MIGRAINE WORLD SUMMIT®

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

WHAT TO EXPECT: NURTEC ODT, UBRELVY, QULIPTA & ZAVZPRET

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Introduction (00:05): Well, gepants have this very interesting flexibility in that the same family of medicines can be used for both acute treatment (or how to manage an individual migraine attack), as well as a maintenance or preventative treatment (how to reduce the frequency- and severity-intensity of the attacks over time). And even in one case, one such medication, rimegepant, which is Nurtec as its brand name, is actually approved for both acute treatment and preventative treatment, so it shows their flexibility.

Paula K. Dumas (00:37): Gepants might be the biggest blockbuster drug of this era for migraine. Like triptans improved the quality of life and ability to function for people in the 1990s, gepants are doing the same for many in the 2020s. Despite having relatively few known side effects, gepants don't work for everyone. If you're taking Nurtec, Ubrelvy, Qulipta, or Zavzpret, or are considering them, this interview will give you the answers you need. Few experts are better equipped to answer your questions about gepants than Dr. Matthew Robbins. His credentials include president-elect of the New York State Neurological Society, board of directors for the American Headache Society, and associate professor of neurology at the Weill Cornell School of Medicine. Dr. Robbins, welcome back to the Migraine World Summit.

Dr. Robbins (01:27): Thank you, Paula. I'm so thrilled to be back with you all.

Paula K. Dumas (01:31): Well, this is a topic that everyone is buzzing about. Let's get started. What are gepants?

Dr. Robbins (01:38): So gepants are a funny term, but they're named after medications that block the receptor for this neurotransmitter or this neuropeptide, that's a small neurotransmitter, called C-G-R-P, which stands for calcitonin gene-related peptide. All of this is a mouthful, and gepants is kind of the easier term to say: These are medicines that are CGRP blockers. CGRP is this small, miniature little protein that is released by nerve endings around the coverings of the brain, and also inside of the brain, in different circuits that's very important in the migraine pathway.

Paula K. Dumas (02:18): And how are gepants different from the CGRP monoclonal antibodies?

Dr. Robbins (02:23): Well, it's interesting because the gepants were actually developed first, but some of the earlier iterations were difficult to engineer either in a pill form or might've caused some side effects, such as liver injury. So that led to the antibodies to be developed against CGRP — these biological treatments, these monoclonal antibodies, which also are, of course, very effective for migraine prevention. But they are different in that they aren't, sort of, drugs so to speak — these engineered compounds like most medications are that would work against migraine.

Dr. Robbins (02:59): So the other sort of difference is that the gepants are also medicines that are used both for treatment of individual migraine attacks as well as prevention of migraine, as opposed to the monoclonal antibodies, which for the most part are thought of as preventative treatments.

Paula K. Dumas (03:18): Makes sense. And a bit more background: Can you please explain what a CGRP receptor antagonist is?

Dr. Robbins (03:25): Of course. So CGRP, as I mentioned, is this miniature neurotransmitter that is important in migraine, in different pathways and circuits in the brain, and nerve endings

around the coverings of the brain and the head and the face. The CGRP has to stick to something, so it sticks to what's called a receptor. These are little proteins that are on the surface of nerve endings or blood vessels, and when CGRP sticks to these receptors, it leads to this cascade of activation where a migraine pain might be perceived or felt by patients once this process happens. So these gepants block that receptor: They stick to that receptor and prevent someone's CGRP itself that's being released because migraine is happening in the brain in such circumstances.

Paula K. Dumas (04:16): It sounds like from your description that we should take it as soon as we feel any kind of migraine attack happening, in order to prevent that whole migraine mechanism from happening. Is that right?

Dr. Robbins (04:31): Yep, Paula, you're absolutely right. It wasn't totally sure if that was going to be the case at first, but there have been some recent studies that have shown that, in fact, that is true: that the CGRP blockers, or these gepants, seem to work better the earlier that they are used in the context of an individual migraine attack. We've known that for a long time about triptans — which are, of course, sort of the first-line, more widespread, and earlier-in-development used anti-migraine-attack medications — that the earlier you use it, the better that they do. It's like if you are putting out a fire and you have the fire extinguisher, it works much better if you apply it to when the fire starts as opposed to once it's spread all over the place. We know that for triptans, and we certainly know that now for the CGRP antagonists or these gepants. So that is a very useful sort of advice that we give to patients: It's just like for a triptan — you should take the gepants as early as possible into a migraine attack.

Paula K. Dumas (05:32): Put out the fire when you see the smoke.

Dr. Robbins (05:34): One interesting thing that's also pretty new that's been presented at conferences throughout 2023 is that the gepants might even work before the pain starts for individual migraine attacks. So, so many people with migraine, as you know, experience this prodrome, or premonitory symptoms, where they can feel — they just know the attack is coming or has started because they have some neck stiffness, or the nausea or light sensitivity already starts before the pain does, or a mood change, or a funny craving. What we know, and so far from what early preliminary results of studies have shown, is that even taking a gepant before the headache itself starts, but when these prodromal symptoms start, might also help to lessen the headache or prevent it from starting in the first place.

Paula K. Dumas (06:20): So, let's talk about the gepants that are currently available. There are four of them, right? Can you talk about each one individually and what they do?

Dr. Robbins (06:30): Sure. Well, gepants have this very interesting flexibility in that the same family of medicines can be used for both acute treatment (or how to manage an individual migraine attack), as well as a maintenance or preventative treatment (how to reduce the frequency- and severity-intensity of the attacks over time). And even in one case, one such medication, rimegepant, which is Nurtec as its brand name, is actually approved for both acute treatment and preventative treatment, so it shows their flexibility.

Dr. Robbins (07:02): So, we have three of these gepants that are approved for acute migraine treatment: So, that's ubrogepant, which is Ubrelvy; rimegepant, which is Nurtec; and then most recently, zavegepant, which is Zavzpret, which is a nasal spray. These are all rescue medicines for migraine. And then we have atogepant, which is Qulipta, as a preventative treatment. And

then rimegepant, which is Nurtec, is also approved as a preventative treatment for episodic migraine.

Dr. Robbins (07:35): So, one medicine has dual approvals; the others have approvals either for acute treatment or preventative treatment. And much of the differences between them has to do with how quickly they have their onset, how long they last for. So those that last for longer, it makes more sense for them to be more maintenance treatments, so as preventative treatments, but some that have onset pretty quickly and also last long — like rimegepant, or Nurtec — might work for both.

Paula K. Dumas (08:06): So, let's talk about the dosage for each one and how you administer it. So, a couple of these are oral, right? Nurtec ODT is below the tongue. So it's not like a traditional oral that you swallow ...

Dr. Robbins (08:21): That's right.

Paula K. Dumas (08:23): And what's the dosage for that?

Dr. Robbins (08:25): So Nurtec, or rimegepant, it only comes in a 75-milligram (mg) orally disintegrating tablet. It's the same medicine, the same dose, whether you are giving it for preventative treatment or as an acute treatment in migraine ... It just sort of — there's no adjustment. It just is what it is, in that way.

Paula K. Dumas (08:46): And if you're using it preventatively, how do you dose that?

Dr. Robbins (08:51): It's dosed in an interesting way: It's dosed one tablet, or orally disintegrating tablet, every other day. And that's because the half-life of it is long enough that it doesn't need to be dosed every single day. Although there's recent studies looking to see if dosing it every day in fact would be better than every other day. So we're waiting to see how those studies go.

Paula K. Dumas (09:16): So, ubrogepant, or Ubrelvy, is an oral treatment, right, and how do you dose that?

Dr. Robbins (09:23): So just like triptans, it comes in two different strengths: 50 and 100 mg. You would take one tablet at the onset of migraine, and you can repeat a second tablet 2 hours or later than 2 hours in the same day.

Paula K. Dumas (09:37): And atogepant, or Qulipta, is a lot like some of the other oral preventives that we have, right? How is that dosed?

Dr. Robbins (09:46): So that medicine has three different strengths: It has a 10-mg tablet, a 30-mg tablet, and a 60-mg tablet. And it's dosed once per day. Although in some of the studies there was some twice-a-day dosing, but it's approved as a once-a-day dosing. And different people are learning different styles of how you would start someone on atogepant, or Qulipta. I think most of the time I typically start on 60 mg — the higher dose — straightaway because in general, it's a very well-tolerated medication with few side effects. And then if there are side effects, I may back off on the dose thereafter. In the clinical trials, it looks like the 60-mg dose might be a little bit better than the smaller amount of milligrams. So that's generally how I proceed with atogepant, or Qulipta.

Paula K. Dumas (10:40): Good to know. And zavegepant is different from the others in that it's nonoral ...

Dr. Robbins (10:47): That's right.

Paula K. Dumas (10:47): So how do you dose that?

Dr. Robbins (10:48): So zavegepant, or Zavzpret, is a nasal spray, and it's a nasal spray that only comes in one dose: 10 mg in a nasal spray. And it's approved to be used just once in a day — the single dose in a 24-hour period is what is to be administered. Typically, it only comes in a six pack, so it comes with a group of six. The prescription information says that the safety of it is just not known if you use it more than eight times in a month, so that's generally what we've been recommending to our patients.

Paula K. Dumas (11:27): So, I was curious: How do you decide which gepant to try for each patient?

Dr. Robbins (11:31): It's a great question ... First, obviously, it depends on what you're using it for, whether it's acute, or a rescue treatment, or as a preventative treatment. I think it depends on the patient. We don't have really any head-to-head studies that show that one is better than another. So I think we're all kind of looking for guidance for which one is better than another for each of the individual acute and preventative categories.

Dr. Robbins (11:59): I think I tend to use, in terms of acute treatment — if the attacks are very long, I tend to use rimegepant (or Nurtec) because it has a preventative effect and it can last for a longer period of time, and in the clinical trials, the outcomes look very positive for sustained pain freedom and relief 24, 48 hours later. Some people like the dissolvable pills, some people like regular pills. If someone has really intense nausea and vomiting, a nasal spray like zavegepant might be the way to go. But because it's such a new medication, sometimes getting it — or often, getting it — authorized for someone who hasn't tried the other medications might be difficult.

Paula K. Dumas (12:42): Of course. And the longer they're out, the more experience everybody has, in terms of getting those things approved. These are all FDA-approved in the United States, correct? And pending approvals in other countries?

Dr. Robbins (12:57): That's right. I think the recent news was for atogepant, or Qulipta, that has been approved in Europe. So, often there's a lag for U.S. versus Europe or in the U.K. and other parts of the world. There are certainly many underserved populations globally that still don't have very good access to even triptans — most of them. So I think there's certainly a ways to go for worldwide access to these medications. In the U.S., we're very fortunate that we have all of the CGRP antagonists or gepants approved, although it's not always so equitable with who gets them and who can afford them. Even government-based insurance like Medicare or certain Medicaid, often it's difficult to get approvals, or copays are extremely high for these medications. So I think there's a ways to go for more equitable access for these medications for everybody.

Paula K. Dumas (13:48): That is definitely an advocacy opportunity. It breaks my heart that many people who could benefit from them don't have access to them. Let's go back to triptans for just a minute because there are a lot of people in our community who are using triptans (or

they've tried triptans), and they're curious how this might be different. How are the gepants as a class different from triptans?

Dr. Robbins (14:10): Well, in many ways. So, I think one thing that people can feel confident about is that they both are working on the same system, so to speak. So, triptans work to activate these serotonin receptors on nerve cells to prevent the release of CGRP as well as other neurotransmitters. So triptans kind of have a broader mechanism. They might — because they're working to prevent the release of CGRP but maybe some other neurotransmitters — they might work for more people, and that's what we see. I think triptans still in general work for a higher percentage of people, although the gepants still do work for a sizable number of people, as well. So, in my practice, I still typically — unless there's a reason not to — would start with a triptan because it has a higher chance of working. But if there was any reason not to use it, a reason where it might not be as safe, such as a cardiovascular problem, then I would go to a gepant.

Dr. Robbins (15:06): But also, because the CGRP blockers — the gepants— are more specific, they tend to have fewer side effects. You know, triptans … about 1 in 5 or so people can experience this very uncomfortable side effect of this warm or tight or tingly feeling anywhere from the chest to the upper part of someone's scalp, and it can be uncomfortable. And the gepants don't [have] that side effect and ... that's really a positive. And the most common side effects that the gepants have are probably nausea and constipation if they're used often, such as in the preventative-treatment-scheduled way, but otherwise seem to have fewer side effects than the triptans.

Dr. Robbins (15:53): And then the other benefit that they might have is that they don't seem to be associated with this medication overuse phenomenon, which is a comforting thing because these same medicines are used as preventative treatments. Whereas triptans, we know sort of regular use of them — probably using them more than two days per week over at least a several-week period of time — can overly sensitize the brain and lead to this acute medication overuse that makes migraine worse or progresses to chronic migraine. So, the gepants don't seem to do that, which is also a reassuring property that they have.

Paula K. Dumas (16:30): Now, if somebody doesn't respond to one gepant, should they try a different one?

Dr. Robbins (16:35): So yes, in some patients one gepant could work better than another. We don't have great studies that really show head-to-head comparisons or whether an individual might respond better to one versus another, but in clinical practice we see that all the time. We saw that with the triptans, as well. It's hard to make total sense of it because they're the same; they're working on the same system. It's the same mechanism of action, but it could be factors related to how someone absorbs a particular medication. It could be related very much so to the root of administration.

Dr. Robbins (17:06): So obviously, someone who might have migraine with a lot of GI symptoms, and they have what's called gastroparesis, where their stomach just isn't absorbing or pumping its contents well enough, maybe giving a nasal spray, or especially if someone has nausea and vomiting, would obviously be better than a tablet. So I think there's lots of probably genetic reasons why one medicine is absorbed or effective more than another. And so, I think to some degree there is still a little bit of trial and error because we don't have perfect personalized

medicine to predict who's going to respond to which of the medications that are on our menu of options.

Paula K. Dumas (17:41): Are gepants effective for both episodic migraine and chronic migraine?

Dr. Robbins (17:47): Yes. So, for prevention, that seems to be the case. Atogepant, or Qulipta, is approved for migraine prevention overall. Rimegepant, at least for now, is approved as preventative treatment for episodic migraine. But I think the belief … and some studies have shown that it probably works just as well for chronic migraine. And we use all of the gepants for the acute treatment of migraine attacks in people who have migraine overall. So, I think there is sort of no hesitation to use these medications in people who have chronic migraine. In fact, because chronic migraine is so commonly associated with medication overuse, in some ways it makes more sense to use the gepants than the triptans in such circumstances.

Paula K. Dumas (18:36): So, how well do they work? What did we find in clinical trials?

Dr. Robbins (18:41): Well, I think for the acute treatment — for rescue treatment for treating individual migraine attacks — they work pretty well, but probably slightly less well on an overall basis than the triptans. If you can get a whole group of patients in a clinical trial, 20% of them pain-free at 2 hours, that's sort of a standard result. And gepants, kind of, get close to that result. But lots of people get better where they get pain relief, not just pain freedom, at 2 hours. And also, other symptoms benefit from these gepants — nausea, photophobia (light sensitivity), phonophobia (sound sensitivity).

Dr. Robbins (19:20): For preventative treatment, they seem to work pretty much in the clinical trials similar to existing preventative treatments, including the monoclonal antibodies. So, on average it doesn't sound very good that 50% of people get 50% better, but that's kind of an averaging effect from clinical trials. In clinical practice people do better than those numbers, so I think many people get a whole lot better and we see a very wide range of improvement from these medications.

Dr. Robbins (19:52): One recent news alert came from a study that is being done by Eli Lilly comparing a monoclonal antibody against CGRP [gepant]: galcanezumab, which is Emgality, versus rimegepant, which is Nurtec. And what they've told us so far — the results haven't been presented at any meeting — is that they both seem to work well, but one wasn't necessarily better than the other. So we don't know yet if the monoclonal antibodies given by monthly injection, for example, are better than an oral gepant as a preventative treatment. This one sort of news alert about the study from the industry release to the media suggested it was the same in that particular study, but obviously we need to — this is a question that's very important in clinical practice because sometimes we're faced with a decision: Well, do we start a gepant — an oral pill every day or every other day — or a monoclonal antibody that's injected once a month or once every three months by IV or injection? And we don't know what is the right answer yet.

Paula K. Dumas (20:58): So stay tuned on that one.

Dr. Robbins (20:59): Definitely.

Paula K. Dumas (21:01): You know we get questions from our community, and Ted is taking Ubrelvy, and he wants to know if he's just wasting pills by taking it during the hangover phase.

Dr. Robbins (21:13): Well, that's a good question. At least for now, as I mentioned earlier, we know that it may help for the prodromal phase. Whether it should be taken once headache is over to accelerate migraine recovery after an individual attack: We do not know. You could theorize that it might be important. The CGRP blockers or gepants have sort of broad mechanisms of action, so they probably work on both nerve endings, but they also work inside of the brain in migraine circuits that might still be revved up during that migraine hangover time. So, he's asking a great question that I don't know the answer for, but it's one that we also don't totally know the answer for other medications either, but hopefully we'll find out.

Paula K. Dumas (22:02): Right, yeah. Can gepants be taken while breastfeeding or pregnant?

Dr. Robbins (22:07): Great question. As far as we know so far, there's theoretical concerns about them. So most of us avoid using them in those circumstances. In pregnancy, if you block CGRP, in theory it might increase the risk of having high blood pressure in pregnancy or a complication of that known as preeclampsia, which can be very dangerous both to the developing baby and to the pregnant individual. So for the most part we avoid it. It looks like the gepants in breastfeeding women don't reach a very high concentration in breast milk, but until we have more reassuring safety data, I think most of us are holding off on using them in such circumstances. The CGRP monoclonal antibodies, however — while we also avoid them in pregnancy and in advance of pregnancy because they have very long half-lives — those might be safer in breastfeeding because they're big proteins, so if any of it gets into breast milk, the baby's GI tract can break it down. So those might be safer than the gepants in that situation.

Paula K. Dumas (23:15): Interesting. A quick promo in our library: You give a great talk on how to manage migraine when you're breastfeeding, or pregnant, or considering that. So anybody who hasn't seen that interview should go back and watch that. Are there any drug interactions that you've seen with gepants?

Dr. Robbins (23:33): Yes, they do have drug interactions. It's mostly relevant for the preventative treatments when they're being used in the long run. So, there's a number of interactions. Often, it's for treating infections. It's come up often with COVID because Paxlovid does have an interaction in particular with rimegepant, or Nurtec, and often people have to hold off on taking it during that five-day period of time when they're on Paxlovid as an antiviral for COVID. They also interact with other antibiotics. Thankfully, it's not ones that are very commonly used: antifungal medications; there's a list of others. Thankfully most prescribing clinicians are aware of these or medical record systems flag whenever there's two such potential interactions that could take place.

Paula K. Dumas (24:22): Good to know. I learn something new in every one of these interviews. Are there any other warnings or risks that we should be aware of?

Dr. Robbins (24:30): I think just the side effects that I mentioned before are kind of the main ones. And I think, you know, "to be determined" about these special populations with migraine: those who have cardiovascular disease, those who are pregnant or breastfeeding. There might be considerations in people with, for example, liver or kidney disease. So, for one example of that is of the CGRP blockers, the gepants: Probably ubrogepant, or Ubrelvy, is preferred for acute treatment of migraine in people with kidney disease, and you would use the lower dose, the 50-mg dose, in such individuals.

Paula K. Dumas (25:10): Got it. Now you probably have patients in your practice who don't respond to gepants. What other options do you recommend to them for acute treatment?

Dr. Robbins (25:19): Yeah, it's a great question. I mean sometimes — and what we're seeing now is kind of this ironic situation where sometimes we see patients who are getting gepants first just because people are hearing about them — there's more awareness, patients are asking for them. And often people are trying gepants before ever having tried triptans. So sometimes it does lead us to revisit the original migraine-specific medication groups, the triptans. Typically, if someone isn't responding to two, three triptans, they're not going to respond to others, but sometimes it might depend on whether the route of administration was appropriate. So it could be a nasal spray, it could be an orally disintegrating tablet for a triptan, even an injection for someone who awakens with tough attacks often or has nausea or vomiting.

Dr. Robbins (26:04): Other sort of migraine-specific medications do exist, which is lasmiditan, or Reyvow, although it tends to have more side effects. But it is a safe medication in those who have cardiovascular risk factors because it doesn't cause any direct impact on blood vessels — unlike triptans, which can squeeze blood vessels and someone who could have been susceptible to a stroke or a heart attack, maybe elevate the risk in the moment of that, but the Reyvow doesn't.

Dr. Robbins (26:33): And then there is this older medicine called dihydroergotamine, which is known as DHE, which now has a newer nasal spray formulation called Trudhesa, which is this specialized pump that leads to the medication to be absorbed more easily. And that's only by nasal spray and that might be a good option for many folks. You know, there's others: Sometimes anti-inflammatories do work better for some people. There's a newer anti-inflammatory migraine medicine called Elyxyb, which is celecoxib liquid, which is an option. There's a migraine powder called Cambia, which is diclofenac, which might help some people. So, I think it's good that we have lots of different options in addition to things that aren't medications at all, like devices, which I know Migraine World Summit covers in a very detailed way. So those are also options for people, too.

Paula K. Dumas (27:28): Yes, absolutely. And by devices you mean things like neuromodulation devices that are worn on the head or the arm or on the neck. So, I encourage people to check out all of our content on devices to learn more about those. So, are there any other gepants that are in the pipeline?

Dr. Robbins (27:49): Not to my knowledge. I think we have these four, and I think some of the flexibility for using them is going to increase. I think we really want to know: Can you use them in short-term preventative treatment strategies, such as in women who have menstrual-related migraine? Could you use, for example, one of these medications on a scheduled basis just for that window of time when someone might be vulnerable to migraine, like we do with anti-inflammatories or triptans to some respect? I think we're looking to see what is the niche for using the gepants earlier into an attack even before the pain starts. We've heard early research that has shown that that might be an effective strategy. So I think there's lots of uses of these newer medications that we're all going to be learning about.

Paula K. Dumas (28:42): Yes, and for the people in the U.K., Canada, and Australia and beyond who are saying: When is it coming to us? About how long have you seen new medications take for global approvals and distribution?

Dr. Robbins (28:58): It's highly variable and dependent on the individual country. Sometimes it's several months, sometimes it's several years, so somewhere in between there is likely. And much of it depends on the cost of the medication, and if it's sort of under a government health service, the cost of the medicine often drives the regulatory decision about whether a national health service like in the U.K. is going to cover it or not. The other understudied population is also children and adolescents. There are active studies for, I think, all of the gepants, looking especially at teenagers because they're a very understudied group of people who have a high rate of migraine, and I think we're going to learn much more about uses of the gepants in children and adolescents, and if it's safe and effective, soon.

Paula K. Dumas (29:49): Dr. Robbins, where can we learn more about you, what you're doing, and follow your work?

Dr. Robbins (29:54): Well, I work at Weill Cornell in New York City, so I'm easily "Google-able" through there. I have a Twitter account, which is at @mrobbinsmd — or an X account, whatever we're calling it these days. So those are probably the main places.

Paula K. Dumas (30:13): Wonderful. We are so grateful for your expertise, for your commitment to this space, and for your time sharing what we need to know about gepants today. Thank you again.

Dr. Robbins (30:24): Thank you, Paula.