MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

THE LATEST DEVELOPMENTS IN MIGRAINE RESEARCH

RICHARD B. LIPTON, MD

Introduction (00:05): I think one of our challenges will be to figure out how to optimize and prioritize treatments when we give new therapies to people. So, the state of our knowledge is that we know a tremendous amount about what works better than placebo. What we don't know enough about is which treatment will be best for a specific patient in front of us. So, I think there are two forms of progress I'm looking forward to: one is the identification of more and more effective treatments, and the other is the development of effective strategies so we get treatment right the first time.

Paula K. Dumas (00:50): If your doctor tells you: "We've tried everything to relieve your migraine, and there's nothing else we can do," well, first, run for the door. And second, don't miss this talk about migraine research. You'll discover all the most important recent findings and potential breakthroughs that could deliver the relief you need this year or in the relatively near future. Today, you're going to hear about the most important research on new drugs, behavioral therapy, diet, lifestyle, and epidemiology from one of the world leaders. Look him up on Google Scholar, and you will be amazed to see that he's the number one most-cited migraine and headache researcher active today, which means he's in the midst of the science that can change your life and mine. Dr. Richard Lipton, we are honored to welcome you back to the Migraine World Summit.

Dr. Lipton (01:40): It's such a pleasure to be here. Thank you for the opportunity.

Paula K. Dumas (01:44): We are always thrilled when we have the chance to talk to you. We often complain that migraine and headache disorders don't get nearly enough research funding relative to their burden on society. And that's what we're here to talk about today. Which entities are behind the majority of our research funding?

Dr. Lipton (02:02): Right, so first, I agree that migraine is underfunded because after all, it's the world's second-leading cause of years lived with disability. And so, if we use as our metric, funding per patient with migraine or funding per year with lived disability, migraine is horrendously underfunded. On the other hand, funding has improved in recent years, and that's a positive sign. In the U.S., the NIH is a major funder through its neurology institute, and also through an initiative called the HEAL Initiative. And HEAL ... stands for Helping to End Addiction Long-term. But the HEAL Initiative has provided a huge increment of funding, both to end addiction and to manage pain better without addictive opioids. The FDA does some funding, as does the Department of Defense, the Veterans Administration through their Headache Centers of Excellence Program. There are many foundations that fund migraine research: the Welcome Trust, the Migraine Research Foundation, the National Headache Foundation, and so forth. And then there's a tremendous amount of funding that comes from [pharmaceutical companies], as well — both their internal funding, which supports the development and marketing of their products, but also external investigator-initiated grants; that's done a lot to support young investigators and senior investigators.

Paula K. Dumas (03:48): You know, people joke and they say, "Well, there's no "Big Broccoli" doing medical research," and it's very expensive to do. Does that explain why we get a disproportionate amount of new research that's related to these new pharmaceutical therapies?

Dr. Lipton (04:00): Well, I think there's been a huge recent investment, both in pharmaceutical therapies and devices. In many ways that reflects the fact that we have pretty powerful animal models — basic science models — that have allowed us to discover pathways that play a crucial role in migraine. So that process of going from the laboratory to the clinic is substantially driven

on the identification of treatable pathways that will lead to disease improvement. And I think that accounts for the explosion of interest from medicine companies and device companies, and of course they provide clinicians like me the tools all of us need to help our patients do better.

Paula K. Dumas (04:56): Yes. It's definitely an exciting time in migraine, and the amount of research that's coming out right now is tremendous. We do have another talk that's going to go into greater depth on new treatments that have been recently approved. So, I want to focus our talk on some of the latest important research and research targets. So, let's dive in with some of the new drug research. Some people just can't get relief with one preventive medication. And so, combinations of drugs are being investigated, such as the combination of onabotulinumtoxinA with CGRP monoclonal antibodies or gepants for prevention. Why is this important?

Dr. Lipton (05:36): Early on, payers were saying, "Well, you have to pick: You can either give Botox, you can give a monoclonal antibody — but if you want to give both, we're not going to pay for it." And as evidence has emerged that combination therapy for people who need it works better than single-agent therapy, reimbursement has dramatically been improved. And we're now able, for the most part, to give people the combination therapy they need, if the combination is Botox and a monoclonal antibody that targets CGRP.

Paula K. Dumas (06:13): That's really encouraging. Have we ... do we have that research with Botox and gepants yet? Or is that in the pipeline?

Dr. Lipton (06:23): There have now been some open-label studies, and actually a large study that we've presented at meetings that we did using the app Migraine Buddy, which shows that gepants, when given on top of Botox or when given on top of the monoclonal antibodies, seem to be quite effective in the acute treatment of migraine. We need more evidence, however. There is, as of yet, no evidence about combining the gepants that are used as preventive therapies. So just over the last few months, a couple of gepants have been approved for prevention: one is rimegepant, which was already approved as an acute treatment — that's Nurtec ODT — and the other is atogepant, which is approved only as a preventive treatment. So, there are open questions about how these gepants will work in combination with monoclonal antibodies for prevention, and also open questions about whether acute gepants will work on top of gepants given as preventive therapy.

Paula K. Dumas (07:37): What does the latest research show us about rimegepant, in particular, which I believe is the first modern migraine medication to be approved for use in this way?

Dr. Lipton (07:47): Well, so first let me say that, as a field, we've traditionally drawn a bright line between acute and preventive treatments. So acute treatments you take at the time of the attack to relieve pain and restore function. Preventive treatments are used whether or not an attack is present to decrease the frequency and severity of attacks. That bright line between acute and preventive treatments has been blurred with the approval of rimegepant as the first agent approved both as an acute and as a preventive treatment. The notion that the same agent might work acutely and preventively has precedent: So, beta blockers, like propranolol, are traditional preventive treatments, but given intravenously, they work acutely. Same for divalproex sodium, in fact. And to some degree, we've always used nonsteroidal anti-inflammatories both as acute and preventive treatment, though previously drugs were labeled exclusively for one or the other.

Dr. Lipton (08:57): With rimegepant, we have a treatment that can be used both acutely and preventively, and that creates some fascinating treatment opportunities. So one is, if a patient is on rimegepant every other day as a preventive agent, and the patient gets a breakthrough headache, they could treat that breakthrough headache with the same agent rather than needing to mix drugs. Another opportunity — because the preventive benefits of gepants kick in very quickly— is that we could use prevention on a shorter-term basis. So, with a typical oral preventive agent like topiramate or a beta blocker, we often have to titrate the dose upward over weeks or even months in order to achieve therapeutic effect. Because gepants have benefits that kick in promptly, it offers the possibility of doing prevention in a time period when a patient has an increased need, in a time period when the patient is under stress, and so forth. So, figuring out how that will work in practice and ultimately gathering systematic evidence that will help us optimize those treatment patterns is, you know, something I'm very much looking forward to.

Paula K. Dumas (10:27): Yeah. I think it's gonna be really fascinating as that line gets blurred.

Dr. Lipton (10:31): Yeah, I agree. One more thing I want to mention is that there are devices that are FDA approved both as acute and preventive treatment.

Paula K. Dumas (10:40): And I think in your article, you also mentioned eptinezumab, or Vyepti, has that potential, even though they're not FDA approved for that, or they haven't sought that label, is that right?

Dr. Lipton (10:53): Yes. So, of the monoclonal antibodies, two are given by subcutaneous injection, and for those drugs it takes a week to get to maximum levels in the blood. So those drugs, though they work quickly, don't work quickly enough to be useful acute treatments. Eptinezumab is given intravenously. At the end of the 30-minute infusion the drug is already at maximum blood levels, and there is evidence that eptinezumab, when given in that manner, works as an acute treatment. So, there may be opportunities in a patient with severe migraine to give [eptinezumab] as an acute treatment, for example, in the emergency room, and then for the patient to continue to have the preventive benefits. Although, as you said, [eptinezumab] is approved for prevention, but not acute treatment of migraine.

Paula K. Dumas (11:49): Good to know. So, this year we've also seen some research to support new products that are based on existing drugs that are delivered or formulated in a way that improves its performance. So, I'm going to ask you about a couple of these and how they compare to our existing options: so, the liquid formulation of celecoxib?

Dr. Lipton (12:11): Yes. So, celecoxib is a what's called a selective COX-2 agent. And the advantage — you know, it's a form of nonsteriodal anti-inflammatory agent — the advantage of selective COX-2's is that they don't cause much GI irritation. The disadvantage of celecoxib as a migraine medication is that it takes a long time for the drug to get into the body. So, what the company that's marketing the liquid formulation of celecoxib did is reformulate it in small bottles that contain a little less than a teaspoon of drug. You essentially swig the drug out of the bottle at headache onset. Self-emulsifiers in the drug speed absorption, and the drug actually gets to maximum blood levels in 42 minutes. The hypothesis was that that would be associated with rapid onset of pain relief.

Paula K. Dumas (13:15): And another older medication, DHE [dihydroergotamine], which has been around for a long time and is deemed quite safe, has come out in a new nasal spray. What does the research tell us about that formulation in that delivery mechanism?

Dr. Lipton (13:32): You know, so DHE has always been an incredibly effective drug. The big limitation is it's a drug that works best if you give it by injection, either intravenously or into the muscle. There has been a DHE nasal spray on the market; that DHE nasal spray formulation was not absorbed so well. The new formulation, which is made by a company called Impel, is called Trudhesa, and it actually uses a gas propellant to deliver the drug deep in the nose where it's better absorbed and there ... So, there is evidence that using this new gas-powered device that you get higher blood levels than you do with previous formulations of DHE, and that should translate into faster onset and greater efficacy. So, I think that is a step forward for all of us.

Paula K. Dumas (14:37): Great, well, some encouraging news in pharmaceutical research development. So, let's jump into diet, lifestyle and behavioral research. The BMJ published a fascinating study this year on the benefits of using an omega-3 diet to reduce attacks. What did it show?

Dr. Lipton (14:55): Yes. So, you know, so there are omega-3 fats and omega-6 fats. Broadly speaking from the perspective of cardiovascular health, omega-3 fats are better for the heart than omega-6 fats. And it turns out that the same is true for migraine. So, if you want to increase the amount of omega-3 fats in your diet, you can do that by eating salmon and other high-fat, cold-water fish — sardines are a good source of omega-3 fats as well. You can also choose the oils that you eat wisely: so olive oil is particularly rich in omega-3 fats; canola oil, interestingly, is not. You can also increase your omega-3 intake by eating nuts, and of the nuts, walnuts are the ones with the richest concentration of omega-3 fats. So those sorts of dietary manipulations provided evidence for effectiveness in this fascinating *British Medical Journal* article.

Paula K. Dumas (16:13): Migraine Québec and Migraine Buddy announced an interesting research project on a ketogenic supplement for migraine prevention that was funded by, interestingly, Nestle — the company that makes it. How promising does this look to you?

Dr. Lipton (16:26): There is evidence that ketone supplementation and a ketogenic diet may have benefits in migraine, but we need more evidence before I would recommend that on a widespread basis.

Paula K. Dumas (16:40): Yes, and it's just a fascinating development that we didn't expect. A little bit out of left field, so it'll be fun to watch. Now, at the American Headache Society conference in Scottsdale this year in the opening session, Rebecca Burch talked about that little else has the same efficacy as cognitive behavioral therapy [CBT], biofeedback, or relaxation in combination with prescribed therapies. How important is behavioral therapy in today's landscape?

Dr. Lipton (17:09): There have been a number of studies that examine the benefits of pharmacologic therapy in combination with behavioral treatments, including cognitive behavioral therapy. And the studies show that medication plus CBT works better than medication alone for the preventive treatment of migraine. Rebecca herself, and Betsy Seng in my group have done studies showing that mindfulness-based stress reduction is effective in reducing migraine disability. You know, I think there's a real spectrum of severity. So, I think

behavioral intervention is always the platform that supports good headache management with drugs and devices. Not everybody needs CBT. People with more severe migraine, people with stress as a trigger, people with comorbid depression, or people who don't get the benefits they're looking for from pharmacotherapy and devices alone, may be the best candidates for CBT. But behavioral interventions are always part of good management.

Paula K. Dumas (18:32): So, in epidemiology, you're co-leading the MiCOAS study [Migraine Clinical Outcome Assessment System] — I hope I'm saying that right — which is funded by the FDA. [It's] a research initiative that's focused on clinical outcomes that are meaningful to patients. What are you hoping to determine through this study?

Dr. Lipton (18:48): One important gap is that migraine has very important cognitive effects that have not been well measured. So, since part of the burden of migraine is that it's difficult to think clearly, difficult to concentrate, people feel like they're in a fog during a migraine attack. We think it's important, and this is just an example, but we think it's important to measure the benefits of treatment on cognitive function in migraine. Another gap, which we may or may not focus on going forward, is driving. Many people with migraine tell us they have difficulty driving. Another gap is that movement makes pain worse. And of course, pain getting worse with movement on the one hand is part of the diagnostic criteria for migraine. But on the other hand, if effective treatment makes it easier for people to move, that should be associated with major improvements and functional status. So bottom line, our hope is to improve the ability to measure what matters most to patients in clinical trials, and to have the FDA mandate those kinds of measurements so that they are incorporated.

Paula K. Dumas (20:12): Very cool. So, let's move on to some new research targets. What is PACAP [pituitary adenylate-cyclase-activating polypeptide], and what promise does it have for migraine treatment?

Dr. Lipton (20:22): Well ... so PACAP is another peptide neurotransmitter. It has much in common with calcitonin gene-related peptide, which is the peptide that's been the basis of the gepants and monoclonal antibodies that have emerged over the last couple of years. So PACAP is found in the brain areas implicated in migraine. If we infuse PACAP, it triggers migraine attacks. And those are also characteristics of CGRP. So, the hope is that if we develop small molecule blockers of PACAP, or antibodies that block PACAP, that we'll be able to develop effective acute or preventive treatments, much as we did for CGRP.

Paula K. Dumas (21:12): Interesting. That's promising. We'll be watching that. The hypothalamus is another area that's getting a lot of attention from researchers as a potential target. What is the hypothalamus, and how does it figure into migraine and cluster pathophysiology?

Dr. Lipton (21:28): Yes, so the hypothalamus sits at the base of the brain immediately above the pituitary gland. It plays a role in regulating the pituitary gland, which in turn is the master gland for the entire endocrine system. So, the hypothalamus plays a role in regulating hunger, in regulating thirst, in regulating sex drive. And in cluster headache, in particular, there's been evidence that on the side of the headache, the hypothalamus is enlarged, and that the hypothalamus is activated during cluster attacks. And similarly, imaging studies show that the hypothalamus also plays a role in migraine.

Paula K. Dumas (22:16): That'll be fascinating to see. What are delta opioid receptors, and how promising is the research that targets these receptors?

Dr. Lipton (22:26): The delta opioid receptors, like the mu opioid receptors, relieve pain, but presumably have little abuse potential. In animal models, if you activate delta opioid receptors, you relieve pain, you improve negative mood, you reverse allodynia. And so, there are drugs that are currently being studied that target the delta opioid receptor, and the hope is to relieve pain as opioids do without the negative consequences that have been so long associated with opioids.

Paula K. Dumas (23:08): So, we just talked about a couple of different receptors, and there's also some research or a number of products that are coming out that are focused on new delivery systems. We talked a little bit about the upper nasal cavity when we addressed Trudhesa, but there's also Onzetra Xsail, and SPG [sphenopalatine ganglion] blocks, and forthcoming [zavegepant] from Biohaven. Why all this attention on the nose?

Dr. Lipton (23:39): We've spent decades, literally, trying to find ways to get drugs into people more quickly — because speed of onset is important — and trying to find ways of getting drugs into people that circumvent the gut, because orally swallowed agents may not be absorbed quickly enough or may be associated with nausea. So subcutaneous sumatriptan was one attempt to avoid the gut and to get a rapid rise of drug in the body to rapidly relieve pain. It turns out some of the traditional nasal sprays, including traditional sumatriptan nasal spray, were not particularly well absorbed from the nose. So, there's been a lot of efforts to increase drug absorption through the nose. So, one strategy is to deliver the drug to the back of the nose, to an area called the posterior nasal pharynx. It turns out that area has lots of blood vessels. Absorption of drug from that area works quite well.

Dr. Lipton (24:49): And the Impel Trudhesa delivery system uses a gas propellent to deliver drug to the back of the nose where it'll be absorbed more quickly. The breath-powered intranasal delivery system delivers drug to the same place. But instead of using gas propellent, you actually use your own breath to deliver the drug back to the nose. Then there's been a lot of work on other strategies for increasing nasal absorption. So, there's a new, a relatively new, formulation of sumatriptan nasal spray. One approach is to add a constituent to a nasal spray that just enhances absorption across the lining of the nose. For [zavegepant], which is the first gepant delivered intranasally, it turns out for that product, the time to maximum concentration in the blood is relatively short. So, it may well be that that drug is absorbed across the nasal mucosa. And recent data suggests that [zavegepant] has a very rapid onset of action, with separation from placebo and pain relief as early as 15 minutes. So that's yet another promising intranasal delivery system. But in addition to these intranasal routes of administration, there have been patches. There's a new patch that contains needles that's a zolmitriptan delivery system. The two reasons for avoiding the gut are to increase speed of absorption in hopes that that will make the drug work more quickly, or to avoid the gut ... altogether to avoid exacerbating nausea, and to avoid the problem of gastroparesis, of slowing down of the digestive pathways during migraine attacks.

Paula K. Dumas (27:06): And bonus, you're not gonna throw up the medication that you just took. That happened to me so many times, I can't even remember because nausea and vomiting were just part of my migraine experience. I imagine a lot of people have that, too.

Dr. Lipton (27:20): Absolutely.

Paula K. Dumas (27:22): Great. Well these new therapeutic targets are so encouraging to people who are struggling to find relief from the currently available therapies. Any final thoughts that you'd like to leave with the audience?

Dr. Lipton (27:34): Yeah. So, I just want to add that in addition to all the targets we've talked about, there are other targets that are being studied. Adenosine, which is actually the target of caffeine, is being studied for drug development. There are potassium channels, which regulate the movement of ions across nerve cells, and sodium channel modulators that are being studied. And in addition to CGRP and PACAP, which are peptides, there's another peptide being studied called amylin, and then there are other neurotransmitters, as well. So, I have to say that headache therapeutics has never been better, that it's been an astonishing five years with the emergence of CGRP-targeted therapies and ditans and devices. And the pipeline looks really robust. So, I think one of our challenges will be to figure out how to optimize and prioritize treatments when we give new therapies to people. So, the state of our knowledge is that we know a tremendous amount about what works better than placebo. What we don't know enough about is which treatment will be best for a specific patient in front of us. So, I think there are two forms of progress I'm looking forward to: one is the identification of more and more effective treatments, and the other is the development of effective strategies so we get treatment right the first time.

Paula K. Dumas (29:23): I am looking forward to that day, too —where your therapy, your treatment plan, is more personalized based on things that we know about each individual, so that people get relief or an effective plan faster. Right?

Dr. Lipton (29:36): Exactly.

Paula K. Dumas (29:38): You can look up Richard B. Lipton. The "B" is important to find all of your work, I have discovered, since there are other Richard Liptons on the planet. Dr. Lipton, it is always a pleasure to talk to you. And let me just say, we are incredibly grateful for the body of work that you have contributed to this field. As a person with migraine, I know I have benefited from it, and multiply me times millions of people around the planet. And that's a wonderful legacy to leave. So, thank you very much.

Dr. Lipton (30:11): That was very kind. Thank you so much. And good luck with the rest of this wonderful summit.

Paula K. Dumas (30:18): Thank you.