MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

INNOVATIONS IN MIGRAINE TREATMENT & THERAPIES

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Introduction (00:05): This is a different time now. And we have all of these therapeutic opportunities and therapies, some of which are medication, some of which are biologics, some of which are oral, some of which are injectable, some of which are noninvasive neuromodulation, some of which are digital, behavioral. And as the list goes on, you start to realize that people who have been discouraged because of all of the older medicines having failed one after the other, may not have even begun to sample what is currently in our armamentarium.

Paula K. Dumas (00:39): Each year, we poll the Migraine World Summit community to ask which actions you are most likely to take after experiencing the Summit. And to no one's surprise, researching or trying a new treatment is consistently the No.1 action. If you, too, are looking for a safer, more effective medication or device with fewer side effects, you're in the right place. And if you're looking for a new, innovative therapeutic option, don't miss this talk. Now, few experts are more engaged on new treatments than Dr. Stewart Tepper, director of the Dartmouth Hitchcock Headache Center. As a board member of the American Headache Society and a prolific researcher, Dr. Tepper is on the cutting edge of new treatments. Dr. Tepper, welcome back to the Migraine World Summit.

Dr. Tepper (01:26): Thank you very much for having invited me.

Paula K. Dumas (01:29): Well, we're thrilled you're here. I'd like to ask you about a number of new treatments and new therapeutic approaches — things like new drugs, new devices, new smart-care solutions — that we now have in our migraine toolkit. How would you characterize the general rate and type of innovation that we're seeing in migraine treatment and care in the last year?

Dr. Tepper (01:52): Well, I'd prefer to look over the last four years and it's been just a meteoric rise of new therapies for people that are just astonishing. And it is a time of immense hope. And I have to say that we've really changed the way that we treat migraine — in the office, with patients, in terms of the kinds of opportunities that people have — it's been a remarkable change, a *remarkable* change. And the changes continue, and they're ... one is more exciting than the next, and I look forward to talking with you about them.

Paula K. Dumas (02:33): There is a lot of new news. And for many people, you know, if they haven't tried something, it's new to them. So, as you said, it's been four years now since the first CGRP treatment was introduced, and then over the last two years, we've seen the widespread launch of one of the newer drugs in that class, an intravenous form of anti-CGRP, eptinezumab, or the brand name Vyepti. Do you think that this IV CGRP could work for someone who has failed the injectable format?

Dr. Tepper (03:05): Well, I think that it's important for me to say that we actually, as providers, are trying to become more patient advocates. The subcutaneous monoclonal antibodies are so dramatic in their effect on people, that patients settle for improvements that are pretty astonishing. But I'm never satisfied until people are really not having any disability or impact from their migraines, and their function across all aspects of their life is back to normal. And so, what happens in my practice, is if somebody has a very good response to a subcutaneous monoclonal antibody, but is still having a migraine or two — an episode of migraine or two per week — and so having four to eight attacks in a month, where previously they might have had 20 headache days in a month, it's a pretty dramatic improvement for that person. But it may not be as good as they can get.

Dr. Tepper (04:14): And there are multiple ways of going at trying to get an even greater drop in headache days, and improvement in quality of life, and in function. And one way, as you alluded to, is to move from a subcutaneous injection of a monoclonal antibody once a month, to an intravenous monoclonal antibody, the eptinezumab, and even move to the highest dose of the eptinezumab. And sometimes somebody who has a partial response to a subcutaneous monoclonal antibody will have an even more significant response with the eptinezumab. You move up the ladder for that person. You see this over and over again. Another option for people who are on the monoclonal antibody is to add what the generic name is, onabotulinumtoxinA, or Botox, back to the monoclonal antibody. A lot of people have tried Botox for chronic migraine before they went to a monoclonal antibody, and again, had partial response. And sometimes the combination of the two will have an additive, or a synergistic effect.

Dr. Tepper (05:28): And I'm greedy; I want people to not have disability or impact. And those two approaches: moving up from a subcutaneous to an intravenous, or adding Botox, or considering a switch to the daily or every other day oral medications and combining — again, those are called gepants — all of these offer opportunities for people to do even better. So that's a long answer to a short question, but I think that each of these additions, or substitutions, offers the possibility of additional improvement for people.

Paula K. Dumas (06:10): Well, I'm glad that you touched upon so many of the therapies that I do want to talk about, and also framed it in such a way where we understand that we shouldn't settle, but we should also identify what success is. And for many people, they are much better than they were before these new therapies came out. Right? And the question is, how good can it get? How greedy should we be? And that's really a decision for an individual and their clinician to work on together, as you do with your patients, it sounds like. So, let's go back to eptinezumab for just a minute and the IV therapy. Can you talk about what some of the advantages of IV therapy might be?

Dr. Tepper (06:55): What makes eptinezumab different: I think it's probably the fastest of the monoclonal antibodies. It has a very prolonged benefit. It is so fast that it has acute benefit as well as preventive benefit. And it can be administered quarterly, so every three months, in half an hour or less, generally without side effects. There are rare side effects: Some people will get a runny nose, some people will have an allergic reaction to it — but boy, are those rare. So most people don't even notice that it went in.

Paula K. Dumas (07:29): That does sound promising. One of the questions that so many people have is, how available is it? You mentioned going into an infusion suite, and that's something that we as patients are not necessarily used to doing to treat migraine. Can you talk about how people get access to this therapy?

Dr. Tepper (07:47): Well, it can be a problem. I mean, it's just no doubt that some of the insurance companies put up obstacles to getting an intravenous treatment. And there are a variety of venues where it can be administered: Some doctor offices have infusion chairs, and so can be done in the doctor's office; some have hospital infusion suites and it can be done there; and there is the availability now of doing it at home, having a nurse come in and administering it at home. I like to have the first one done in either an inpatient or an in-office setting, just in case somebody's allergic. But once they've had it, they're not gonna develop an allergy later. So, once they've had it once in the hospital setting, or an infusion setting, they probably can have it done at home, and that is another way to do it. So, in many headache offices, IV chairs are available

to administer rescue medicines for people when they're in the throes of a particularly bad migraine. And the use of the eptinezumab is just a bit of an extension of that.

Paula K. Dumas (09:00): Neat. Well, that's great. I'm glad to hear that people can have availability even in their home as well as the doctor's office and infusion suites. So, you mentioned gepants before, and most people who have been watching the Migraine World Summit are pretty familiar with those now. They go by the brand names of Ubrelvy and Nurtec ODT, as well as another one we'll get to in a second that's preventive specifically. But there was one development this year — in this past year — the research said, that the FDA approved rimegepant, Nurtec ODT, for the prevention of future attacks. So, how does that work and how effective is it?

Dr. Tepper (09:41): Well, it's a very, very interesting story, and again, as with eptinezumab — where you have the breakdown between acute and preventive medicine — turns out that's kind of a difference without a distinction because the eptinezumab works acutely and it works preventively. So too, with gepants. And in the Nurtec — Nurtec is rimegepant — and in the rimegepant trials, it became fairly obvious that the more that people took the rimegepant, the less headache they had. This was the opposite of rebound; this was the opposite of developing medication overuse headache from taking too much acute medicine. It turned out the more people took it, the less headache they had. And so, people thought, "Hmm, maybe gepants could be used preventively?" It makes sense that they should work preventively because what they do is they block the ability of the CGRP to land on a docking station or a receptor, and that can work acutely. And if you block that receptor every day, or every other day, you can prevent the CGRP from landing and causing migraine and have a preventive effect.

Dr. Tepper (10:55): So, what occurred was, after the rimegepant studies for the acute treatment of migraine were completed, a series of studies were undertaken to evaluate rimegepant on an every other day basis for the prevention of migraine. And the study that was published actually included both episodic and chronic migraine people, who took rimegepant every other day for prevention. But the FDA only approved it for episodic migraine prevention, so for the prevention of migraine with less than 15 headache days per month. And that's where things stand right now. But it is the only treatment that is FDA-approved for both the acute treatment of migraine and the preventive treatment of migraine.

Dr. Tepper (11:49): Another study that was presented this year, it is on atogepant — that is Qulipta, the daily gepant for prevention of episodic migraine. The data were presented on atogepant for the prevention of chronic migraine, and it worked just as well as it worked in episodic migraine. And we would anticipate that the FDA will approve atogepant for the prevention of chronic migraine in 2023, and that in 2023 atogepant then, Qulipta, will be approved for all of migraine, both episodic and chronic. That same is not the case for Nurtec. Nurtec, there are no plans currently to study or submit it for chronic migraine. But we'll at least have one gepant that will be approved for all migraine: with and without aura, episodic and chronic, with and without medication overuse. And as you said, this is a big shift in how ... in the kinds of therapies that we can bring to patients.

Paula K. Dumas (12:54): So, the latest new gepant is zavegepant. It doesn't have a brand name yet because it's not yet approved by the FDA. How is it different from the others? And specifically, from rimegepant (Nurtec ODT), which is made by the same company?

Dr. Tepper (13:09): Well, zavegepant was in the pipeline, as they say. So, the same company developed rimegepant and zavegepant. And zavegepant is being studied in two different ways. First of all, it has been studied as a nasal spray for the acute treatment of migraine. And it is before the FDA in late 2022 with a consideration for the indication for acute treatment of migraine, and I would anticipate that zavegepant will be approved by the FDA for the acute treatment of migraine, in the nasal spray form, in 2023. And at the same time — and I'm not 100% sure of this because I'm not privy to the inside information — but I believe that oral zavegepant is being studied for the prevention of chronic migraine. And that company will then market rimegepant, that's Nurtec ODT, for acute treatment of all migraine [and] for preventive treatment of episodic migraine; zavegepant nasal for the acute treatment of all migraine when it gets FDA-approved; and likely oral zavegepant for the prevention of chronic migraine. And that's where the trajectory is likely to go in 2023 and 2024. And it will be nice to have multiple gepants — people are more different than gepants, so some people prefer one gepant to another, or get one better response with one gepant than another — and I look forward to having all — one, two, three, four of them — available for people as quickly as possible.

Paula K. Dumas (14:55): It is exciting. I want to pick up on one thing you mentioned, that ... zavegepant is being studied as a nasal spray, and that's useful whenever you're dealing with attacks that involve nausea and vomiting and you want to make sure that you get the drug in as early as possible. Another medication that is based on that same principle is called Trudhesa. It's kind of a device with an older drug, DHE, that's packaged in a new way. So that was recently introduced. How does it work and how effective is it?

Dr. Tepper (15:31): Nasal DHE has been available for almost 20 years in a form called Migranal. But Migranal turned out to be a bit disappointing in multiple ways: access is a problem, cost is a problem, inconsistent delivery is a problem, lack of effectiveness is a problem. And what Trudhesa is, is the company took the Migranal liquid DHE and figured out that they could put a device on top of it, which would propel it through a similar propellant to what is in asthma inhalers. And this propellant sends the DHE up — very high up in the nose — where the absorption is likely to be better. It seems that by doing that, the likelihood of response is better than for the older drug — the older formulation, although it's never been directly compared — the consistency is better; and I think probably the side effects are a little bit better, as well, in terms of tolerability. Trudhesa thus represents a very exciting, patient-friendly way to take DHE at home with a greater likelihood of absorption, and a high reliability for terminating difficult-to-treat attacks through a nasal route.

Paula K. Dumas (16:58): You know, as in every other disease state, medical devices, especially those that are controlled by a smartphone or linked to data collecting apps, are showing really great promise, especially for people who are looking for a drug-free option. So, a lot of people might be familiar with Cefaly or gammaCore or Nerivio, but the biggest development over the last year was the introduction of a new device called Relivion. Can you tell us what is it and how does it work?

Dr. Tepper (17:26): The five devices that are FDA-cleared all work to terminate migraine acutely; they all have a clearance for the acute treatment of migraine. And Relivion is a device that's a little bit like a halo, or a crown, — very lightweight — and it sits over the front, above the nose, similar to Cefaly, but it also sits over the back where we as providers provide occipital-nerve blocks over the occipital nerves. And the delivery of the neurostimulation from the Relivion is both front and back. From a neurologic standpoint, these are two different routes to get into the brain, and it was a very deliberate decision by the designers of Relivion to try to get

stimulation front and back so that they could access the brain to stop a migraine from the two different routes at the same time and get additive or synergistic benefit, compared to, for example, some of the other noninvasive neuromodulation devices.

Dr. Tepper (18:40): There are five devices, as I said, that are cleared and all five are cleared for acute treatment and those are: Cefaly; the SAVI, single-pulse transcranial magnetic stimulator (sTMS); gammaCore, the noninvasive vagal-nerve stimulator; Nerivio, the remote electrical neuromodulation device; and Relivion. Both the Nerivio device and the Relivion device are also being studied for the prevention of migraine. And the first three devices — Cefaly, SAVI, and gammaCore — are FDA-cleared for the prevention of migraine. And what's exciting is we keep coming back to the same point, which is that acute and preventive distinctions are falling away and the whole treatment of migraine is shifting because people are suddenly enabled to use the same therapy acutely and preventively. And this is seen with the noninvasive neuromodulation devices, as well as with Nurtec ODT, as well as with eptinezumab. And I think we're just beginning to understand that we can move in both ... that people can move in both directions and have this freedom, to both prevent and to treat acutely.

Dr. Tepper (20:00): The Relivion device is turned on for 45 minutes to terminate an attack, and it, as I say, is being studied also for prevention. The Nerivio device is turned on for 20 minutes to ... excuse me, also 45 minutes to terminate an attack. Both of them are going to be studied for shorter periods of time on a daily, or every other day, basis to prevent migraine. The biggest problem for the noninvasive neuromodulation devices though, is access. Because right now our payers are inexcusably refusing to cover these devices except for the VA. And these are not experimental devices — these are well-studied, FDA-cleared devices, and it's up to us to insist to the payers that we get coverage for people because these are wonderful devices and so many people want them.

Paula K. Dumas (20:56): How effective, as a class, would you characterize the devices relative to some of the drugs that we have availability for right now? The most effective medications — the gepants and the CGRPs — how effective are they, or what type of attack would you use them for, or what type of patient would you use the devices for?

Dr. Tepper (21:18): They've never been directly compared to drugs. So, we have to take the usual outcome measures and see if the noninvasive neuromodulation devices, in a good study compared to a sham device, works to a similar extent. And a good example of that — very, very good, high-quality studies were done with both Nerivio and Relivion. And if one looks at two-hour pain-free ... likelihood of pain-free at two hours, pain freedom at two hours or relief at two hours, these devices compared to sham look very similar to triptans or gepants or lasmiditan. And I think it's pretty clear that Nerivio works best if taken within the first 30 minutes of an attack. That makes them potentially less useful for somebody who wakes up with an episode, rather than have the onset during the day.

Dr. Tepper (22:19): So, I like to use them for people who need acute treatment and can get the device started with their smartphone or put the crown on the head and turn it on during the day. But I need to make a point that Peter Goadsby made many years ago, which is a very hopeful point: If you're somebody who has had many, many drugs fail — one drug after another fail, either for acute, or for preventive or both — the way that I look at that, is we haven't figured out what the proper target is to turn off that particular person's migraine. We've tried a bunch of chemicals, and those chemicals address certain targets, and those targets were not the right targets. But with noninvasive neuromodulation devices, we are modulating the brain. We

are modulating targets that we know about, targets that we don't know about; we are adjusting the brain pathways. And we see very frequently in the office people for whom one medication after another has failed, who do great with the noninvasive neuromodulation devices.

Paula K. Dumas (23:34): Yeah. I think it can be a great asset to have in your toolkit — to have both devices and medication, and then work with your physician to figure out which type of attack, or in what ways, you combine those two things in order to get the best outcome. So, I'd like to move to some new smart-care solutions. As people wear smartwatches and carry smartphones, we're seeing a host of new smart-care solutions that make migraine treatment easier, more effective, and more accessible. And one of the behavioral health solutions that has come out recently is called Juva Health and that offers biofeedback — a behavioral therapy — on your smartphone. So how does that work and how effective is it versus an in-office treatment?

Dr. Tepper (24:17): These are very exciting developments, the digital therapeutics. And it's not clear to me which one is the best. The opportunity though, for people — as in my area, in New Hampshire, which is a rural area where we don't have a lot of psychology services — for people to be able to get online and access behavioral management apps for management of migraine, that's a real important step in the right direction.

Dr. Tepper (24:47): And I would add to that, there is another company developing online behavioral apps for the treatment of migraine called Click Therapeutics. And on Dec. 16, 2022, Click Therapeutics received an FDA designation for their migraine treatment as a Breakthrough Device designation. It's the first digital therapeutics for headache that has gotten an FDA Breakthrough Device designation. That's a very exciting development. It suggests that the FDA reviewed this company's behavioral apps and thought it might be really important for people to be able to access around the world. And I look forward to all of these digital therapeutics being tested in clinical trials so that we get FDA approval or clearance, and we can recommend them to our patients on an ongoing basis. I think it's a very, very important step for people.

Paula K. Dumas (25:50): And just the convenience of being able to do it at home and on your smartphone is a game changer too. So, we talked about behavioral health; lifestyle changes are also proven to help reduce migraine. And there's an app from Ctrl M Health that is a wellness app designed in collaboration with Jefferson Headache Center to facilitate those lifestyle changes. What does it offer beyond tracking and content?

Dr. Tepper (26:17): Well, Ctrl M Health is a way of, in an ongoing manner, improving lifestyle to reduce severity, duration, and frequency of migraines. And again, these digital therapeutics are really tremendous for people, and I encourage patients to access them and try them out. I think they're really worth doing.

Paula K. Dumas (26:43): Yeah. The digital coaching is something that we're seeing in the Ctrl M Health app, as well as in Migraine Buddy's MBplus, within their app. And it's really a way for us to not only make some of the behavioral changes that we need to, but have that kind of coaching and prompting using a smartphone app to stay on top of it because it's very hard to be that disciplined. And then there's more than one company that's entered the telehealth space, offering migraine and headache care. So, first, we heard about Cove, and then Neura Health, and as I was researching for this interview, I noticed that even Amazon is offering some of these things. How do these telehealth services improve life for people with migraine?

Dr. Tepper (27:31): Many of them offer specialists, and the specialists will talk to a patient and, or, a person, and try to figure out what's going on, and what might be an appropriate treatment for that person. The disadvantage, of course, they don't do an exam. But the advantage is, if it is a common enough disabling migraine situation, they can provide medicines that have low side effects; they can provide access to noninvasive neuromodulation devices and prescriptions; they can advise recommendations for digital health; and most importantly, I think, of all, they can generally provide diagnosis, which can help a person in terms of trying to map out how to proceed with their therapy. So again, for me, the more options for people, the better.

Paula K. Dumas (28:23): Definitely. And you know, each year Migraine World Summit publishes a treatment directory that captures every single treatment that is mentioned by one of our experts, like you — everything you've talked about today will be in that treatment directory. Yet still, there are people who feel like they've tried everything, or everything that their doctor has recommended. So, how do you as a clinician respond to people who feel like there are no new treatments left to try?

Dr. Tepper (28:50): Well, it's usually not true. And people feel discouraged because they've tried 10, 20, 30, 40 different treatments without success. But this is a different time now and we have all of these therapeutic opportunities and therapies, some of which are medication, some of which are biologics, some of which are oral, some of which are injectable, some of which are noninvasive neuromodulation, some of which are digital, behavioral. And as the list goes on, you start to realize that people who have been discouraged because of all of the older medicines having failed, one after the other, may not have even begun to sample what is currently in our armamentarium. And I encourage people to see headache specialists who are interested in the new therapies, and who are willing to work with a person in an alliance to try to match patient need to the new therapies. And I think you're more likely than not, to find things that will work, even with a long litany of medications that have failed in the past.

Paula K. Dumas (29:59): Dr. Tepper, this has been very insightful. Are there any other resources that you'd like to recommend, or offer to our audience, as they're on the quest to find better health?

Dr. Tepper (30:10): I always recommend Migraine World Summit. I also recommend the American Migraine Foundation [AMF] website. I think the NHF (the National Headache Foundation) website is a useful site, as well. And those three sites are the ones that I send my patients to, and I hope you'll avail yourself of them. The AMF website is specifically vetted so that the information is accurate with American Headache Society experts looking at everything that goes out. So that might be a good place to start, at the AMF website.

Paula K. Dumas (30:43): Dr. Tepper, thank you so much for being with us here today on the Migraine World Summit.

Dr. Tepper (30:47): It was a pleasure and an honor, and thank you.