to put it on the neck. But to me, as a clinician, there's no reason for people outside the VA to ever be prescribed gammaCore. They can be prescribed Truvaga Plus. If they can afford the $500 one time, they can use it for all of these different kinds of headache disorders. Which is very good news. And that increases the potential use of noninvasive vagal nerve stimulation.

Elizabeth DeStefano (29:03): And my understanding, Dr. Tepper, is that because the Truvaga is positioned as a lifestyle type of device, that it may come without the customer or patient support that could come with the gammaCore Sapphire. Do you see that as an issue that would present itself often?

Dr. Tepper (29:17): It can happen. But that's where the person who prescribes it has to help the patient to use it. The mechanism of action is that, for the most part, this device sends an inhibition pathway up to the thalamus again. And as with the single-pulse transcranial magnetic stimulator, it stops the aura generation wave. So it has two similar mechanisms to the sTMS device, but through a different access point.

Dr. Tepper (29:53): So the sTMS is a magnet from the back and this is an electrical from the vagus in the front. But they may do similar things, both acutely and preventively. The nVNS device, the vagal nerve stimulation, is the only device that is cleared for all of those other disorders — cluster and the other trigeminal autonomic cephalalgias.

Dr. Tepper (30:16): The next device is the remote electrical neuromodulation device, or Nerivio. And this device is a sticky pad that goes on the arm that you turn on, and it has a little band that keeps it on the arm. You can put it underneath the shirt, and it requires a smartphone app. And the app turns on the device, and it vibrates the arm. And initially, people are instructed to increase the intensity of the vibration until it hurts, and then pull it down so it's a strong vibration, but it should not hurt.

Dr. Tepper (30:52): And when it's turned on, it turns on for 45 minutes, and then turns off automatically. And it is cleared for the acute treatment of migraine, and every other day for the preventive treatment of migraine — 45 minutes every other day — all the way down to age 8. So it is not just adolescent and adult, but pediatric dosing as well. It looks like it actually works acutely and preventively in kids. And again, a nonsignificant risk device; it doesn't have significant side effects.

Dr. Tepper (31:25): It works by a reflex called the conditioned pain modulation, in which pain in location A inhibits pain in location B. And what the device does is to fool the brain into thinking that it's receiving a pain signal from the arm, but it's not, because the person took it down so it doesn't hurt. And that signal goes up into the brain, and through a reflex, turns off the migraine.

Dr. Tepper (31:55): In the U.S., it costs $50 for the first device. Each device has enough juice in it to treat 18 times, then it has to be thrown out. It's not rechargeable. So people turn it on for 45 minutes every other day for prevention. That's 15 doses in a month, and there's a few extra for as-needed treatment. And after the first device, it costs $200 for three devices, so $67 per device thereafter. This is the one where there is some insurance coverage through one of the big pharmacy benefits managers nationwide.

Dr. Tepper (32:32): But unless you have CVS Caremark as your pharmacy benefits manager, most likely it will not be covered. Although there are little areas in the country where there is coverage — in Massachusetts and in the South, there are some areas — and so it's always worth asking whether it could be covered. Of course, it'll be covered at the VA.

Dr. Tepper (32:59): So that is the remote electrical neuromodulation device. I use it a lot for kids and adolescents, because they don't want to take drugs; their parents don't want them to take drugs, and it actually works. And the cost is affordable for most people.

Dr. Tepper (33:18): The last device that's FDA-cleared is a combined occipital-trigeminal neurostimulator called Relivion. And this device takes the Cefaly and HeadaTerm workings in the front and adds a stimulator or neuromodulation device in the back, and it sits in a lightweight device that is circumferential around the head and very lightweight.

Dr. Tepper (33:43): And when they developed it, they specifically wanted it not to hurt. So they wanted it to work like Cefaly but not hurt in the front. Most people say they don't have any side effects with it at all. It's FDA-cleared for prevention, and people turn it on for 45 to 60 minutes preventively. But there are some descriptions of it working preventively when used 20 minutes daily, five to seven days per week. So the duration of the stimulation can be set by a person, and they can use it preventively even though it doesn't have FDA clearance. So again, I think that's a difference without a distinction, and I think it can be used both ways.

Dr. Tepper (34:34): And the difference between this device and Cefaly — besides that it doesn't hurt — is that there are two ways to get into the bottom of the brain to turn off migraine: the trigeminal system, which is in the front that Cefaly and HeadaTerm work on; and the occipital nerves in the back where people will sometimes get nerve blocks, and that system comes up from the spinal cord and then goes into the same area as the front. And the idea for the Relivion device is that it includes the front and the back.

Dr. Tepper (35:10): And the big problem with Relivion is cost again. It's $150 for the first two months, but then people have to buy it. And the cost is $650. And so a lot of people don't want to do that. But it is well tolerated and effective, and I think effective both acutely and preventively.

Elizabeth DeStefano (35:35): Thank you for walking us through that. And you covered this as you went, but to recap, which of the external neuromodulation devices are cleared for children or adolescents?

Dr. Tepper (35:47): For adolescents: The magnet, sTMS; the noninvasive vagal nerve stimulator; and the remote electrical neuromodulation, Nerivio. Nerivio is also cleared all the way down to age 8, the other two down to age 12.

Elizabeth DeStefano (36:05): And which of the devices are considered safe in pregnancy and breastfeeding?

Dr. Tepper (36:12): I'm glad you mentioned that because I forgot to talk about the Nerivio study. There was a Nerivio study, that's the remote electrical neuromodulation study, in which — it was called a case-controlled trial — half the patients used the Nerivio device during pregnancy and half did not. It was a very sophisticated study that looked at the time of the birth, the safety of the birth, the weight of the baby, how well the baby developed, all of those aspects, birth defects, everything. And there was no difference in the people that used Nerivio during pregnancy and those who did not.

Dr. Tepper (36:51): And so this year, the FDA actually took out the warning on Nerivio, saying that it had not been tested in pregnancy. That's different than saying it's safe in pregnancy, but it's the most important step that the FDA has ever taken with any migraine therapy, as far as pregnancy is concerned. And so Nerivio is my No. 1 go-to treatment during pregnancy, both acute and preventively.

Dr. Tepper (37:18): Second would be the single-pulse magnetic stimulator, but cost becomes the issue there. And also it's not, the FDA hasn't weighed in on that one, although in the U.K., the National Health Service has. Those are the two that I use . . . Before these data became available, I also used Cefaly quite frequently in pregnancy, because it's hard to imagine that just stimulating the head would do anything to the fetus, but we don't have any data on it. And so because of the data that was generated on Nerivio, I've switched to that.

Elizabeth DeStefano (37:52): Are there any people who should not use any of these options for safety reasons?

Dr. Tepper (37:59): I don't like using the noninvasive vagal nerve stimulator in people that have vascular disease, heart arrhythmias, and so on. It's supposed to only go up into the brain and not down into the heart. But I have actually seen one patient who I thought had what's called a vasovagal effect and passed out with it; and once burned, twice shy. So I avoid the vagal nerve stimulator in people with coronary disease and vascular disease and arrhythmias.

Dr. Tepper (38:27): People with indwelling devices, the magnet probably should not be used. Those with implants in the head, plates in the head — some of these devices, you have to be careful. But for the most part, they're extremely safe and can be broadly prescribed.

Elizabeth DeStefano (38:52): So when do you think of neuromodulation for a patient living with migraine?

Dr. Tepper (39:03): Well, the list just goes on and on. The American Headache Society weighed in about four years ago. Jessica Ailani was the senior author on describing the kinds of patients — and this was partially a list of people for whom it's appropriate: People with an inadequate response to

migraine-specific medications; those with frequent attacks who are at risk for developing medication overuse headache because they're taking too much acute medicine; patients who prefer to avoid medication; and I would add young people with episodic migraine who don't want medicines, including tech-savvy young people who like to embrace new technology.

Dr. Tepper (39:41): So at one end, people with intermittent attacks that are young; those who have a poor tolerability or have contraindications to medicines — and there's a lot of people that can't take one medicine or another for those reasons; on top of medicines, so as an adjunct to existing treatment; those planning pregnancy or pregnant.

Dr. Tepper (40:12): And at the other end: People who have chronic migraine for whom multiple medicines have failed, either because of a lack of effectiveness or side effects; or an older patient who's taking multiple medicines that have high potential for drug-drug interactions — and here you can add treatment that is not going to cause drug-drug interactions. At the far end, in the chronic migraine people, they will think that all the other options are close to exhausted, and yet I've seen them respond to noninvasive neuromodulation. So you can see it's a very wide net for whom these therapies are useful.

Elizabeth DeStefano (40:53): Do you ever recommend that those living with migraine consider them as a bridge approach during a wearing-off period, maybe for a medication they use that's dosed quarterly or transitioning off preventives, perhaps?

Dr. Tepper (41:10): Not usually, because it takes too long for them to kick in. They could use them acutely for attacks that break through during the wearing-off, but they won't work preventively unless they're used repeatedly over periods of time.

Elizabeth DeStefano (41:27): Yeah. So let's talk about efficacy. You have authored multiple papers on neuromodulators and migraine treatment. What can you tell us about really what types of results people with migraine can expect based both on clinical trials and real world post-study use?

Dr. Tepper (41:46): I think for those that are well studied — vagal nerve stimulator and remote electrical neuromodulation and the Relivion device — the acute effects are quite similar to acute medication in terms of likelihood of pain freedom or pain relief at two hours. Consistency remains high; they don't appear to wear off. And preventive effects for those that are appropriately studied are probably a little bit less in the drop of monthly migraine days than some of our anti-CGRP therapies.

Dr. Tepper (42:21): But in the case of remote electrical neuromodulation (the REN device, the Nerivio device), the study was done in such a way that effectiveness was established for both prevention of episodic migraine and chronic migraine. And so it has clearance for prevention of both. And the outcome measure for the Nerivio device was in the second month, not the third month. So it may work faster. So one has to counsel people that it's worth trying, that there's not a downside in terms of significant side effects, and that it's a two- or three-month trial to see.

Elizabeth DeStefano (43:03): Do the devices treat migraine symptoms other than pain?

Dr. Tepper (43:11): Yes. For the acute treatment and also for the preventive treatment. In fact, I had somebody in this week who has a lot of cognitive fog, and I thought, “Well, let's see whether the Nerivio will work.” We'll know pretty quickly in the first two months. And he wanted to avoid medicines. He'd tried a ton of them. So we'll see. And I said, “Our target will be not just the frequency of your attacks, the intensity of the pain, but also the associated features.”

Elizabeth DeStefano (43:38): If one neuromodulator doesn't work for someone and access isn't a barrier, is it worth them trying a different one?

Dr. Tepper (43:50): I think, absolutely. The ones that are similar are Cefaly and HeadaTerm. So if one didn't work, probably the other wouldn't work. But I've seen patients who didn't respond to Cefaly, who responded to Relivion, because Relivion has both the front and the back. And then the vagal nerve stimulator, the magnet, and the Nerivio device, those work by completely different mechanisms. And yes, I think it doesn't matter what the previous lack of response was. It's worth trying a different one if access can be afforded.

Elizabeth DeStefano (44:22): So as with medications: If one doesn't work, trying a different medication with a different mechanism of action here, that applies as well?

Dr. Tepper (44:30): Yes.

Elizabeth DeStefano (44:31): So let's touch base briefly on implantable devices and the neurostimulation surgeries that are involved with them. What are the criteria that would make someone a candidate?

Dr. Tepper (44:43): Nobody should be a candidate at this point, except in a study. The occipital nerve implantable stimulators have been studied now repeatedly, and not one of those studies met the primary endpoint for reducing migraine frequency. There were methodologic issues, but still, I think you have three very large prospective studies from different companies where the occipital nerve stimulators were ineffective in the primary endpoint.

Dr. Tepper (45:06): At least one of them had its CE mark approval in Europe rescinded because of other problems in terms of device migration and pain and infection. I'm not recommending implantable occipital nerve stimulators for patients. There are two studies going forward nationally to implant foil devices in the forehead, similar to Cefaly. I'm perfectly willing to review those data when they become available. They are sham-controlled studies.

Dr. Tepper (45:39): But why would anybody implant when they could try Cefaly or HeadaTerm, which works in the front and which is noninvasive? Until that's been done, I don't think implanting is appropriate. I think there's a big division between pain doctors who love to implant devices and headache doctors who are reluctant to implant, given that we have so many good options now in both episodic and chronic migraine. I can't think of the last patient I recommended implantation for.

Dr. Tepper (46:13): I have no hesitation in recommending somebody who wants to be involved in a sham-controlled trial. One of the problems with these devices — and when I was at Cleveland Clinic, this was made very clear to me — is who manages them after they're implanted? The implanters don't like to generally see the patient follow-up on the migraine frequency, do the headache calendars, go over everything, alter the stimulation parameters of the device, and so on.

Dr. Tepper (46:41): And the headache doctors are not qualified to do so. So that's my other concern, is that when these devices are implanted, people kind of jump off a cliff and nobody's there to catch them. So at this point, I don't recommend any of them. However, there are two national studies on two different foil devices that can be implanted in the forehead if somebody wants to participate in a study.

Elizabeth DeStefano (47:09): And those studies are about devices that are being referred to as minimally invasive implantable?

Dr. Tepper (47:15): That is such nonsense. That's such nonsense. They're implantable devices that turn on. I mean, yeah, they go in the forehead. I suppose that's different than putting them in the heart. But it's still an invasive procedure. There is a device that was studied and approved in Europe for prevention and acute treatment of cluster headache that's put in through the mouth in local anesthesia. That's probably minimally invasive.

Dr. Tepper (47:39): But to actually put something in under the skin unless it could be done locally, which I don't think it can, I'm not 100% sure, but I don't think it can. If general anesthesia is involved, I think it's disingenuous to call it minimally invasive. It's invasive. It's a procedure.

Elizabeth DeStefano (48:06): And when people are desperate and experiencing tremendous pain — frequent pain, disruption of their life — it's understandable that they can be drawn to anything that might feel like it could help. So I think it's very important for people to understand, really, where this is positioned by an expert right now in light of the risks and the lack of data. Thank you for sharing that.

Elizabeth DeStefano (48:30): So looking ahead, Dr. Tepper, what are the most important next steps in neuromodulation research? What type of advancements do you hope to see in five years?

Dr. Tepper (48:41): I want our payers to reimburse for these treatments. That's where the attention should be given. We have good devices. We have good data. We need people who want these devices to insist that they be reimbursed for them. They're less expensive for the most part, long term, than a lot of the migraine-specific medications. They don't have the side effects. And I think it's access. It's all access.

Elizabeth DeStefano (49:16): How can people living with migraine advocate for improved access, practically speaking?

Dr. Tepper (49:24): Good question. I mean, I've watched this over decades now. I think you have to work through patient advocacy groups such as the American Migraine Foundation, the National Headache Foundation, CHAMP. There are a number of patient advocacy groups, and they can steer you to people who would be interested in advocacy.

Elizabeth DeStefano (49:48): Well, Dr. Tepper, you have shared such incredible information here about neuromodulation; the role that it plays for you as a clinician with your patients in comprehensive migraine management; some fundamental advantages it offers in terms of safety profiles, low side effects; the ability to act preventively and acutely without risk from frequency of medication overuse headache; the potential to treat the whole brain; options for different patient populations, whether those are pregnant or breastfeeding patients, children, adolescents; and how the different available devices can care for and treat different people within those groups. Thank you so much. Where can we learn more about you, Dr. Tepper, and the work that you do?

Dr. Tepper (50:35): Well, I'm vice president of the New England Institute for Neurology and Headache (NEINH) in Stamford, Connecticut, and you can contact me through our website. And I'm happy to respond to questions and steer you to people in your area who might be knowledgeable in headache medicine.

Elizabeth DeStefano (50:56): Are there any resources that you'd like to recommend or point our audience to on this topic?

Dr. Tepper (51:02): The American Migraine Foundation has a number of online educational programs and offerings that include neuromodulation and which are all vetted by board-certified members of the American Headache Society so that the accuracy is guaranteed.

Elizabeth DeStefano (51:19): Wonderful. Thank you. And we'll link to the resources that you've mentioned below your interview for ease. Thank you so much, Dr. Tepper, for joining us yet again on the Migraine World Summit.

Dr. Tepper (51:30): Have a great day. Thank you.