INTERVIEW TRANSCRIPT

DISCUSSIONS WITH WORLD-LEADING EXPERTS

Understanding Migraine Drug Side Effects

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Introduction (00:05): Sometimes we find a treatment that works only to experience crippling side effects. Sometimes the risks are well known, and other times our doctor denies the medication is responsible at all. What's really happening and how do side effects of migraine treatments — old and new — compare? Today we'll explore this with Dr. Teshamae Monteith, a leading migraine specialist and researcher. Dr. Monteith, welcome back to the Migraine World Summit.

Dr. Monteith (00:28): Thank you so much for having me. This is a really important topic. I'm glad we're covering it.

Carl Cincinnato (00:33): With so many advancements in migraine treatment, why do side effects remain such a critical and often frustrating concern for patients with both established and newer therapies?

Dr. Monteith (00:44): The brain is complicated, so targeting the brain is going to sometimes be associated with not only efficacy, but also side effects as well. We know even in people with migraine, it's been shown that they may be more sensitive to side effects than people without migraine. And so it's really a complicated situation.

Dr. Monteith (01:02): Targeting the central nervous system is associated with — there's a lot of neurochemistry, multiple receptors — and some of these drugs that we use can be "dirty." So they can be associated with multiple targets that affect different systems. And so I think that is part of the reason why we can see so many different side effects. And many of our treatments that we've used up until recently have been nonspecific treatments, so these are treatments that are used for multiple conditions. So when you have a drug that can be used for multiple conditions, including migraine, you may imagine that it may be associated with some side effects. Some side effects that we'll talk about may even be wanted to treat certain, even other comorbid, conditions.

Carl Cincinnato (01:53): So let's go through some of these main classes of treatments, and then talk about some of the side effects for each of them. So, what would be some of the most commonly prescribed preventive medications for migraine disease in the United States today?

Dr. Monteith (02:02): Yeah — and that's probably changing over time. But we have what we call the established oral preventive therapies — and those are antihypertensive drugs, so things like beta-blockers. These are first-line treatments for prevention of migraine, episodic migraine. Used less commonly are the ARBs [angiotensin II receptor blockers] or candesartan that can be used to prevent migraine as well.

Dr. Monteith (02:30): There are antidepressants that are used, so these are most commonly drugs like tricyclic antidepressants — amitriptyline, nortriptyline. There are SNRIs [serotonin-norepinephrine reuptake inhibitors] — so this is like venlafaxine, duloxetine — that can be used for prevention. SSRIs [selective serotonin reuptake inhibitors], while used widely for depression and anxiety, actually have really poor evidence for prevention of migraine.

Dr. Monteith (02:54): We also have the anticonvulsants, so these are drugs like topiramate and valproic acid, that can be effective to prevent migraine. And topiramate is probably one of the most commonly prescribed medications to prevent migraine still today, at least within neurology clinics. And I would say beta-blockers are certainly widely used in primary care clinics. So these are the nonspecific treatments.

Dr. Monteith (03:21): And then, of course, we have some of the newer treatments that are available for our patients, and those include the CGRP monoclonal antibodies. So these are monoclonal antibodies made in the lab — so our bodies are making monoclonal antibodies all the time to fight off certain viruses and things like that. And so the monoclonal antibodies specifically target a protein —

calcitonin gene-related peptide — either the peptide itself or the receptor. And so these are the first migraine-specific medications for migraine prevention — really exciting.

Dr. Monteith (03:53): And then we also have what we call the gepants. These are small-molecule receptor antagonists. They target the CGRP receptor in a different way — and so that's atogepant [Qulipta, Aquipta] and rimegepant [Nurtec ODT, Vydura]. And then, of course, onabotulinumtoxinA [Botox], which is currently — to this day — still the only neurotoxin with evidence for prevention of chronic migraine, but does not have at least an FDA label for episodic migraine.

Carl Cincinnato (04:19): Thank you for sharing that. It's a great recap of different options that are available in terms of entire classes of treatment. Let's go through each of them in a little bit more detail, looking at the most common side effects that patients might experience with these treatments. Let's start with the beta-blockers.

Dr. Monteith (04:38): The beta-blockers are, as we mentioned, antihypertensive drugs. So we have to warn our patients about the potential for dizziness or fatigue. Some patients may experience exercise intolerance with these medications as well. Technically, patients may experience depression or even weight gain — which is … I almost rarely see weight gain — but it's listed as a potential side effect. So those are the main things. And, of course, patients that have a history of asthma, we generally say they should avoid using the beta-blockers. These can be used for other indications. And so patients that have a history of essential tremor, for example, it might be a good option to try a patient on propranolol, for example.

Carl Cincinnato (05:21): And what about antidepressants? What kind of common side effects exist with that treatment class?

Dr. Monteith (05:27): With antidepressants — these are just by nature of the type of drugs they are — mood altering drugs. If patients have a history of bipolar mood disorder and it was either diagnosed previously or unknown to them — or they have a strong family history of bipolar mood disorder — these are patients that can cycle from highs and lows in terms of their mood instability. And there are many symptoms of mania. If you put a patient on an antidepressant that has undiagnosed bipolar mood disorder, they can actually go into mania. So we always screen our patients before we start a patient on an antidepressant and ask about their history of depression as well as their family history of depression or bipolar mood disorder. So I think it is really important.

Dr. Monteith (06:19): Other symptoms that patients have — these can be activating drugs. So patients may actually get a boost of energy, but they can also then feel very anxious. And so that's something to warn patients about. They may have difficulty sleeping. They can also feel very fatigued. Weight gain can be a problem, especially with SNRIs. So these are some things that we have to think about with our patients. There is a warning sign from the FDA for suicidality in adolescents. So that's something to ask about, think about. It doesn't mean not using the medications, but to just kind of monitor for symptoms and potential side effects.

Carl Cincinnato (06:59): We've learned recently that some people with migraine have trauma and perhaps PTSD [post-traumatic stress disorder]. Can this be a helpful synergistic treatment if it's — does it help with that as alongside migraine for those people that might have both?

Dr. Monteith (07:10): Yeah, it can, especially if there's comorbid depression associated with that. And so certainly I think it's important to ask patients — you bring up a great point. It's important to ask patients about history of trauma because they may have different side effects because of that traumatic history and the sensitization that might occur and the symptomatology.

Carl Cincinnato (07:38): And tell us about the side effect profile for antiseizure medications.

Dr. Monteith (07:43): Yeah, so there are two real main ones that we use. Topiramate — as we mentioned — that's kind of a "dirty drug." And some people have even hypothesized that's why it works so well for migraine. So [with] topiramate, the most common side effects that patients will report are really paresthesias — these are tingling of the body, ants crawling sensation. Fatigue may happen. Cognitive impairment may happen. I find in clinic that the cognitive impairment tends to be the one side effect that makes patients want to stop the drug. They have that, they call it — I mean, there's even like a terminology for it — they call it "Stupimax" or "Dopamax;" you may have heard that.

Dr. Monteith (08:23): And kidney stones — we always warn patients about kidney stones. It's about 2% on the label — 2% chance of having a kidney stone. Now that might be higher if there's a family history of kidney stones or there's a personal history of kidney stones. We often tell our patients to make sure that you maintain hydration to avoid any risk of kidney stones. But topiramate is actually — really can be a highly effective drug for many patients.

Dr. Monteith (08:49): I've had patients that have had kidney stones — sometimes many kidney stones — and have either refused to get off [of] topiramate, gone somewhere else to get the prescription, and then come back to me to fill the prescription for topiramate. And so, again, this is always a risk-benefit scenario. If someone is extremely disabled — they have 20 migraine days per month — topiramate seems to be the only thing that really is very effective, then that might require a conversation with urology and how are we going to manage and prevent these renal stones.

Carl Cincinnato (09:23): And for someone who hasn't tried any of these treatments, we don't want to frighten people off.

Dr. Monteith (9:27): Right.

Carl Cincinnato (09:28): Just because we're listing all these side effects doesn't mean that you will experience every single one of them — and sometimes you may not experience any of them.

Dr. Monteith (09:35): Well, the majority of people don't experience side effects. Side effects happen, but there's usually a minority of people that are going to experience these side effects. And so, the nice thing about some of these older therapies is we tell our patients to start generally low, go slow, and increase over a period of time. And if you do that, it gives you enough time to determine whether there's a potential side effect for many of the side effects, like cognitive impairment, for example.

Dr. Monteith (10:03): And so, with topiramate, where we know that cognitive impairment is something that is common to the drug, we can tell people to, "Well, OK, let's try and figure out the dose that works for you — that you're less likely to get that side effect. When I came out of fellowship, we had these guidelines and ways and dose recommendations for patients. But in clinical practice, it's become clear to me that not every patient needs to get up to that ideal dose.

Dr. Monteith (10:29): Certainly, if a patient is not responding to the treatment, you want to get to that ideal dose. But there are patients that can do very well with pretty low doses, and that's true for topiramate and other drugs, too.

Carl Cincinnato (10:42): I would imagine as well that sometimes you'd get a small woman, maybe 50 kilograms (kg), and then you're giving them a dose. But they have the same maximum dose as, let's say, a larger male who might be 100 kg or, in this case, 220 pounds versus 110 pounds.

Dr. Monteith (11:00): Yeah, so there are a number of factors that can be associated with why someone would get a side effect. And you just reminded me to mention that weight loss can be a side effect of topiramate. It's usually not considered a negative thing. Most people are trying to get on that

topiramate, and they're hoping to lose weight. It's really about 1 in 10 that are going to lose weight on topiramate.

Dr. Monteith (11:20): But I think that is also true of efficacy. I had one patient that — speaking of topiramate — that he was put on topiramate; and he had two prescriptions in the pharmacy, and he got confused, and he ended up taking both. Now, this guy was probably close to — he was like 6'5" — and he was … I don't remember how much he weighed. He was a huge, big guy. And accidentally taking that double dose, it was the first time he had a reduction, a significant reduction in his migraine frequency.

Dr. Monteith (11:53): This is someone that fell like 12 feet and injured himself and had severe post-traumatic headache of migraine-like phenotype. And it was really the large dose that helped him. So I think dosing matters at the end of the day — and that is true of efficacy, and that is true of side effects.

Carl Cincinnato (12:15): So far, we've talked about different treatment classes that all are oral tablets — but Botox [onabotulinumtoxinA] is different. Can you tell us about the side effect profile for Botox?

Dr. Monteith (12:23): Yeah. So Botox has been FDA-approved since 2010. This is, I think, a case where if you look at the original clinical trial data and you look at some of the adverse events that are part of the clinical trial data, oftentimes when a drug comes to market and there's usually an accumulation of post-marketing data where side effects tend to accumulate over time or increasing the likelihood of a potential side effect over time.

Dr. Monteith (12:51): I think part of the long expertise that people have been able to accumulate over time with the neurotoxin, people have gotten really good at doing these injections. So the rates of neck pain, for example, have dramatically dropped with better understanding of the functional anatomy associated with injecting neurotoxin. So I think that's really exciting.

Dr. Monteith (13:17): Headache remains to be a side effect where people sometimes report worsening headache for a short period of time after getting the injections. Is that worsening headache, or is that taking a while for the Botox to kick in? Because we know there's this wearing off that I think we didn't fully appreciate when Botox was first FDA-approved.

Dr. Monteith (13:41): And ptosis, I think, is something that can happen. These droopy eyelids that patients may experience. That's a very rare phenomenon and that may happen with patients that have preexisting weakness. And so we do now screen for these preexisting weaknesses and these risk factors that might be associated with adverse events. But I think that is one example of a drug that tends to be very safe for our patients.

Carl Cincinnato (14:06): And I think just the format itself distinguishes it significantly because it's not going and giving, as you mentioned, the "dirty drugs" that sort of affect other areas. It's an injection, so it's not passing through the gut or the liver or the kidneys. It's just working on its local site.

Dr. Monteith (14:24): Yeah, it's generally very peripheral. There are some distant side effects that people have reported like dysphagia — problem swallowing — for example. But those are extremely rare side effects. And so a little bit of the neurotoxin can get in the blood. But the doses are so small and likely really insignificant.

Carl Cincinnato (14:45): And tell us about the newer CGRP monoclonal antibodies and their side effect profile.

Dr. Monteith (14:50): CGRP monoclonal antibodies — we now have four. We've had three that were FDA-approved in 2018 and then one in 2020. And so [with] these drugs, we now have really good experience with them in terms of their side effect profiles. They're generally extremely well tolerated. As I mentioned, they're monoclonal antibodies. So your body, if you think about it, these are biologics — your body is making monoclonal antibodies. So your body understands what this monoclonal antibody looks like.

Dr. Monteith (15:20): But it does target a very important protein called — as we mentioned — CGRP, which is a potent vasodilator. The main side effects to this day, really, for the three injectable therapies — the most common is injection site reaction. And these are generally considered pretty mild. There are very rare patients that would stop the injections if they work very well because of the injection site reaction, with some exceptions. Even in the clinical trials, the discontinuation rates were really low associated with that. But I think that can be a problem. And I've seen numbers as high as 50% in terms of the injection site reaction, so that's something. Hypersensitivity reactions or allergic reactions tend to be a problem for some patients — a small number — but it can be a problem. And that, of course, is across the four injectable therapies.

Dr. Monteith (16:12): And for erenumab [Aimovig], these are the receptor … the monoclonal antibodies that block the receptor — so that's erenumab. It's been associated with constipation. Constipation can sometimes be severe. And we know that patients with migraine are at risk for IBS [irritable bowel syndrome], which sometimes may be associated with constipation. So it's good to really try and screen patients that have constipation and maybe consider avoiding a drug like erenumab or even the receptor antagonists that we'll talk about.

Dr. Monteith (16:42): And then, of course, the FDA recently added hypertension — new or worsening hypertension — to the label of all CGRP inhibitors. And this was not something that was seen in clinical trials. This is something that was captured post-marketing. And I think the thought is that maybe patients with preexisting hypertension weren't adequately represented in the clinical trials. So based on these reports that — first with erenumab and then it became something associated with all the CGRP inhibitors.

Dr. Monteith (17:22): And so there have been a couple of papers that tried to look at that and look at that risk. And they really did not find any association between the hypertension and the CGRP monoclonal antibodies. So it's important to note that. But I think the main point is that we should be considering it, talking to our patients about it.

Dr. Monteith (17:48): If a patient has hypertension that's out of control, probably the CGRP inhibitors should not be the first line. Obviously, you may want to consider antihypertensive medication if [it has] not been tried. And so I think that that is important. And then just kind of making sure patients are monitoring their blood pressure the first week after they get the prescription — and certainly by the time they come back and see you. Now, the suspected blood pressure elevation is really still about a few points. But those few points may make a difference if you already have some prehypertension that's going on.

Carl Cincinnato (18:26): And the last class that we spoke about were the gepants. These are the small molecule anti-CGRPs. Can you tell us about the side effect profile for them?

Dr. Monteith (18:35): Yeah, so really we're talking about atogepant and rimegepant [Nurtec ODT]. And so both drugs have been associated with some fatigue and some GI [gastrointestinal] symptoms. Atogepant in particular has been associated with constipation, and so I believe that's one. We talked about dose relationship. There are different doses of atogepant — so there's 10 milligrams (mg), there's 30 mg, and there's 60 mg. While we want to sometimes consider 60 mg up front with our patients, if you have significant constipation, that might be a time where you consider a lower dose or at least certainly warn a patient about the potential of aggravation with that.

Dr. Monteith (19:14): Now, because it's in the class of CGRP inhibitors, we've mentioned that hypertension and worsening Raynaud's could be a potential side effect of these drugs as well. So that's just something to watch out for. Generally speaking, the CGRP monoclonal antibodies and the gepants are very safe. We have good open-label data going on for five years, and there's really been no cardiovascular signals appreciated.

Carl Cincinnato (19:43): So we've heard recently from our community members as well saying that they've experienced side effects on some of these newer meds that they don't feel [are] as often discussed. How do the newer CGRPs compare versus the older classes when it comes to the side effect profile, just in general?

Dr. Monteith (19:58): First, I would say that if you've experienced a side effect that is new, it's not on a label, your doctor didn't tell you about it, and then you looked it up, you went on the website and it's just not been appreciated, that might be a time that you can report that. There's a database called the FAERS [FDA Adverse Event Reporting System], which patients can certainly report side effects that they're experiencing, because that's the way that we're able to capture and screen and really monitor.

Dr. Monteith (20:19): And sometimes that results in a label update. So if you're really noticing some potential side effects, then go ahead and put in your comorbidities. And it's OK if it's not really related — maybe you had a flu or something else. If you really strongly believe that this was related to the drug, go ahead and put in that item. And so that was the first thing.

Dr. Monteith (20:38): Generally speaking, if you compare the — just broadly speaking — if you compare the older drugs to these newer drugs, the newer drugs certainly outperform the older drugs in terms of safety and tolerability. We don't have a lot of direct evidence — most of this is based on clinical observation, as well as real-world data. However, there was one study, which was a head-to-head study; this was comparing topiramate to erenumab, also known as Aimovig. And it showed that when looking at patients that were randomized to either arm, those that were randomized to receiving the Aimovig had far less side effects. They stayed on the medication longer, and they actually had better outcomes in terms of reducing migraine days. So I think this is important because now we have some options in terms of trying to reduce side effects for our patients.

Carl Cincinnato (21:42): When a doctor says this drug is generally well tolerated, what does that actually mean in practice for the patient?

Dr. Monteith (21:54): That generally means that the risk of having many or severe side effects are very low. And that's a statistical kind of way of stating that. Of course, if you're that — what we call N-of-1, that 1 in 100,000 — it doesn't feel great to get pancreatitis on valproate, for example. But the risk can be generally very low. And so that's generally what that means.

Dr. Monteith (22:22): It's also important to note that these drugs are not drugs that you need to be on for the rest of your life. These can be things that maybe you need to be on for three months, six months, one year, or even two years. If you're in medical school, for example, and your migraine attacks are out of control, and you need to be on a preventive therapy — that might be a short-term period when you're having poor sleep, you're skipping meals, you're having chronic stress, and there may be other factors going on. And so that should also be taken into consideration.

Carl Cincinnato (22:54): One of our viewers, Janis, noted that CGRP is involved in various functions in the body outside of migraine-related pain — and she's wondering how blocking CGRP might impact those other functions.

Dr. Monteith (23:07): Calcitonin gene-related peptide is what we've mentioned as the most potent vasodilator in the body. But there are many vasodilators in our body. So there's likely to be

redundancy and parallel functioning of some of these chemicals so that blocking CGRP, you're not blocking all of CGRP — we're blocking a significant amount to reduce migraine attacks, but this is not necessarily all the CGRP.

Dr. Monteith (23:33): So not only are we not blocking all of it, but these parallel systems can take over. And to that point, we've not seen any significant side effects other than the ones we've mentioned in other organ systems. But it's something that we need to certainly be aware of and be alert to.

Carl Cincinnato (24:02): What does it mean when the term "half-life" is used when describing the effect of a drug? And how does that influence the side effects a patient might feel? So for example, do drugs with a longer half-life carry a higher risk of lingering side effects? And does a shorter half-life mean the side effects resolve more quickly?

Dr. Monteith (24:17): The relationship between half-life and I think side effects — there certainly is a relationship. A drug needs four to five half-lives to reach steady state. And then when it reaches steady state, that seems to be the period of time where it's most likely to be working for whatever condition that you've prescribed it for. And so in the same manner, it needs to have at least four to five half-lives to be considered out of your system. But that's in terms of like drug levels, I think. There certainly are people that can have very long-term side effects, even though the medication is technically out of their system. I've certainly seen that in certain circumstances.

Carl Cincinnato (25:04): Are the side effect profiles more dependent on the class of drug, or do they vary significantly drug to drug? So for example, if someone experiences side effects on one drug, are they likely to experience the same side effects with another drug in the same class? So we know with triptans, for example, if one triptan fails you, it's still worth trying another. But are the side effects likely to carry across each triptan? And same for the CGRPs — we know that with CGRPs, it's still worth trying another antibody if one doesn't work. But are you likely to have the same side effects?

Dr. Monteith (25:37): It's not always easy to understand why someone's had a particular side effect. I would say that if you've had a side effect to a particular drug, and you use a similar drug within that class, there's certainly a significant chance that you may also have a side effect to that drug that's within that class.

Dr. Monteith (26:00): So in terms of triptans, we're talking about serotonin agonists — there are seven of them. Now there's different routes of administration of triptans — there are nasal sprays, there are injectables. So some of the side effects may not be fully related to what we call a class effect — it can be related to the route of administration. For example, if you give someone a sumatriptan injectable therapy, they can respond very quickly. But they could also have pretty significant side effects like palpitations, for example, which they may not see with a nasal spray — or to that point, a long-acting triptan like naratriptan.

Dr. Monteith (26:35): I would not throw a drug class out if you've had a side effect to one drug within that class. I think that you may want to have that discussion with your doctor. And there are ways to get around improving tolerability and side effects. Now, of course, if there are other options available, for example, you had a very severe side effect to a triptan, well, maybe that might be an opportunity to go to another drug class like a gepant or something else.

Dr. Monteith (27:02): And so these are all really important questions and conversations that we have. But certainly, I've absolutely seen patients where they've tried three or even four triptans and had side effects or they didn't work — and it was that fourth one that they just didn't have side effect to, and they also responded really well. Because we know that within even the triptan class that there is a variability in terms of potential AEs or adverse events in those clinical trials.

Carl Cincinnato (27:42): Yeah, I mean, that's great news. If there's five to seven triptans available, depending on where you live in the world, then knowing that there's five to seven options and potentially if you don't respond well or you have intolerable side effects on one, that you've got other options — and likewise for the CGRPs.

Dr. Monteith (27:57): There are some patients that respond to sumatriptan, but with 50 mg, they don't have side effects. But with 100 mg, they have horrible side effects. And so I think this is where a little bit of the art comes into play in addition to the science.

Carl Cincinnato (28:14): Yeah. So not only do you have the different treatments, but you've got the dosage and you've got the formats because you're talking about oral versus inhaler versus injection. So there's different options there, too. So there's lots of options for us, which is great.

Dr. Monteith (28:27): And that also goes with, I think, the gepants. If you try one gepant, it doesn't mean that you're going to be a gepant failure or you're going to have side effects to all the gepants. And we also now have [an] intranasal gepant available. So we have different options for our patients.

Carl Cincinnato (28:46): How do you distinguish between someone who's had an adverse event or a side effect — a significant side effect — versus a reaction or an allergy or an allergic reaction to a treatment or a treatment class?

Dr. Monteith (28:57): I see a lot of times when I look at patient charts that they report allergies to medications. And when you dive into what that symptom was, you find that it really wasn't an allergy. It was just a side effect, a known side effect, and even part of the mechanism that could explain that. So we see those things like sedation, for example — or even nausea, for example — that may sometimes happen to patients.

Dr. Monteith (29:26): And so true allergies are things like hypersensitivity reactions — rashes, swelling of the throat, for example. Sometimes patients experience shortness of breath and signs of anaphylaxis. And so it's really important to tease that out because we don't want to throw away a drug class if a patient has had a side effect that, if you switch that drug to something else, they can do really well with.

Carl Cincinnato (30:02): What other conditions should patients and doctors be especially mindful of when weighing the side effects of a treatment?

Dr. Monteith (30:06): It does depend on the drug. And there's no, like, kind of pan side effect. Obviously, if you feel anything new or different, whether it was reported or warned to you or something you've noticed yourself, feel free to reach out to your doctor. I think that your doctors want to hear from you, especially when it comes to things like side effects. And so it really is drug dependent. And we expect to see these things coming.

Dr. Monteith (30:33): Weight gain, for example, that can be associated with valproate, with tricyclic antidepressants, with SNRIs. And so these are some things that you do have to kind of check for and be warned about that there is — beta-blockers as well — that there may be a potential for weight gain. And so maybe a good idea to once a week get on that scale and make sure that you haven't gained any significant weight.

Dr. Monteith (30:56): We know about the topiramate that patients may experience brain fog, and that's something that can sometimes creep up on you. I've had many patients that have been very concerned about that. They're in a certain profession that they really need to be very fluent. And so, you know, these are all conversations we have, but it is really kind of on a drug basis.

Carl Cincinnato (31:20): Is it safe to combine different therapies like a gepant and CGRP, which are both sort of blocking CGRP to some extent in the body?

Dr. Monteith (31:31): We don't have clinical trial data to support that. And so hopefully one day we will. We do have, I would say, an emerging amount of real-world data that seems to suggest that combining gepants with CGRP monoclonal antibodies are safe. They do both block CGRP mechanisms. So for that reason, checking blood pressure — you may want to be a little bit more diligent with checking blood pressure. But we really don't have the clinical trial data to support this. But I think there's certainly an emerging real-world sense of that they are safe, but the data is still pending.

Dr. Monteith (32:15): Now, there was a tandem study that looked at atogepant and ubrogepant [Ubrelvy]. So these are two different gepants — one for abortive and one for prevention. And it seemed like based on this study that combining gepants seems to be safe. I would like to see the efficacy data. I think we need more of these kinds of studies because we're finding patients that are needing these different types of unique combinations.

Carl Cincinnato (32:41): And CGRP seems like it's involved in bone metabolism. If anyone has a bone-related condition, would that sort of urge more caution or should that urge more caution in the doctor when prescribing CGRPs or combining them?

Dr. Monteith (32:58): Yeah. Again, we just don't really have the data. I think that an obvious potential case could be someone with osteoporosis. And we just don't have those patients adequately represented in clinical trials. But certainly that's the case for things like topiramate where you'd have to certainly watch. So it's not just these newer drugs — these CGRP drugs — that you have to think about; you have to think about that for some of the older drugs as well.

Dr. Monteith (33:27): And so this is where it's a risk-benefit, especially in the setting of the absence of evidence and where it's really important that even though you love your neurologist or your headache specialist or the person that's caring for your migraine, that you're also seeing your primary care doctor or your woman's health physician and you're getting that holistic care.

Carl Cincinnato (33:56): What role do the liver and kidneys play in processing migraine drugs? And what does that mean for patients who are taking these treatments long term?

Dr. Monteith (34:03): We know things like acetaminophen, which some people use excessively to treat their migraine attacks, when used every day that can be associated with medication overuse headache. But that can also be associated with liver disease and liver toxicity — hepatotoxicity. So you really do have to be careful with even things like simple analgesics.

Dr. Monteith (34:28): There are some very obvious drugs like valproate, which we've mentioned, that can be associated with liver toxicity. And we know this, that we actually screen patients — this is one of the few times that we actually get blood work for patients to monitor for any increased levels of liver enzyme abnormalities. And so that is important, too. There are the gepants in the setting of severe liver disease. These were not patients that were included in the clinical trials. So [with] these patients, you may need to look at the dosing of the gepants in this setting.

Carl Cincinnato (35:05): It sounds like if we're taking a lot of drugs over our lifetime to treat migraine — both preventively and acutely — we want to take care of our liver and kidneys. Are there any tips that you'd give the audience to do that?

Dr. Monteith (35:19): Again, most migraine drugs are very safe. And I don't think that our patients should worry — especially on the preventive side of things — need to worry too much about hepatic toxicity. I do think with things like, again, some of these over-the-counter medications like

nonsteroidal anti-inflammatories [NSAIDs], when used excessively — we're talking about excessively — you may put yourself at risk for kidney disease, chronic kidney disease.

Dr. Monteith (35:45): And so that's why it's going to be a balance between appropriate acute treatments and preventive treatments to get those migraine attack days down. So you don't have to expose yourself to excessive amounts of nonsteroidal anti-inflammatories that may impact the kidney, but also may put you at risk for gastric ulcer disease. And thus, I think it's important to just be very healthy overall — to maintain hydration for kidney, good kidney function; that is important.

Dr. Monteith (36:15): And avoid things that could also affect your kidneys, such as reducing blood pressure, if that's a problem, right? Because we know blood pressure also impacts kidney function. And with liver disease, it's certainly important to lead a healthy lifestyle to avoid any potential harms on your liver.

Carl Cincinnato (36:42): And probably reduce any excess alcohol consumption, if alcohol is a big part of your routine?

Dr. Monteith (36:47): Absolutely. I mean, I think when we compare migraine drugs to things like alcohol, excessive acetaminophen use, there are other things, too. That's why we talk about making sure that you live an overall healthy lifestyle so that your organ health is fully protected.

Carl Cincinnato (37:10): In your experience, what are some of the most common areas of misconceptions or anxiety that patients have when it comes to understanding and managing side effects from migraine treatment?

Dr. Monteith (37:22): I think a really common thing is that when I sometimes hear people say, "Oh, if there's going to be a side effect, I'm going to have it." And it really makes it hard to start off a conversation with, "OK, this is how we're going to get you better and need to get you better."

Dr. Monteith (37:37) Of course, there are other options other than drugs. There are nonpharmacological options; there are devices; there are vitamins, supplements; there are lifestyle interventions. But just because you had a side effect with one drug that had a completely different mechanism of action doesn't mean you're going to have a side effect with another drug. And we can certainly work around that concern or fear by starting generally, as we mentioned, maybe even starting lower than what we normally would do and go up even slower than what we normally do. And I think that that's very helpful.

Carl Cincinnato (38:18): One of the things I just wanted to get back to briefly was you mentioned acetaminophen or paracetamol, which is essentially like Panadol or equivalent brands [Tylenol]. And you also mentioned NSAIDs, nonsteroidal anti-inflammatories like ibuprofen (like Advil), or other brands as well. Does it help to take those with food? Does that reduce the potential harmful effects in the gut? And at the same time, it's hard to take food if you're taking these treatments in the middle of the night because you've woken up with a migraine. So it's understandable for patients to be taking these just as needed when it's urgent. But does that help prevent some of the damage that could be done?

Dr. Monteith (38:58): So for acetaminophen, it doesn't matter whether you take it with food or not. But for nonsteroidal anti-inflammatories these NSAIDs, as you mentioned — ibuprofen or naproxen — it is helpful to take it with food just so that it can act somewhat as a barrier. Because we know these drugs can reduce a chemical called prostaglandin that's really important for gastric mucosal lining. And so taking it with food can be helpful as a buffer, if possible.

Dr. Monteith (39:23): Obviously, if you're nauseous, you're vomiting, that might not be realistic. And if it's in the middle of the night, that also may not be realistic. But maybe you don't skip breakfast that morning, right?

Carl Cincinnato (39:41): So broadly speaking, if a patient develops side effects, when and how can they discuss this with their doctor?

Dr. Monteith (39:47): Yeah. Obviously, it depends on the side effect. If there's a severe side effect or allergic reaction — I often tell patients, "If you're having a severe allergic reaction or you're short of breath or you're having some chest pain or palpitations, you should probably go to the emergency room," right? If it's a rash, that's something that can be managed; you can certainly call your doctor.

Dr. Monteith (40:09): And not only should there be a discussion about the symptoms and maintaining the symptoms, preventing it from spreading, but there should also be a discussion as what are we going to do for the next step to help you with your migraine? Sometimes patients have side effects. And even [with] the setting of the side effects, they may still be able to stay on the medication. And so having that conversation with your doctor is very essential.

Dr. Monteith (40:31): You can easily, in the United States and where I practice, we have an EMR [electronic medical record] that patients can write in, take a picture, they can upload their picture, they can show me that rash. I'm not a dermatologist, so that's always my disclaimer. Sometimes I need comanagement with primary care, but I think that, you know, let us know. I think when it comes to side effects, we really want to know. Don't be shy.

Carl Cincinnato (41:04): When should someone consider stopping or switching treatment because of the side effect or side effects?

Dr. Monteith (41:07): Yeah. Sometimes when patients are placed on medications over time, the side effects can wane. And so it really depends on what type of drug they're on, what side effect they have. Is this something they can tolerate? Is this something that they can see whether that will settle out? A good example of that might be fatigue — that they feel very fatigued. They started a beta-blocker and they feel really fatigued — this is day two, day three.

Dr. Monteith (41:34): Sometimes you say, "OK, well, let's kind of see, let's keep it where it is. Let's give it a week. Let's give it two weeks." Now, obviously, if you fall asleep while driving, that's dangerous. And so it really depends on the level of adverse event. And also, if you're able to determine that it's actually somewhat helpful, then you may want to stick it out a little bit longer.

Dr. Monteith (42:02): There are certainly exceptions to that. In my experience, the common side effects of topiramate, while they can wane, they tend to persist. And then some people may get used to certain things like tingling with topiramate. You may have tingling of your toes and your feet. And that might be something that, "Oh, yeah, it bothered me at first, but now I'm totally used to it." And then what other treatments have you tried? What other options do you have?

Carl Cincinnato (42:32): What final message would you like to leave with people living with migraine about side effects?

Dr. Monteith (42:38): When it comes to side effects, this is not in a vacuum. We have to combine the potential of side effects with efficacy, cost, convenience. I think we need to come together to make a decision … And we didn't even talk about pregnancy, right? And the potential of some side effects to the fetus and avoiding certain drugs like topiramate, valproate, and even CGRP inhibitors if you think you're going to become pregnant.

Dr. Monteith (43:07): And so I think having a conversation with your doctor about your concerns, about your past experiences. Because we know that patients that get put on these oral preventive therapies — in six months, for patients with chronic migraine — only 1 in 4 continue to take their treatment; at one year, it's close to 10%. So we know that people are going to stop taking treatment. So how do we optimize that? I think it's going to be having that conversation, that shared decision-making.

Dr. Monteith (43:38): If you have a side effect, let us know, because we can either work around that side effect, we can reduce the side effect. There are strategies. It's not all or none. And I think the most important thing is just having that conversation.

Carl Cincinnato (43:52): Dr. Monteith, thank you so much for joining us again on the Migraine World Summit.

Dr. Monteith (43:57): Thank you for having me.