



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT



LATEST MIGRAINE TREATMENT LANDSCAPE

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Introduction (00:04): I mean, certainly there are people that are doing well on whatever they were taking before 2020, or whenever the first gepants came out — I think it was 2021 — anyway. But there are other people that have not really gotten satisfactory relief. And so, the new treatments have promise for them. You know, that said, there's nothing that works for everybody, right? So, we were all excited about the gepants and certainly they have been miraculous for some people, but there's a substantial proportion of people that they just haven't worked for, or they didn't tolerate them. So there's still a lot of work to be done.

Elizabeth DeStefano (00:46): You can consider a migraine-management approach in several different ways. You can divide it by methods of preventing attacks versus acute treatments during attacks. You can consider nondrug therapies versus pharmaceutical approaches. Then when it comes to those pharmaceutical approaches, you can further consider not only the wide variety of medications themselves, but also different routes of administration — from oral, to nasal, to intravenous infusion, or injection. Joining us today to outline today's options in the landscape of migraine management is Dr. Deborah Friedman. Welcome back to the Migraine World Summit, Dr. Friedman.

Dr. Friedman (01:25): Thank you. It is always a pleasure to be here.

Elizabeth DeStefano (01:29): So, to begin broadly, what are the goals of acute treatment as compared to preventive treatment of migraine?

Dr. Friedman (01:39): Acute treatment is essentially getting rid of the attack, right? It's for each individual attack, and we're looking for something, regardless of what category it's in, that's going to make the attack end quickly and not come back. Preventive treatment is something that is either a medication, or perhaps a device, that reduces the frequency of migraine attacks overall.

Elizabeth DeStefano (02:08): And are both medicinal and nonmedicinal options for both acute and preventive treatment?

Dr. Friedman (02:15): Absolutely.

Elizabeth DeStefano (02:17): Great. OK, so let's start with everyone's first wish: preventing attacks before they ever occur. When are preventive approaches warranted?

Dr. Friedman (02:27): So, the American Headache Society and the American Academy of Neurology have published guidelines about when we should consider prevention. And the conditions under which we would do that include attacks occurring more than four days out of a month — so basically, once a week or more; attacks that are not well controlled by acute medication; patients who have hemiplegic migraine or migraine with brain stem aura — it's pretty much an automatic prevention regardless of the attack frequency; and just patient preference. So, there are some people that have headaches that are much less frequent than four times a month, but because of how disabling the attacks are, or because of their other responsibilities that need to be taken care of, they don't even want that many attacks. So the patient has a lot of input into this as well.

Elizabeth DeStefano (03:25): Understandably. And that applies to pharmacologic approaches. Would you say that nonmedicinal preventive approaches can apply to any frequency of attacks, regardless?



Dr. Friedman (03:38): Yes, I think so. Certainly there are more risks when we use pharmacologic approaches, and the possibility of having side effects. Or for young ladies getting pregnant when on a medication that shouldn't be taken during pregnancy. But we don't really have those issues with devices, for example. So, they really could be used by anybody who wants to try and prevent their attacks. And some of those devices can also be used for acute treatment. So it's kind of a, you know, double benefit.

Elizabeth DeStefano (04:10): Great, great. Would you say that preventive strategies are underutilized?

Dr. Friedman (04:16): Absolutely. And I'm not the only one that says this. There are studies that show it. So, in some studies, upwards of 40% of people that get interviewed or surveyed would meet criteria for prevention, and typically fewer than 15% are actually on it. And it's not clear why that's the case. If it's just a matter of access to a physician that can help the patient decide on a preventive medication, or suggest a preventive medication, or perhaps it's resistance by patients to take a preventive medication. It's not really certain. But it is markedly underutilized throughout the country, and probably throughout the world.

Elizabeth DeStefano (05:04): So, let's review some of the nonpharmacologic, nonmedicinal preventives that we can try to reduce [the] frequency of attacks. And you certainly mentioned neuromodulation as one possibility, right? So those exist, and those will be covered also in-depth in another interview this year. Anything you'd like to share for us to consider about neuromodulation, first of all?

Dr. Friedman (05:31): I think neuromodulation is a good option for a lot of people. Particularly people who tend to get side effects, people who are on a lot of other medications and they don't want to add more medications, and pregnant women; it seems to be quite safe. So there are circumstances there that it would probably be the first-line treatment. And cluster headache would also be among those situations. You know, the limiting factor for a lot of the neuromodulatory devices is their cost. And so, many of them are not covered by insurance. In fact, I'm not sure that any of them are. Some are available without a prescription, others you need a prescription. And when you amortize the cost over a year, it usually doesn't turn out to be much more than most preventive medications are, but the fact that they're not covered by insurance can be limiting for many people.

Elizabeth DeStefano (06:27): I'd love to talk about lifestyle modifications too. In a recent *Neurology Reviews* supplement, you explored the impact of migraine triggers and noted that many with migraine would be better served with actually a greater focus on healthy lifestyle measures than on trigger avoidance. What lifestyle choices matter most?

Dr. Friedman (06:48): Well, first of all, it is true. And triggers are kind of controversial in the headache world, among my colleagues. Most people with migraine feel like they have at least one trigger. The most common triggers if you look at population data are stress; menstrual cycle, as well as other hormonal factors; missing meals; changes in weather; and then there are a whole host of other things like odors and alcohol and foods and things like that. But sometimes I think people ascribe a certain food or a certain environmental condition to triggering their migraines when perhaps it's just a coincidence sometimes.

Dr. Friedman (07:36): And I don't mean to be derogatory about any of this because I do think that there are people that have clear triggers, but sometimes triggers can take over somebody's



life. And I've seen a lot of patients who avoid every food that tastes good, and they never go outside during the rain, and, you name it — they're watching the barometric pressure all the time, and they're basically not living, right? And it would be, I think, a much better decision — and allow people to live their lives better — if maybe they considered either a neuromodulation device or preventive medication.

Dr. Friedman (08:19): Often I think people get a bit of anticipatory anxiety when they're exposed to something that might be a trigger. And sometimes there's kind of a threshold with a trigger. You know, like, “I can have a few M&M's but I can't eat the whole bag,” kind of thing. So, sometimes I think that just trying to be healthy, and exercise in moderation, and don't skip meals, and just doing the things that we generally recommend people do to take good care of themselves, would probably be sufficient for most people.

Elizabeth DeStefano (09:00): Haven't we also learned that sometimes those things that we perceive as a trigger may actually be part of the migraine attack in progress?

Dr. Friedman (09:07): Yes, absolutely true. Is it really the loud noise? Is it really the bright light? Or is that your prodrome? That all of a sudden, the lights seem too bright, the noises seem too loud, that food that you think might be the trigger might actually be part of a craving that's a premonitory symptom, or a prodrome.

Elizabeth DeStefano (09:29): Building on that, an extra focus on the lifestyle factors that we can control can be one of the preventive strategies that we can use, aside from therapeutic drugs to help prevent attacks. What about behavioral therapies? Which ones can be a part of helping to reduce frequency of attacks?

Dr. Friedman (09:49): I think that the best ones that have been shown in studies to work are cognitive behavioral therapy and mindfulness meditation. Cognitive behavioral therapy — it's kind of a strange term — but it's basically when you are exposed to something that you think might upset you, or you think might trigger your migraine, to kind of sit back and you, not reframe your environment but reframe your response to whatever that situation is. And then mindfulness is essentially focusing on the present, and there's a component of stress reduction that goes along with that. But both of them can be quite helpful.

Elizabeth DeStefano (10:35): OK. And finally, another preventive strategy that a number of people employ to try to reduce frequency or severity of attacks is nutraceuticals or supplements. What role can they play in that endeavor?

Dr. Friedman (10:49): There are some supplements again that have been shown in studies to be helpful. One is vitamin B2, coenzyme Q10, magnesium, and there is a certain brand of butterbur — you have to watch out with butterbur because some of the butterbur that's on the market can potentially cause liver problems — but Petadolex is actually safe; there may be others that are safe, as well. But I think with supplements in general, you have to really be careful — they're not regulated. And I often see patients that come in and they're taking 10 different supplements, and you really don't even know what's in the pills. When it comes right down to it, there's a wide variation in the quality of these things. And you know, if anybody reads *Consumer Reports*, they sometimes will do features about analyzing what's in these various nutraceuticals or supplements and finding out that what's supposed to be in there is not even in there at all. So, you know, you have to be a good consumer when it comes to these things.



Elizabeth DeStefano (11:59): So, when do pharmacologic approaches become appropriate in prevention?

Dr. Friedman (12:04): If the patient meets criteria and they're willing to try, then we'll think about pharmacologic therapy. With the young women, again, we always have to take into consideration whether they are planning to become pregnant, because there are a few things that we don't want to use during pregnancy, and a lot of things that we just don't know what their effect will be during pregnancy. So we have to, kind of, plan for all of that. But I think a lot of people, when they realize that there are good preventive options out there, may be more willing to ask their provider to discuss them.

Elizabeth DeStefano (12:42): So, speaking about the variety of options available now, what are the main categories of drug therapies for preventive treatment of migraine?

Dr. Friedman (12:51): So, I guess we can, kind of, think about it like the older ones, which are oral; and the newer ones, some of which are oral, some of which are not. And the older medications, without exception, I think, they were all made for something else. And we found out that they helped to prevent migraine pretty much serendipitously. People took them for the other condition and found out that their migraines got better. So, when we talk about taking antidepressants for example, it's not necessarily literally to imply that the patient is depressed, it's just because they work on serotonin, they work on norepinephrine, and other active chemicals that are part of the migraine process. So, in the antidepressant category it's usually tricyclic antidepressants — venlafaxine has evidence for it. Sometimes we'll try other antidepressants as well, even though they've never been studied in clinical trials.

Dr. Friedman (13:53): There are antihypertensive drugs that we use for blood pressure control. Now, a lot of people with migraine have pretty low blood pressure to begin with, so that might be a limiting factor. But the beta blockers, the calcium channel blockers — candesartan, and lisinopril, and medications similar to them, in that class. And then the third major category is anticonvulsants. So, some of the older ones, valproate or Depakote; topiramate, which is marketed as Topamax. And again, depending on the type of migraine, we might think about using some others in those categories.

Dr. Friedman (14:32): So, the newer medications are the ones that were designed specifically to treat migraine and they target CGRP, or calcitonin gene-related peptide, which is released during the migraine process. It gets taken up by those trigeminal nerves that feed into the back of the brain and keeps the migraine going. So what we're trying to do is prevent CGRP from working, one way or the other. So, there are three injectable medications. I'll give you the generic names and the brand names, at least in the U.S. — they may have different brand names elsewhere in the world. But we have erenumab, which is Aimovig; fremanezumab, which is Ajovy; galcanezumab, which is Emgality; and then there's also an intravenous formulation, which is given once every three months, which is eptinezumab or Vyapti. And then there are also oral medications that we use that target CGRP. The two that are used for prevention are atogepant, which is Qulipta — it's taken every day; or rimegepant, which is Nurtec, and that's taken every other day for prevention. And Nurtec is unique because it can also be taken for acute treatment.

Elizabeth DeStefano (15:53): And so that first category of the CGRP-related medications that you reviewed, some people may hear referred to as the monoclonal antibodies, right? And then that second group that you discussed is referred to as the gepants?



Dr. Friedman (16:06): That's correct. And then there's also onabotulinumtoxinA — also known as Botox — [that] in the United States [is] FDA-approved for migraine. It's been FDA-approved for the prevention of chronic migraine since 2010. And so, there are 31 injections, they're given in a standard location, and they are given once every 12 weeks. And that's also very effective for patients who have chronic migraine.

Elizabeth DeStefano (16:36): You sometimes hear about some other categories that are, I guess a little bit less in that main category. I've heard some people talk about being prescribed muscle relaxants in an attempt to treat migraine. How common is that?

Dr. Friedman (16:49): It's actually pretty common, and at least one of the muscle relaxants, cyclobenzaprine, has a very similar chemical structure to the tricyclic antidepressants, so that may be one of the ways in which it works. And I do think it's important to know that you can mix them — a lot of them you can use more than one. So, there are many people who have really refractory headaches, that one preventive medication is not going to do the trick. So we would probably try to pick, you know, more than one that has different mechanisms of action — say a CGRP monoclonal antibody and onabotulinumtoxinA is often a good combination, or maybe, use it with one of the oral preventive medications. And sometimes that strategy works very well.

Elizabeth DeStefano (17:39): We've certainly had a lot of interest in that — the idea of combined therapies and prevention — and success in pursuing that. So thank you for mentioning that. So, now having really talked about these approaches from a pharmacologic prevention category, we get to now, the idea of treating when attacks occur. Because regardless of whether an individual uses preventive approaches to managing migraine, they often turn to treatment acutely during an attack. Now, whether or not they're aware that what they're experiencing is migraine may affect how they treat it, of course, just as the familiarity their healthcare provider has with migraine, may too. So, let's start first with the pharmacologic means of treating attacks. What are the categories of drugs that can be used in acute treatment of migraine?

Dr. Friedman (18:31): So, we have simple analgesics like acetaminophen; aspirin; combination analgesics such as acetaminophen with aspirin and caffeine — also known as Excedrin in this country, a lot of people get in trouble with Excedrin; nonsteroidal anti-inflammatories; other combination medications that some of them we even get compounded because they're not manufactured anymore. There's one that used to be called Midrin, it's isometheptene, that, unfortunately they don't make it anymore because one of the ingredients is no longer made. So, a lot of us will find a close substitute and get it compounded; helpful for many people. Triptans, of course; the gepants; the ditans; the, what else do we have left? ... devices, the neuromodulation devices. And then there are the drugs that we don't really like to use very much, right? Butalbital-containing compounds, opioids — every so often we do have to use those for extenuating circumstances, but we really just try not to overall because there's so many downsides and risks associated with their use and potential for becoming dependent on them, and making headaches worse.

Elizabeth DeStefano (19:57): And how do the ergotamines factor in?

Dr. Friedman (20:00): So, there's ergotamine tartrate — old drug, been around for decades and decades — as well as dihydroergotamine, which is also an old drug that's been around since the 1940s. And initially as an injectable, or an intravenous preparation, now available as a nasal preparation. I think we're seeing a lot of that actually; I call them, "old drugs, new tricks." But



we're seeing a lot of comebacks and it's good, because a lot of these medications are tried and true. We've had them around for a long time and we just have to tweak them a little bit, and you know, make them better.

Elizabeth DeStefano (20:39): So, what about nonmedicinal options for acute treatment of migraine in addition to neuromodulation?

Dr. Friedman (20:47): So, a lot of people find out about these things by themselves, right? Rest, ice or heat — one is not better than the other, it's just whatever you prefer — going into a dark quiet room, meditating. I have a lot of patients that they kind of try to put themselves into another place, so that their pain is not registered so badly.

Elizabeth DeStefano (21:11): I hear some people talk about how exercise can help, or exercise can be disastrous, or that fine line between the right amount, or the right type of exercise, I think it is such an individual...

Dr. Friedman (21:23): Yes, I think you're right. I think most people, at least when they have migraine, they don't want to move. But there are other people that find that exercise helps them.

Elizabeth DeStefano (21:34): Yes. Or maybe in prodrome an attempt to thwart with the right light-type of exercise. Perhaps that's a little bit of a foreign concept for me personally, but I've heard some people mention it. Great. Well, so the American Headache Society issued a consensus statement with an update on the integration of new options into patient care. So, in practice, how much has migraine management really shifted in recent years with the advent of the new therapies?

Dr. Friedman (22:03): I think it's shifted considerably. I mean, certainly there are people that are doing well on whatever they were taking before 2020, or whenever the first gepant came out — I think it was 2021 — anyway. But there are other people that have not really gotten satisfactory relief. And so, the new treatments have promise for them. You know, that said, there's nothing that works for everybody, right? So, we were all excited about the gepants and certainly they have been miraculous for some people, but there's a substantial proportion of people that they just haven't worked for, or they didn't tolerate them. So there's still a lot of work to be done.

Dr. Friedman (22:45): But I think that what is important, if you'll allow me, is tailoring the treatment to the patient. And as people out there listening, you can really help your provider a lot. So, the first question is, what formulation are we going to be looking at? And I realize that people with migraine often have different kinds of attacks. Not every attack is the same, right? So, some people will have attacks that have a prodrome, they may have an aura, they may have, you know, hours go by before their pain peaks in intensity, they're not really nauseated at the beginning, but they get more nausea as the attack progresses. And so, for these people, oral medications taken early probably work well.

Dr. Friedman (23:38): But then there are other attacks, that either wake people up from sleep in the middle of the night — and when that happens, it's kind of like the train has already left the station. Often the attacks are pretty much close to full blown when it occurs, people are nauseated. And we know that the changes in the brain that occur with a migraine, which are called peripheral and central sensitization. The peripheral sensitization comes first, that's like the part of the trigeminal nerve that's outside the brain. The central sensitization is inside the



brain and it takes about an hour for central sensitization to occur. And once that occurs, the migraines get much harder to treat.

Dr. Friedman (24:22): In addition, once people start getting nauseated, they're much harder to treat. And we know that the gut's not working well in general during a migraine, even without nausea. So, once people start getting nauseated, the likelihood of being able to swallow a pill — have it dissolved, have it be absorbed, and be effective — goes way down. So, it really helps if people let us know: how long does it take for their pain to peak in intensity? And if the pain peaks in intensity — we know once the attack starts, within an hour or less — we're going to start thinking about using nonoral treatment, either an injection or a nasal spray or, in other countries, a suppository. We're going to start thinking about using more aggressive antiemetic treatment, either a suppository or a transdermal. Because we have to bypass the gut — the gut's not working in our favor, right? Headaches that people wake up with, right? First thing in the morning — same thing; it may be too late to take an oral medication. And I think for a lot of people, the reason their acute treatment fails is because it's not the right acute treatment.

Elizabeth DeStefano (25:38): Well, thank you so much for sharing that point, because when you're talking about your medication choice and oral or nonoral, you're not just talking about what most of us might think of as the barrier— whether we have nausea/vomiting — and thinking, well, if I don't have nausea/vomiting, I'm clear to take the oral. It's not just about that. It's about, also, where the attack is in progress, and whether, even if you can keep the medication down, it will be absorbed or not.

Dr. Friedman (26:04): Sure. I mean, it's not just ... part of it is how long does it take for the pain to peak in intensity? But the other part of it is ... how long does it take before you're really nauseated or you're vomiting? And then there's some people that also have diarrhea just to add to the mix, right? And so that is kind of limiting too. You can't use a suppository in somebody who has diarrhea. So, things can get a little complicated, but if we don't know what's going on from the patient's vantage, it makes it a lot harder for us to prescribe the right thing. And so, I think that for a lot of people that have gone through like every triptan, nothing works, maybe there's a reason every oral triptan — maybe there's a reason for that. Maybe oral medication is not the best option for them.

Elizabeth DeStefano (26:52): So, it sounds like in addition to sharing a lot of the things some of us have been coached to share about frequency of attacks — and whether we have aura or not, and prodrome, and length of attacks, and so forth — that you're talking about getting a little bit more specific. So we can tailor treatments not just to each individual patient, but also for different attack types that each patient has. And some of the things we should be sharing should be what kind of timeframe we have — from when we first become aware of an attack, to then when the pain starts — so that we can help our doctor help us make some of those tailored decisions.

Dr. Friedman (27:31): Absolutely. You know, and the old advice still holds true, right? How long does it take for your medication to work? Do you get recurrence? Does the headache come back — which is called recurrence, right? How often does it work? What percentage of the time is your acute medication effective? I mean, I see a lot of people and they take whatever medication. I say, "How well does it work?" "Pretty well." "Well, what percentage of time does it work?" "Oh, maybe 30%." I mean, that's not effective.



Dr. Friedman (28:01): And similarly to preventive medications, we combine things, right? So the medication itself; an antiemetic, you know; maybe a different medication as well; so maybe like a triptan, or a gepant with a nonsteroidal, or whatever combination. The only thing you can't really use together is a DHE and a triptan, or a ditan — lasmiditan you're not supposed to take with DHE either. But other than that, assuming there's no medical contraindications or tolerability problems, we can mix stuff up. And it is important for people to take their medication early. And I know that creates problems for people with frequent migraine, like, “Am I taking too much?” But a lot of people, I think, have very good insight into what their headache is going to be like and can make a good judgment about that.

Elizabeth DeStefano (29:00): Well, so there are so many options, and as you've pointed out, too, combinations thereof, now in migraine management, which can be encouraging, but also daunting. So, thank you so much for really painting us a picture of this broad landscape in migraine. I'll also mention that the Migraine World Summit has information about hundreds of different options that can be used in migraine summarized in their treatment directory. So, for personal reference, and also that we know many people have used in discussion with their providers to explore new ways to most effectively treat migraine. So, I wanted to ask, Dr. Friedman, where can we learn more about what you're doing, or follow any of your work?

Dr. Friedman (29:43): That's a good question: www.neuroeyes.com (N-E-U-R-O-E-Y-E-S dot com). So, at least it'll tell you who I am and what I'm up to, and hopefully where my next step is going to be. And then I speak at the American Headache Society and the Southern Headache Society and various venues around the country.

Elizabeth DeStefano (30:08): Are there any resources on this topic that you'd like to point our viewers to, in considering their landscape of options?

Dr. Friedman (30:18): You know, I think the Migraine World Summit is a great resource. And then the American Headache Foundation, as well as the National Headache Foundation, are all good resources and I'm sure there are other very good ones in other countries as well.

Elizabeth DeStefano (30:35): Wonderful. Well, thank you so much, Dr. Friedman, for joining us yet again on the Migraine World Summit. We greatly appreciate you being here to walk us through all of our options.

Dr. Friedman (30:44): You are most welcome. Anytime.