MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

BALANCING RISKS & BENEFITS OF MIGRAINE TREATMENTS

AMAAL J. STARLING, MD, FAHS, FAAN
NEUROLOGIST
MAYO CLINIC, ARIZONA

Introduction (00:05): What that does is, when there are untreated migraine attacks, that increases the risk of transformation to chronic migraine. Individuals who have untreated migraine attacks within the next year are more likely to develop 15 or more headache days per month, with at least half of those with migraine features. In addition, when they have untreated migraine attacks, they're more likely to have reduced function, increased disability, increased sensory sensitivities. All of those symptoms just increase and snowball.

Elizabeth DeStefano (00:43)**:** When it comes to taking medications for migraine — or any condition — one of the first things we consider is how the potential benefits compare to the potential risks. While some people experience no side effects while taking medications, unfortunately, that's not the case for many people. And then there are the long-term impacts to consider. Will we pay a price down the road for relief now? Dr. Amaal Starling is here to discuss the risks and benefits in migraine treatment. Dr. Starling, welcome back to the Migraine World Summit.

Dr. Starling (01:14)**:** Thank you so much for having me back and also to be able to have the opportunity to talk about such an important and very relevant topic for our patients.

Elizabeth DeStefano (01:25)**:** So, sometimes it feels like there are not many options for migraine treatment, especially for people who haven't had help from medications that they've tried or who have experienced really challenging side effects with them. Can you share your thoughts about the quantity and quality of treatments that are now available for migraine?

Dr. Starling (01:44)**:** Yeah, really, over the last 10 years, we have had an incredible increase in the number of options that are available. But I think even before talking about those specific options, it's important to think about migraine as a disease that is present on a daily basis, whether you're having an attack every day or not. And I also like to think about migraine as kind of a threshold disease, and a lot of these preventive medications that are aimed at reducing the frequency and the severity of attacks are trying to raise that threshold so that it is less likely that you are to have a migraine attack. So, when we think about those preventive options, there are many — there are lifestyle changes or modifications that can be helpful. There are biobehavioral treatment options that can be helpful. And then there are also medications, some of which might be oral, some of which might be injectable. There's also neuromodulation. So, there are these devices that can be helpful for the prevention. So, I think it's important to remember that prevention may be indicated for many people. There are many, many different options out there, and this is where we can individualize the treatment option for the specific patient.

Elizabeth DeStefano (03:02)**:** So even while we focus on medications, it's important to think about the other options outside of medication that are available in treating holistically a patient who lives with migraine.

Dr. Starling (03:15)**:** A hundred percent. So, those nonmedication approaches that we think are helpful at raising that threshold including good sleep hygiene, eating regular healthy meals, exercising — specifically aerobic exercise — preventing dehydration, and stress management, learning how to cope with the stress that we all have in our lives. Those things are important. And I'm not saying that for someone who has chronic migraine — which is defined as 15 or more headache days per month with at least half having migraine features — that someone with chronic migraine, if they learn how to manage their stress, that their migraine attacks are going to resolve. I'm just saying that that will help raise the threshold so that another medication that may be layered on top of that modification can raise it even further. In addition, I find that if we

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can maximize those lifestyle modifications, that we may be able to use a lower dose of a medication rather than having to get up to a higher dose.

Elizabeth DeStefano (04:16)**:** Interesting that you mentioned the use of lower doses. Are there instances — or can you talk a little bit about the instances in which reducing the dose of a medication can bring that efficacy but with the reduced risk? Our viewer, Lynette, who has used triptans for decades, noted that just recently her physician has prescribed a lower-dose triptan now due to her age.

Dr. Starling (04:42)**:** In triptan medications, they do have the potential risk of lowering or narrowing the size of blood vessels. So, when individuals who have a history of poorly controlled vascular risk factors, like poorly controlled blood pressure, or if they have a history of a heart attack or a stroke, triptan medications are contraindicated or should not be used in those individuals.

Dr. Starling (05:11)**:** Now there is a myth that individuals who are older and maybe beyond the age of 65 but are otherwise healthy — don't have a history of poorly controlled blood pressure, no history of heart attack or stroke — that those individuals should not be on triptan medications. That's not true. With triptan medications, the dose itself is really important to break that attack.

Dr. Starling (05:40)**:** Often people will use a lower dose, whether it be recommended by a physician, or they feel like, "Well, let me cut the pill in half." Or I have patients that are cutting it into fourths — which I feel like they're giving themselves crumbles of the triptan medication at that point — because they have this feeling that, "If I use less, then I'm going to have less potential side effects." And unfortunately, when you take less of the medication, it may not actually stop the migraine attack. So, you're still getting exposed to the medication, but the migraine attack is not actually being stopped. Maybe it just takes the edge off for a couple hours, but then you're having to re-dose again. So my preference is really that when someone's having a migraine attack, you take the right dosage or the right combination of medications. Stop the attack right then and that you don't have to re-dose.

Dr. Starling (06:28)**:** And in fact, there's data that shows that when triptan medications are taken too late in the attack, that they don't work as well. And so it's really important to take that as-needed medication right when you feel the symptoms coming on. If there are concerns about side effects or if there are contraindications, the good news is we do have a lot of new options that are available that don't have an effect on the blood vessels.

Elizabeth DeStefano (06:57)**:** Are all medications equal in their likelihood to produce side effects?

Dr. Starling (07:03)**:** No, they're not, which is why one person's migraine symptoms may be different than the next person's migraine symptoms. And this is also why what works for one person with migraine may not work for another person with migraine. And then going back directly to your question, which is also why some people may have side effects from one medication but may tolerate another medication perfectly well, and for another patient, it's exactly the opposite.

Dr. Starling (07:33)**:** So, migraine treatment is very much individualized, and I always urge my patients that — just because you've talked to friends and family members who have had side

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effects or you've read online about the different side effects of medications — I really want to try this effective option for you because your body might handle this medication differently. Now I mentioned friends and family, and I do want to go back to that a little bit.

Dr. Starling (08:01)**:** Migraine is genetic. So I do like to ask people about, well, if your family members have migraine, what has worked for them, or what hasn't worked for them? And I do take that into consideration when I choose a medication option. And then I also think about what the patient's medical history is. What are their comorbidities or other diseases or conditions that they also carry in addition to migraine? And I try to select then a medication that might actually help with that other comorbid disease process or condition. Or at least find a preventive treatment option or an as-needed treatment option that will not worsen or will not affect the other disease process [and] will not interact with their medications.

Dr. Starling (08:51)**:** So I'm able to select my options based on an individual's medical history. Which is why it's really important to make sure when you go to a doctor's appointment that you have a list of all of your medical conditions and other medications that you're taking so that they can appropriately evaluate which option would be a good one for you. So, I think this is important to keep in mind because often patients feel like they are being treated as a guinea pig and just medications are being thrown at them. And I always reassure patients that the reason we have all these different options is because they have been studied in well-designed clinical trials, and in these clinical trials these medications have been more effective than placebo, or that "sugar pill." And those are the medications that we then say this is effective for migraine for some people. I unfortunately don't know which person that is, but I can predict some side effects or some benefits of the medication based on an individual's clinical history.

Dr. Starling (09:56)**:** So it isn't a shot in the dark; it is an educated guess that's based on clinical trial data, as well as medical knowledge about side effects, to identify which option will work for that patient. But that first option may not be the best option for that patient. It's something we might try for three to six months. If we don't find efficacy, if we find side effects, we'll move on to another option. So I always am asking our patients to come back and follow up with me because the first or the second option may not be the one that is perfect for them. But we continue to work with patients until we find the options that are effective both for acute treatment and preventive treatment for patients.

Elizabeth DeStefano (10:39)**:** And it's so understandable why we — when starting a new medication — can have so much hope that that is the answer that we've been searching for and waiting for, and how much of a hit that hope can take when it's not. So for us to recognize in partnership with our provider that we need to recognize that this is a marathon and not a sprint. So, though they are not accessible yet everywhere around the world, you mentioned how recent years have brought several new classes of migraine medications into the picture: So CGRP-targeted medications including both the monoclonal antibodies and the gepants, and a ditan. What recent safety data is available on any of these newer medications?

Dr. Starling (11:22)**:** Yeah, there is quite a bit. So, in the clinical trials, in addition to looking at if a medication is effective compared to placebo, they also look at side effects compared to placebo. So if we talk about the CGRP medication — so again CGRP is a protein that is present in everybody but it is elevated in people with migraine; it's elevated during a migraine attack. And these medications, they're lowering the activity of CGRP.

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Dr. Starling (11:54)**:** Now, CGRP does a lot of different things in the body in addition to being involved in migraine. And so it is important to look at what are the potential side effects of lowering CGRP activity — even if that's helpful for migraine, what are the other side effects? So, if we look at the CGRP monoclonal antibodies themselves in the clinical trials, three out of the four CGRP monoclonal antibodies actually had no side effects that separated from the placebo group, which was really striking. And even after a medication comes out on the market, whenever we think of a potential side effect — if a patient says, "Oh, I'm having some body aches or pains" or "I'm having some anxiety" — and they're on these medications, I, as well as the patient, report them to the FDA. And so the FDA keeps track of all of these potential side effects, and they're monitoring it on a larger national scale. And then, when there is something that seems to hit a signal above the general population, they then are actually publishing that data, as well.

Dr. Starling (13:03)**:** Now the gepants are CGRP receptor antagonists, so it's not a monoclonal antibody. It's a pill rather than an injection, and it blocks that CGRP receptor. They also have been found to be really well tolerated compared to our oral generic medications — better tolerated than those for the most part. But they do have some risks of constipation and nausea that were present in the clinical trials and also seems to be present in my clinical population.

Elizabeth DeStefano (13:36)**:** And we now have a nasal option, as well.

Dr. Starling (13:39)**:** Yes, exactly. We have zavegepant, which is a nasal spray. Nasal sprays are a great option because it bypasses the stomach. So if someone has a lot of nausea, that's because your stomach is shutting down during a migraine attack. If your stomach is shutting down, you're not going to be absorbing an oral tablet really well. And so it's really important to use then a nasal spray or an injection that bypasses the stomach completely and goes directly into the bloodstream.

Elizabeth DeStefano (14:08)**:** For those medications that have been around and used longer in migraine, what is known about long-term use? One of our viewers, Nancy, shared that she's been using triptans for 30 years — which I can relate to — and is curious if there have been any studies about impact on the brain after that amount of time.

Dr. Starling (14:26)**:** Yes. So triptan medications have been used by many people with migraine for a very long period of time. They have been found — in registry data as well as retrospective studies for many, many years, really decades — to be safe in that setting. We don't have any data that shows that long-term use of appropriate medication use for as-needed treatment of migraine has an effect on the brain.

Dr. Starling (14:54)**:** What I can tell you, though, is that when an individual is not effectively treating their migraine attacks because maybe they're concerned, right? "Well, I don't want to take a medication because I'm concerned about the short-term, medium-term, or long-term side effects of this medication. So, I have a really high pain threshold, so I'm just going to tough it out. I'm just going to go into a dark room that's quiet and try to just ride out these migraine attacks." We do know that that does have an effect on the brain.

Dr. Starling (15:27)**:** What that does is, when there are untreated migraine attacks, that increases the risk of transformation to chronic migraine. Individuals who have untreated migraine attacks within the next year are more likely to develop 15 or more headache days per month, with at least half of those with migraine features. In addition, when they have untreated

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migraine attacks, they're more likely to have reduced function, increased disability, increased sensory sensitivities. All of those symptoms just increase and snowball.

Elizabeth DeStefano (16:05)**:** Well, I'm so glad you mentioned that because so often when we think about the risks of using medications, we are focused on what that medication introduces and not focusing really on what the risk might be of *not* using medication.

Dr. Starling (16:23)**:** Exactly. In addition, we have studies that show that when we look at brain function — so brain function is evaluated by doing functional imaging studies, which are looking at the uptake of glucose or sugar, which is needed for energy production, right? [We're] also looking at kind of the function of the electrical networks of the brain. When we look at that, we see that there are differences in brain function. When we look at people without migraine, we look at people with migraine, and then we compare that to people who have chronic migraine.

Dr. Starling (17:01)**:** The other thing I always talk about with my patients is that, number one, migraine is not a structural disease process. That's why when you do just a regular MRI, they'll say, "That looks totally normal; I'm not sure what's going on." Well, that's because migraine is not a disease of abnormal structure; it's a disease of abnormal function in the brain. And these medications are trying to normalize the function.

Dr. Starling (17:30)**:** So, often, that helps patients get over that barrier of taking a medication. They feel like it's an additive, right? It's something they're taking in addition to what's happening in their body. Rather than saying, look, your brain is not functioning normally, right? There's a piece that's missing in normal function and this medication is adding it back so that we're normalizing brain function. We're trying to bring your brain function back to normal. And that works for as-needed medications as well as preventive medications. The other thing, like we talked about, is that migraine is a disease that's present every day. Sometimes patients will say, "Well, I don't want to expose my body to a medication regardless of which way it's being administered. I don't want to expose my body to a medication every day if I don't have migraine every day." We want to reset that thinking.

Dr. Starling (18:22)**:** Think about migraine like asthma. We don't think about asthma as being present when someone is having an asthma attack and not present when someone's not having an asthma attack. We say this person has asthma every single day. And yes, sometimes they have asthma attacks. People who have very severe asthma may have asthma attacks even every day or asthma symptoms every day, right? Some people with very minimal asthma symptoms may have asthma attacks a couple times a year or even less.

Dr. Starling (18:54)**:** Think about migraine the same way. We sometimes will need medications to treat the underlying disease process, raise the threshold, make it less likely that you're supposed to have a migraine attack. But then there are days where you have a breakthrough migraine attack, like a breakthrough asthma attack. And when you have a breakthrough migraine attack, you need to have your as-needed or acute treatment options to stop that individual migraine attack. So that's your preventive options and your as-needed options. But if you have that type of management plan, you can live a full life with a good quality of life, reduced disability, and improved burden of disease with migraine.

Elizabeth DeStefano (19:34)**:** What an important way to think about it. How do you develop a strategy to help find the best balance of reduced migraine impact with tolerable medication effects?

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Dr. Starling (19:46)**:** Yes. It really starts with having a trusted relationship between the patient and the healthcare provider and the understanding that this is going to be a journey and that they're both going to walk this journey together, literally hand-in-hand, and that the first or the second option may not be the right option. But we do have to go through the different options in a systematic manner because some of these preventive options, they don't work quickly. The goal is always monotherapy, meaning I always want for a patient to be well managed on one medication or one treatment option, if at all possible.

Dr. Starling (20:27)**:** But for those patients that you're describing with very severe disease, I often will have to figure out a combination of options. We may add some biobehavioral treatment options, those lifestyle modifications, a neuromodulation device. It needs to incorporate not just efficacy but also tolerability and side effects because my goal for a patient is not that I reduce your migraine attacks if you don't do anything. No, that's not going to work. My goal is to improve your function. And so that's the main outcome measure that I always talk about with patients: "How much are you able to do now? How much work have you missed? How many social events have you missed?"

Dr. Starling (21:06)**:** I saw a patient just recently who has very, very severe migraine disease, and we've been working together for about a year now, with different treatment options, slowly layering different things. And she's able to do a lot more now than she did when she first started seeing me. If all I had done is asked her, "Well, tell me about your pain." And she said, "I'm still in pain 24/7." Then an option that I had is, "Well, nothing that we're doing is working, so let's stop all of this and let's figure out a new plan." But then I would've missed the fact that she has this improved function likely because of her treatment options, and I would've probably ditched some of those effective treatment options for her to try to find something else.

Dr. Starling (21:55)**:** So it's really important to concentrate on function, especially for our patients who have daily migraine symptoms. The first thing I want you to talk to your healthcare provider about is your level of function. In your treatment goals, focus on function. Pain is important, as well. Other migraine symptoms are important as well, but focus on function is number one. And then all those other things are kind of the co-primary endpoints.

Elizabeth DeStefano (22:20)**:** Thank you for that. You mentioned the idea of stopping things and starting over, and I wanted to ask you about a question one of our viewers, Rebecca, had about whether ever coming off medications, including preventives, and trying a "reset" of sorts ever makes sense. Rebecca takes a number of different medications, which are not optional for other conditions. She says she also takes a CGRP monoclonal antibody and topiramate for migraine prevention, and then a gepant for acute migraine treatment. And she talks about the fact that she often really just sleeps off attacks because of extreme fatigue. So, do you ever have patients start over with their migraine medications? What are the risks or benefits of doing so?

Dr. Starling (23:04)**:** Yeah, so there's kind of two groups of patients that we can talk about with that question. One is, what about the patient who's doing well on their preventive treatment options? When can they discontinue, or should they ever discontinue their medications? I always tell people: A preventive medication is not a life sentence. It means that you currently need this preventive option, but we will always reevaluate if we still need it longer. And so if someone is doing really well on their preventive options and — what is really well in my mind — they're functioning where they want to function with respect to migraine-limiting functions. In addition, where they're having less than four attacks per month and those less than four attacks, those three to less attacks per month, are effectively treated with an as-needed option. That's

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when I start saying, "Well, let's see if we could lower the dose of the medication that you're using."

Dr. Starling (24:02)**:** Or if it's like an onabotulinumtoxinA injection or one of the CGRP monoclonal antibody injections, I say, "Let's see if we can lengthen the time between injections." And we're able to see if, number one, we're able to get a lower frequency of dosing or a lower actual dose of the medication. And so even if we go from 100 milligrams (mg) of topiramate to 50 mg, once we get to 25, they're like, "Oh, no, my attacks are coming back or they're more severe." Then I'm like, "OK, let's go up to the 50 [mg]." And that's still a win. We've gone from 100 to 50 [mg]. That's a win. However, if their attacks kind of come back, we'll go back to that prior dose.

Dr. Starling (24:42)**:** There have been studies — and this is before the novel medications came out — but there have been studies that looked at individuals who were effectively well managed on oral medications like topiramate, amitriptyline, propranolol, venlafaxine. They were well managed on that. They weaned those patients off of those medications, and the vast majority of patients do worsen. There's a small group of people who continue to have benefit even beyond the medication being on board, but the vast majority actually returned to their prior migraine frequency.

Dr. Starling (25:21)**:** And there was one study that showed that reinitiating that oral generic medication actually didn't bring them back to the efficacy they were at before. And then, with the CGRP monoclonal antibodies, I don't have as much data about continuation versus discontinuation. We do have some data from European studies that do show that with discontinuation that the frequency of attacks comes back. But we don't have data that shows that reinitiating it has any negative or positive impacts.

Dr. Starling (25:51)**:** But then there's the other patient, right, that you mentioned that I think it sounds like they're on a lot of other medications that are not even related to migraine. And they have migraine disease, and maybe they're on two or three different migraine treatment options from a preventive perspective, and maybe they're still not doing great. And they actually don't even know what's helping or what's not.

Dr. Starling (26:12)**:** And that happens often with my patients, especially when they come to me as a new patient. They're on several different medications, and I'm like, "So tell me about the amitriptyline. Do you think it's helping?" And they're like, "I don't know. I've been on it for, like, five years. I don't know what it's doing." "OK, well, how about the gabapentin?" "Again, I don't know what's helping and what's not helping." So in that situation, starting over or slowly trying to discontinue medications is a great idea to try to get to a clean slate so you can figure out what is needed and what is not needed. Again, I don't say, "Stop all three of your medications at once." But I say, "OK, let's select the medication that has the most side effects, or at least you think has the most side effects."

Dr. Starling (26:56)**:** So, for this patient, they were concerned about a lot of sleepiness, or sedation, or fatigue. So, if they were on amitriptyline, I would say, "Well, amitriptyline does have the risk of sedation. So let's try to decrease the amitriptyline." Let's try to decrease the sedating medications and see if they were actually doing anything and then move on to the next medication. And maybe we get off, completely off of that medication, and it made zero difference. Well, great, let's get off something that's not helping you at all. There's no reason to continue that. Now, that's for the preventive medications.

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Dr. Starling (27:28)**:** For the as-needed treatment options, that's a little bit more urgent. You really want to try to figure out what can bring you back to at least your baseline more quickly rather than completely washing off all as-needed options. Because remember, poorly treated attacks lead to an increased frequency and severity of migraine. And so that one, you always want to have something that helps bring you back to your baseline, whether that baseline be some level of pain or no pain at all.

Elizabeth DeStefano (27:59)**:** Well, the idea of balancing risks and benefits when it comes to migraine management is obviously a very complex topic and very individualized to so many people who live with this disease. So, thank you so much for being here to talk us through this and to share some really important perspectives on that balance. Thank you, Dr. Starling.

Dr. Starling (28:22)**:** You're very welcome. It is a really difficult conversation, and often the conversation is just between the patient and themselves to come to terms with having to take a medication for this disease that they never asked for. It almost seems a little bit easier to take a medication [for other conditions] for many of my patients than to take a medication for migraine. And that's because there's the stigma of migraine: "That migraine is occurring just because I am a weak person." But that's not true. It's a disease process just like all the other disease processes, and we need to normalize the function of this disease process so that we can get you back to what you need to do. People with migraine are literally the strongest people that I know. There is nothing weak about taking a medication. There is nothing weak about having migraine. It's a disease of abnormal function. Medications and treatment options normalize that abnormal function so that you can live a full life with migraine.

Elizabeth DeStefano (29:23)**:** Beautifully said. Dr. Starling, where can we learn more about you and the work and research that you do?

Dr. Starling (29:32)**:** So, I do work a lot with a lot of the patient advocacy organizations. For example, [the] American Migraine Foundation, as well as of course doing different talks over the years with [the] Migraine World Summit. And both of those sites are really, really good information from many people like myself, as well as people that are my peers, that talk to patients about migraine disease, talk to patients about the medications and the treatment options about migraine, and also talk to patients about the stigma of migraine, which is one of the essential first steps of understanding so that you can start living your life with migraine. But those are all great doctor-verified sites [where] you can get good, helpful information.

Elizabeth DeStefano (30:20)**:** Thank you, Dr. Starling, for everything today. We appreciate you.

Dr. Starling (30:25)**:** Thank you so much. Happy to be here.

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