Stopping Pain in Its Tracks: Optimizing Acute Migraine Therapy

CMEO Podcast Transcript

Jessica Ailani:

Hello everyone, I'm Dr. Jessica Ailani. On behalf of CME Outfitters, I'd like to welcome you all and thank you for joining us today for this educational activity entitled Stopping Pain in its Tracks: Optimizing Acute Migraine Therapy. Today's program is supported by an educational grant from AbbVie Incorporated and Biohaven Pharmaceuticals. Today's activities brought to you by CME Outfitters, an award-winning joint accredited provider of continuing education for clinicians worldwide. So once again, in case you've forgotten the last few seconds, my name is Dr. Jessica Ailani. I'm the director of the MedStar Georgetown Headache Center, vice co-chair of Strategic Planning and Neurology and Professor of Clinical Neurology at MedStar Georgetown University Hospital located in Washington, DC. I have the pleasure now of introducing my esteemed co-host here and my good friends. First, I have Dr. Peter Goadsby who's a professor of neuro at the university of California, Los Angeles in Los Angeles, California and also professor at Kings College in London, England. Welcome Peter.

Peter Goadsby:

I thought I should start in the formal Zoom way. Thanks for asking me to be here.

Jessica Ailani:

Excellent, you're starting us already in such a great mood.

Peter Goadsby:

We've got 11 things.

Jessica Ailani:

And also I'd like to welcome Dr. Gretchen Tietjen, who's the distinguished university professor of neurology at the University of Toledo College of Medicine and Life Sciences in Toledo, Ohio. Thank you for joining us, Gretchen, tonight.

Gretchen Tietjen:

Oh, thank you for having me. I'm looking forward to it.

Jessica Ailani:

So let's get us started on the first learning objective for today's activity, which is to develop strategies to address the challenges in acute management of migraine. So let's begin by asking you all a polling question, you should be seeing the question on your screen and you can vote now. The question is, what is correct about the CGRP receptor antagonist gepant class of agents in migraine. Why don't we actually take a jab at answering the question ourselves, Gretchen and Peter, if you want to join me here and let's talk about CGRP receptor antagonist gepants. What do you guys think is probably the most prominent side effect that we see? We know that gepants tend to be really well tolerated.

Peter Goadsby:

Yeah.

Jessica Ailani:

So I don't know, have either of you seen or know about dizziness being a potential side effect or contraindications with these medication classes?

Gretchen Tietjen:

Well, I believe it can be a potential side effect that someone can have but I don't know that it was much higher than what you would see in the placebo in the studies. So it wouldn't be real prominent, I think something like nausea would be more prominent with gepants as with most medications. So, that probably wouldn't be one that I would choose out of this group.

Jessica Ailani:

Right.

Peter Goadsby:

Yeah, I completely agree. One of the complexities is that things that are reported as side effects are very often part of the attack, that's why they're no different from placebo and dizziness is... people say dizziness a lot. They mean lightheadedness, they mean vertigo but that is a very common thing with a migraine attack and very often the drugs are blamed. Not that the drugs are innocent, of course, but they're blamed for things that are part of the attack. So, I agree with Gretchen, it's nausea and the metabolism thing just to move to that one is, well, that's about... it's liver metabolized, these drugs so that's not a thing.

Jessica Ailani:

Right? So the correct answer for that case was that there are not contraindicated in patients, the vascular disease, and that's what can make them very exciting to use as a new category of medication. So let's actually talk about-

Peter Goadsby:

Can I just say I don't... I think also we're not saying to the audience that it's common to just to throw them around on every... on the worst vascular path you can find. Is this the... well-

Jessica Ailani:

Yes, absolutely. This is a very good point, very good point.

Peter Goadsby:

We're saying there's a broad safety thing to it never replaces good sense in taking a decent history and knowing the rest of the medicine, I think.

Jessica Ailani:

Yeah, it's absolutely a great point Peter. So let's move to our first case and Gretchen, why don't you go through this case and this is a very typical case, I would think.

Gretchen Tietjen:

Yes, it is. So the patient that we have before us is Laura, who's 29 years old and since her teens, she's had a diagnosis of migraine with aura and she's having currently about eight days of migraine per month, which she's been treating predominantly with ibuprofen. She's able to work outside the home, she's a realtor and one of the reasons that she's coming in to the visit is that she is considering pregnancy and she would like a more effective medication than ibuprofen. She had been on oral contraceptives but stopped those six months ago and in anticipation of trying to become pregnant and hadn't really noticed a lot of change in her headache frequency.

Jessica Ailani:

Yeah. So I think this is a pretty typical case and, as I said before, so we're going to think about treatment options. Before we start to discuss treatment options, I thought this would be a good opportunity to give that survey try one more time, but to ask all of you, what do you think about a good treatment option might be for someone like Laura? So what would be your first line treatment choice for acute migraine in our patient Laura? All right. So, Peter what do you think about these responses?

Peter Goadsby:

It's sort of a bit of a low ball question in the sense that amitriptyline and toxin type A just aren't useful... they're not acute treatments and it leaves you with... it's reasonable not to be sure, that's a reasonable thing to say because here's a young woman with typical migraine who's obviously not greatly happy with a nonsteroidal and thinking about pregnancy. I think whenever a woman sits down and says to me that they're thinking about pregnancy, I'm not exactly sure what to do next either because you've got to really sort of flesh out what they're thinking and where they are in that journey, what their partner thinks, what's the sort of... what does risk really mean? Because I can quote them the risks, which are negligible for sumatriptan, which I think is the best choice here, but that doesn't mean that you don't know what the individual's like. They may have had some birth out mal problem with their sister or in the family so they're over concerned about it or maybe they're not concerned at all.

Peter Goadsby:

So I think it's tricky and so it's reasonable to say I'm not sure because there's no perfect answer here. I think Butalbital would be the not perfect answer and sumatriptan... the one thing for the triptans, is we have a lot of good data from the pregnancy registers particularly the Norwegians have done the sumatriptan pregnancy register and well, there's never enough data. Over the last 30 years, nothing, no problems emerged in pregnancy using sumatriptan so it's a good choice with an appropriate conversation with person who's going to have-

Gretchen Tietjen:

Yeah. One of the things that I'd like to add is that sometimes when people are trying to get pregnant, it can take months and months or longer and they want to know what's the safest thing to do during that period of time. And I oftentimes recommend that from the beginning of the menstrual cycle to day 14 when they're not likely to be pregnant, to feel free to use medication like sumatriptan, if they have reservations about using any medications at all. And then for the last half of the cycle, when there's a possibility of pregnancy to use something like acetaminophen or whatever. But during pregnancy, when you think about it comparing it to something like butalbital both were in the now defunct FDA classification C for use during pregnancy, but the level of evidence for sumatriptan being effective in migraine is so much higher than for butalbital. And as Dr. Cosby had said, there's a lot of safety data during pregnancy for sumatriptan. So that would be one medication I would definitely consider using for an acute attack during pregnancy if other remedies had failed.

Jessica Ailani:

I think these are excellent points and important conversations to have with our patients that are women considering pregnancy, not to let them think that there's absolutely nothing they can do because we shouldn't forget that migraine can be extremely crippling and dangerous on its own to women who are having severe attacks while pregnant, nauseous, vomiting, bedridden sometimes for days on end. This has to be a risk benefit ratio conversation and I definitely feel like over time with more and more registry information has been mentioned, I think many of our comfort levels with things like sumatriptan has increased. So Gretchen, I thought it'd be nice if you talked to us a little bit about the burden of migraine, as we all have a good understanding that those with migraine can really struggle with this disease process itself, but what about the burden of disease on our economy and on the patient itself?

Gretchen Tietjen:

Well, migraine is an expensive condition to have health wise. The cost from a study that was published in 2017, showed that the direct cost for health related costs in migraine was over nine billion per year in the states and that did not factor in the indirect costs of lost time at work or going to work with being less productive than usual, nor did it factor in that when you have migraine, you are also at risk of other conditions that we know are comorbid with it, like anxiety, depression, having trouble sleeping, increased risk of stroke, and even myocardial infarction, and also epilepsy and as our patient has asthma that could also have costs economically for the economy. And they can also make people out of work for longer periods of time and these are important to just be aware of since most of the people that are getting migraine are in their most productive years from a work point of view and their societal contribution so that is something that... there's a really big toll from this condition.

Jessica Ailani:

So since migraine is such a disabling condition and has such a big toll, Peter, why don't you talk to us about how we can start treatment in patients with migraine focusing on acute treatment?

Peter Goadsby:

So the goals... what am I trying to do? Well, I think everything's about restoring function. It's not the endpoint that's used in registration studies but I'm really in getting people the days back that they're losing. They say that migraine doesn't kill anybody but it certainly robs them of time in their life and they don't get a free pass later on. So I'm keen to make them as functional as possible, which is the combination of as relief from symptoms, pain and associated symptoms. I want them to use... I don't want them to feel that they need to be worried that they're going to need a rescue or some other thing's going to happen. I really would like them to be able to treat and go on with their day. I want them to be in charge of the disorders.

Peter Goadsby:

I mean the worst thing you can do with migraine is go to a place that's noisy and has bright lights and sometimes malodorous and people move you about. I mean those are the cardinal symptoms that will come to the diagnosis and there's nothing an ED can really do for you that we shouldn't be able to give patients to be to do at home. I want to avoid unnecessary imaging and all the things that are happening and I want them good tolerability. So I think that's how you balance that along of course, with the problem of costs and having that discussion with patients is the kind of discussion I like to have. What's happened in the past? What side effects do you have? What are your concerns? So I can try and match the therapy, we have the range of therapies that when that's therapy with the person's problem.

Jessica Ailani:

So before we can actually start treatment on a patient, we do have to be able to make an accurate diagnosis. So Peter, how do we as clinicians make an accurate diagnosis of migraine, both with and without aura and are there particular criteria, hint, hint, I'm showing you a slide here that we use in clinical practice?

Peter Goadsby:

Well, yes, you're showing the international classification of headache disorders in its third edition published in 2018. And they offer I think a very reasonable guide to the kind of questions you have to address in history. So how do we make the diagnosis? You take a proper history and that's part of the... I think it's part of the whole therapeutic process. They have someone understand they're actually interested in what's going on and you're interested in their symptoms and when you talk about or you're interested in the way it... in the development, the match up the arm or the match of the visual change and that's what these aura criteria are describing and they're a little of a base. I mean it's hard not to admit that but they underlie the principle that we are looking for particularly visual, 90% of aura is going to be visual.

Peter Goadsby:

And then some are sensory and after those the rare reforms which I think if you think you're seeing retinal migraine, you would refer that straight away because you... I mean that's extremely rare. And of course, the length of the aura, those criteria that I mentioned. I think the main thing about aura for me to take out of those criteria is the progress. Nothing progresses quite slowly and matches up an arm like a migraine aura. So the careful history and then I think we're going to go in the next slide, if I'm correct. Yes, to migraine without aura which is the majority of patients, maybe 70% depends a little bit on the age group. I mean IHS wants you to have five attacks. I'd be happy if you if had less than five but through a lifetime that's not complex.

Peter Goadsby:

So these are attacks with typical pain symptoms, one-sided pulsating, severe pain and the aggravation with movement and then nausea, light and sound sensitivity. The core symptoms that we need to get out of people when we take in history. It looks a little bit arduous at some level but asking particularly about the migraine without aura symptoms is pretty much bread and butter I think.

Jessica Ailani:

Yeah, it is bread and butter. And I feel as a headache specialist, it's very much the meat of what we do every day and it's in the back of our heads every day. It's like a checkbox, right? But it's a little bit cumbersome if you're in general practice or you're primary care provider. So there are a little bit easier methods that are based on these criteria to really get about to meeting these diagnostic criteria and one easy one that I like to talk a lot about to my residents and medical students is one ID Migraine, it's a screener test. ID Migraine is a screening tool and it's three simple questions it's asking about these associated symptoms and impairment related to the migraine attacks. It's photophobia, eyes for impairment and for nausea called pin the diagnosis. Photophobia, the question is, do lights tend to bother you when you have a headache? Impairment eye, do you feel impaired or avoid activities when you have a headache? And for nausea, do you feel nauseous when you have a headache?

Jessica Ailani:

I will often ask if they're like, "I don't know what you mean by nausea, I don't throw up." I ask, "Do you feel queasy? Do you want to avoid foods? Does your stomach get a little upset?" Because sometimes patients automatically equate nausea with vomiting. If the patient says yes to two out of three of these, there's a very high chance that it's migraine and then we can just delve more into the history itself. Now that we have a better understanding about how we have diagnostic criteria and how we can really start to make this diagnosis of my migraine, let's get a little bit into treatment options that we have, what has been studied, where we are with consensus and guidelines. So Gretchen, can you take us through some of the evidence for acute treatment options for migraine?

Gretchen Tietjen:

Yes. On this slide, we have the medications that have either established efficacy or probable efficacy. So you could look at that as sort of level A and level B and meaning that for any one person these are reasonable options, all things being equal, but we also have it divided then under each efficacy level as far as whether the drug is migraine specific, meaning designed for migraine or a nonspecific drug that may be effective or probably effective for treating migraine. So under the migraine specific though with established efficacy, those would be certainly ones that we'd want to see about trying one from that category. There are the triptans, which we've discussed a little bit, there's ergot derivatives such as DHE, intranasal, there's the gepants, the CGRP small molecule blockers, and then lasmiditan, which is also one of the newer groups that we'll talk about a little bit more with regards to what targets those are hitting.

Gretchen Tietjen:

The nonspecific ones are familiar to us all with regards to aspirin and ibuprofen, which our patient had been taking and Naproxen. But then there's a new one, the celecoxib oral solution that's now been approved and available. And then there's the old standby of combination analgesics those such as acetaminophen plus aspirin, plus caffeine, which is used a lot over the counter by patients but does have established efficacy for migraine. Other migraine specific drugs that are probably efficacious, one back on the market after having been gone for a while is ergotamine plus caffeine. But then some of the newer... well, some of the older medications that we have used such as DE, the new ones are the intranasal, but the old ones that I think they backed in 1945 when they were first approved was the parental administration.

Gretchen Tietjen:

So giving it as either an IM in the IV or a subcutaneously and that's DHE and then the nonspecific things that are used are some of the other nonsteroidals that are listed here, ketorolac given IM or IV which is commonly used particularly in emergency rooms. There's a combination of acetaminophen with either acetaminophen or with Tramadol, or with coding, IV magnesium which has been used for migraine with aura, and then antiemetic drugs. And these are frequently used parentally in the emergency room, like an IV of medical provide or prochlorperazine but there are anti-nausea medications that also have efficacy in migraine. So these would be the ones that would be at the top of my list when I'm considering what's appropriate for any given patient.

Jessica Ailani:

So thank you Gretchen. So Peter, can you explain to our audience the targets of different coming classes of treatments and what's important to consider when it comes to contraindications and adverse events that us as clinicians need to really be considerate and aware of when prescribing medications.

Peter Goadsby:

It is remarkable what has happened to migraine therapy in the last year and a half. We use have basic triptans and if you think about ergots in terms of serotonin receptor agonism they fit into that and now we've two new classes, specifically the ditans, serotonin, one F receptor agonists, and the gepants, CGRP, Calcitonin Gene-Related Peptide receptor antagonists. They're both small molecule intake, both small molecule drugs. It's quite extraordinary when you think about the Cox drugs, particularly Cox two drugs as you work through these classes on the slide, there's a seriousness now to the pharmacology. The downside of course, is there's more to know the upside is there's so much more we can do. Of course, each of the classes bring their own nuances in terms of adverse events are things we know and love about the nonsteroidals, kidney problems, gastrointestinal problems.

Peter Goadsby:

The triptans, which we have become used to I think in the last 30 years or so, they're not drugs who give to people with act cardiovascular disease or uncontrolled hypertension but that's just good medicine to control that. We've got the ergots as Dr. Tietjen said, Dihydroergotamine's been around since 1945 and all ergotamines conceded since the 19th century specifically when the French first identified their use in headache disorders, there's nothing new under that sun for sure. For the ditans the particular problem was that about 15% of patients in the clinical trials had dizziness. Now there are the driving restrictions, which does actually factor into discussions that what's talking about patients. Now on the op side, they're purely neural drugs, no evidence at all that ditans will affect blood vessels, which is good news in clinical practice and for patients. There are swings and roundabouts, you might say, in the middle of that, the gepants, CGRP receptor antagonist, ubrogepant, and rimegepant. From the clinical trials it's hard to find a difference between them whether you talk about efficacy or side effects.

Peter Goadsby:

It sounds a bit ridiculous but this is very actually very little to say, one can talk about hypersensitivity to the ingredients but applies to everything and there's a little bit of nausea compared to placebo. These are really well tolerated drugs. It's a rich collection and I see it as an opportunity to have choices. It's very unusual these days for someone to walk into have had everything in all the right doses. There's always something you can do daunting but that's an important part of modern clinical practice.

Jessica Ailani:

Yeah, you definitely said it right, exciting but sometimes quite daunting as we have so many options and we are very comfortable with some of these older options now like triptans been around such a long time exactly what to expect when you see the patient. But some of these older drugs do have quite a discontinuation rate and we know that though we have so many treatment options for patients, sometimes patients will stop using treatments and this can be true for acute treatments as well. Gretchen, I wonder if you could talk to us a bit about why patients might stop using their acute migraine treatments?

Gretchen Tietjen:

Yeah, there's a variety of reasons. I'd say probably the main one is that they don't feel that it works for them. Sometimes they take it and their headache does not go away, but it may be that they take it and they get a side effect that is intolerable, either sleepiness, dizziness, nausea that type of thing. And sometimes it depends on they may have been prescribed the wrong route of administration, maybe they need a subcutaneous drug or an intranasal drug but they're taking it orally or maybe they're needle phobic and that's exactly, they don't want a drug that involves the needle. So sometimes we've prescribed for them a route of administration we think might be convenient and actually just for whatever reason, they don't like it.

Gretchen Tietjen:

The cost though, I think is the saddest thing that keeps people sometimes from taking medications oftentimes because these drug drugs can be so costly if their insurance companies do not cover them, that they will not use them until they're sure the headache is worthy of it. And oftentimes that means they've waited a while and the headache is pretty severe by the time they start, and with the triptans that had been a particular issue. The other thing too is just cause of the cost of drugs. Oftentimes people will say like, "Oh, well, if the headache's not too bad I will take an over the counter medication." And that can be okay if it works for them. But oftentimes with certain ones, particularly those that can contain caffeine the acetaminophen, aspirin, caffeine combination, they might start taking too many of them and then turn into an overuse situation.

Gretchen Tietjen:

Sometimes people I've taken care of over many years, they'll be taking a triptan, for instance, they think it works great and then they develop heart disease, not because of the triptan, but because of their genetic predisposition to it and risk factors, cardiovascular risk factors that they have and then they have to stop taking it and they need another medication. And until these, there was [inaudible 00:27:03] and the gepants came around, there weren't many options that were migraine specific. And so we have to always think that they may not have a contraindication when you start them on a medication, but they may develop one later and then the medications have to be changed.

Jessica Ailani:

And these are all in important points about reasons that patients might stop treatment and you did mention that sometimes efficacy can be a problem in root of administration. And one thing to point out is that root of administration can definitely be a problem for patients to have migraine, especially those that have a significant amount of nausea. So we see this a lot in patients with severe nausea or have vomiting, they perhaps take a pill and then they don't know if the pill has been effective or if they maybe threw up the pill and honestly, I'm not sure either. "Oh, I took a dissolvable tablet and I threw up 15 minutes later. Do you think it was absorbed?" So I think it's definitely important having non-oral options and actually just viewing some of the questions our audience agrees and is very curious about non-oral options for migraine as well.

Jessica Ailani:

And in fact is asking if Peter, have you even heard about maybe this new drug called zavegepant and if that's a possible option for patients with migraine? So Peter, could you talk to us a little bit about non-oral migraine treatment options? And if you do know a bit about zavegepant if you want to just throw a line in there about this treatment option as well, to answer one of our audience questions.

Peter Goadsby:

Yeah, for sure. I mean you got the list there of ways you can do things non-orally and pretty much now, whatever for all the classes we went through, there are some non-oral options, DHE sprays that are now coming along, as well as injectable dihydroergotamine, there's triptan sprays, sumatriptan available as a spray. They have their adherence might say certainly sumatriptan injection as it remains just one of the great reliable treatments you can bank on the absorption, you can also bank on the side effects, which is problematic and you've got injections of nonsteroidals. As the question is asking, probably seen the press release, zavegepant is the latest of the gepants, the hints in the last two syllables CG, small molecule, CGRP receptor antagonist and the phase three studies were just announced by the owners, the sponsors by Haven and it's effective against placebo, they've got good two hour Pain free and most bothersome symptoms by the standard outcomes, and they reported an earlier study at the American academy this year.

Peter Goadsby:

So in this GRA in this slide, we'll have another box in perhaps a year's time which you'll say gepants and it'll have a nasal option because as you say, some patients this is an important option. And we must... I think here, we don't want to forget neuromodulation is an entirely different approach to the same question, it's an entirely different approach to tolerability and to things like nausea, the STMS, VNS, the ETNS and the combination of superorbital and occipital stimulation, these range of things which don't have any of the disadvantage that we've been talking about. I mean they have their advantages and their drawbacks. So neuromodulation I think is underused can be complex because of costs and the logistics around it but is offering yet another dimension for patients. So we can get a really good combination to get in control of their treatment.

Jessica Ailani:

Yes. Thank you Peter and thanks for throwing in the little information about zavegepant. I do want to just close out the rest of the question that also asked if Rimegepant is available as a non-oral. Rimegepant is an oral dissolvable tablet but does not come as a nasal or injectable option. zavegepant if it is FDA approved in the future would be the only non-oral gepant at that point. So let's move on to our second of three learning objectives and we're going to now look to apply data on efficacy and safety of recently approved therapies for acute treatment of migraine to optimize migraine treatment, to say for our patients with migraine. I think this is very important in clinical practice. So Gretchen, let's go back to Laura, if you could just briefly tell us any updates on Laura at this point.

Gretchen Tietjen:

Well, Laura comes back it's now 18 months later, she's had a baby. She is not currently nursing so that's one thing that sometimes can complicate deciding what medication to use on a person and she's come back because just having a little one and needing to care for her baby, she doesn't want to be drowsy. And she had found that sumatriptan was fairly effective for her but it did cause some drowsiness and she found that she did best when she took it and could lie down for a little while. She's still having her migraine with aura, she hasn't developed any new cardiovascular risk factors. She did have a complication of gestational diabetes during her pregnancy and has asthma, but she's not on any medications for that. So anyway, she's looking for a medication that she can use instead of sumatriptan because she wants to avoid that side effect of drowsiness.

Jessica Ailani:

Yeah, and before we talk about what we think might be a good idea, let's see what our audience thinks. So what medication class would you recommend for Laura at this time? All right Gretchen, so what do you think about these results?

Gretchen Tietjen:

Well, I think that a lot of people came up with I think some good answers, the main problem with continuing a triptan for this patient specifically is just that, that for her the drowsiness was a side effect and I don't know that just switching to a different triptan would be much of an option. There are some people that do not have the side effect at all it really depends on the patient. The ditans would be one that you probably would not want to go to next just in that as we had just mentioned that they have that driving restriction due to both the dizziness and the drowsiness that can come with them that can last a good eight hours.

Gretchen Tietjen:

So that might be something that you'd want to avoid in this patient specifically. Nonsteroidals can have drowsiness but I think for her, the main problem with them is when she was on ibuprofen it didn't seem to be particularly effective, but maybe there would be a different one that could be used. But a gepant a seems like a good answer just because drowsiness does not seem to be any type of a major side effect with this so it's not prominent in any of the studies. So, I think that would have probably be the one that I would've got to next.

Peter Goadsby:

It's remarkable, isn't it? That year ago, a little bit more, what we would've done is probably a discussed how we cycle through different triptans and work out, maybe which one was better tolerated.

Gretchen Tietjen:

Mm-hmm (affirmative).

Peter Goadsby:

And 18 months later, we actually have an option that's evidentially better which is... not that it would be wrong to say try almotriptan as an example, if you had sumatriptan because there's RCT evidence to show, I would better tolerated but the dimension of things has just gotten better. It's quite exciting like that, that you could be right in a number of ways here and I totally agree with you that the gepant is the standout option.

Gretchen Tietjen:

Yeah.

Jessica Ailani:

I will say though, there's almost a third of you that weren't sure and I just have to say, we are very happy that you're here today because we didn't expect you to come in with any kind of answer. So you're in the right place, we hope that we're going to get you these answers very shortly. So Gretchen, since we didn't want to keep Laura on a triptan because of the drowsiness, let's talk a little bit about efficacy of triptans and acute migraine and really take this conversation from there. Could you review some of this information for us?

Gretchen Tietjen:

Yes. So some of the things that we look for in looking at what we think how effective a drug is and as we wanted to look at the freedom from pain in two hours. So headache relief means that you still have some pain but you feel like you're somewhat better and freedom from pain would mean that you no longer having the headache in two hours. And with the triptans, there's a wide range of how people respond to them and from these different studies but up to three quarters of people had some relief at two hours, it ranged from 42 to 78%. But freedom from pain at two hours was anywhere between 18% and 50%. So if you're at that upper limit I mean upper level of a 50% that means that's not a bad particularly for migraine drugs, it's not bad efficacy.

Gretchen Tietjen:

But also at 24 hours with the triptans, some people had relief that lasted up to 24 hours with them and nearly a third had sustained freedom from pain in 24 hours. And then the other thing to look at is, did they need to take another medication? They took their triptan and then they needed a rescue medication and when people use triptans between 20 and 34% needed a rescue medication, but that's compared to, in these studies, to over 50% that needed it if they were taking placebo. So triptans are not a bad drug and certainly when you add them to something like a non-steroidal anti-inflammatory drug, that can be very effective people maybe more effective than the triptan alone but that's not going to do anything about the drowsiness, which is our patient Laura's main complaint about the triptan. So not so much lack of efficacy but a side effect.

Jessica Ailani:

Yeah, that's very true. So when we take a look at those triptan studies when they were initially approved, we've come quite away with how we've designed clinical trials and some of the new endpoints and these endpoints apply particularly to these newer products that we're using today. So we thought we'd have a few minutes and really talk about the new primary outcomes and the primary outcome measures when it comes to the newer trials that we're looking at today. Peter, could you take us through some of these primary outcome measures and patient reported outcomes?

Peter Goadsby:

Yeah, thankfully as the slide says that the baseline, as in migraine with and without or over 18 certain number of attacks a month and with and without preventive medications, not dissimilar to what was happening in the triptan era, indeed the age and definition. ICHD definition of migraine really hasn't changed since 1988 and so that's useful in terms of comparability. What has emerged is that the co-primary endpoint that the FDA insists on for regulatory purposes is pain freedom, which is that we ever thought that not being free of pain was a good idea is complex to think of, so pain freedom which clearly a great is the right outcome and freedom from their most bothersome symptom. And the way that's defined in all of these trials and that's helpful because you can slot everything we are saying into this was that the patient would nominate either nausea, photophobia, or phonophobia, so sensitive your light or sensitive to sound most bothersome symptom for that attack.

Peter Goadsby:

And that symptom had to be gone at two hours and to have a migraine treatment, you have to hit both pain freedom and hit the most bothersome symptoms. So that's been an interesting development and of course we've gotten more interest as we should in expanding patient reported outcomes returns to normal function, the patient global impression of change, the use of the 24 hour disability scales to show disability reduced and of course, satisfaction scale. So we are looking at the sort of things that you might expect that we're actually asking patients in many ways when they come back and you see that data bubbling through all the new studies that we are talking about today.

Jessica Ailani:

Yeah. And so as we have newer outcomes, we also have a little bit of a better understanding on therapeutic targets. So Peter, could you briefly describe the content... context, sorry, of therapeutic targets to us for these newer treatment options in migraine?

Peter Goadsby:

Yeah. So what you see on the slide, it is fantastic that we now have three clearly established, clear evidence and regulatory approved and so forth target for acute. We have triptans, 1B serotonin, 5SG, 1B, 1D receptor agonist so they turn those receptors on, ditans which are serotonin 1F receptor agonist and then gepants, which are CGRP receptor antagonist. The diagram on the right is a little bit detailed but the core thing is to remember that the important pathway the trigeminovascular system with a vessel and the nerve innovation, what the triptans do is constrict the vessel and block the nerve and in the central nervous system, they block the nerve. What ditans do is they do nothing to the vessel and they just turn the nerve off and what GCRP receptor antagonists do is they block the effect of the release of the CGRP. And I'm sorry to be wiggling in front of my face like that.

Peter Goadsby:

But we've got a really good understanding of how these medicines work because they're very specific and how they interact with this pain system. So that we can be it's... yeah, I think it's useful knowledge at some level because patients can sometimes be interested in why these things are different and in the difference, it explains much of the... actually explains all of the sort of things we've been talking about in terms of effects and adverse events.

Jessica Ailani:

Yeah, so these differences are definitely extremely unique in what make these products very special and what lead to how they can fit into the clinical space. And I think Peter, your excitement, our excitement is definitely dry our audience to ask tons of questions for us. `So Gretchen, maybe you could briefly tell us a little bit about what clinicians should take away from the primary efficacy endpoints for Ubrogepant in its primary clinical trials titled ACHIEVE I and ACHIEVE II.

Gretchen Tietjen:

Yeah. So in ACHIEVE I, what they looked at was pain free two hours after the initial dose and they looked at a 50 milligram dose and a 100 milligram dose. So the lighter blue is a 50, the darker I guess that's blue is the 100 milligram dose compared to the placebo in the gray and both were significantly more effective than placebo at either of the doses. And what we found was that pain freedom, it was around 20%, 21% of people had pain, freedom compared to 11% in the placebo. But in the most bothersome symptoms, freedom from that two hours was over a third so that numbers, there are like 38.8 and 37.7%.

Gretchen Tietjen:

But placebo didn't do terribly at 27%. Now the ACHIEVE II, which is another phase three trial, the dose that were used was a little bit smaller that they compared to is ubrogepant 25 and 50 milligrams but they didn't see much difference between the 25 and 50. And both of them performed well against placebo and it was very similar in that again, it's close to 20% that were pain free at two hours with the initial dose in the dosage strengths. And also, at the most bothersome symptom being gone after two hours and again, it's about a third, a little bit more for that end point. So I think that's something for people to know that the primary endpoints were achieved for these three different dose are the three different doses that they studied.

Jessica Ailani:

Yeah, it's interesting. It's probably why they called it ACHIEVE, right? I always fancy names they come up with for these clinical trials. So Peter, I think this next slide brings up an important point because we are going to get asked this in the question part about triptans versus gepant and we naturally are going to prescribe gepants in patients who tried triptans before. So tell us a little bit about this post-talk analysis of Ubrogepant in patients who've tried triptans or maybe weren't able to try triptans before.

Peter Goadsby:

Yeah. So what we did and Andy Blumenfeld is the first author on this study published in headache, was to look at the phase three studies that Gretchen's just spoken about and do what you do what you're going to do when someone walks into the room. Who you see have you had a triptan before? Triptan naive? If you had a triptan, did it work? You are a responder or was it insufficient? Were you not satisfied with it in some way you were, non-responder either terms particularly in efficacy terms and what you see across here is that there's no difference when you look at the treatment by subgroup a interaction that is naive responder or insufficient responder between the triptan naive, the triptan responder and the triptan insufficient responder group. That is to say that when someone walks says that they've had a triptan, and it wasn't any good for them, they're just as likely to respond to Ubrogepant as a person who walked in the door and hasn't had either a triptan or ubrogepant.

Peter Goadsby:

So that it's important in clinical practice to be able to say with a very straight face still patient that if they've had not a great response with the medicine before that actually there's a very reasonable chance that they're going to get an effect from the new therapy. I think it's very reassuring to have data like this.

Jessica Ailani:

Thank you Peter. So now let's talk about another gepant called rimegepant. Gretchen, what can you share about the medication and this particular data over the next two slides?

Gretchen Tietjen:

Okay. So in this first slide with rimegepant, we're looking at the same primary end points that were looked at on the ubrogepant ACHIEVE trials and for rimegepants. So that means the pain freedom two hours after the initial dose and the doses that this is data for 75 milligram oral dissolvable tablet, and then the most bothersome symptom freedom two hours after the initial dose. And the data looks very similar to what we had seen on the other slide as far as about 20 or it's 21% of people were pain free which was about twice the placebo group and then we're again just over a third, I think it's 35% here. We see for freedom from the most bothersome symptom and significantly better than the placebo. So then the next slide is looking at Rimegepant in the same dose, the 75 milligram dose but instead of it being the oral dissolvable tablet, it's with the oral tablet that would be swallowed whole and then processed in the GI system.

Gretchen Tietjen:

And here, the data looks very similar, both for pain freedom at two hours where it's almost 20% with most bothersome symptom at two hours, which again is over a third it's 37.6% and both of these results for these primary endpoints are significantly better and reaching them than the people that were on the placebo.

Jessica Ailani:

Right, great. So we talked earlier about another category of medication called ditans. There's only a single agent in this category called lasmiditan and remember that Peter had told us that this is primarily more essentially acting drug and has no effects on the blood vessels. Very, very exciting stuff, as you can can imagine. So Peter, why don't you take us through this data here about efficacy endpoints and what does the clinical trial results show us about Lasmiditan?

Peter Goadsby:

Yeah, so these are the Spartan and Samurai studies, as I think creatively named. And the data, the Pain free most bothersome symptom outcome as we've described significant across the doses, 50, 100, 200 milligrams in Spartan and 100 and 200 milligrams in Samurai. So these are the two phase three studies, there are actually two phase two studies that were positive as well. So all together, there are four randomized parallel group placebo controlled trials that clearly demonstrate that lasmiditan is effective as an acute migraine agent and that says two things. Firstly, it says that there's a drug that does not do anything to plug vessels and is effective in migraine and so when you're thinking about migraine, it really says, think about the neural mechanisms. I find it's a very comfortable drug to discuss with people who've... where you're nervous about something going on the cerebrovascular... on the cardiovascular so I should say because these drugs just don't act and act on blood vessels at all very clear.

Jessica Ailani:

Yeah. And I think I've... you and I have discussed this before and I always keep this in mind with a patient who I'm the most tense concerned about with vascular issues that I will consider this first for those patients because probably it is the safest for a vascular patient as it does nothing to the blood vessels. So we have talked about several migraine specific acute treatment options. We have our older medications for ergots and triptans which we briefly mentioned and then our newer medications, two Gepants, ubrogepant and rimegepant and one ditan, lasmiditan. So that's a total of five migraine specific acute treatment options, really exciting stuff. But as Peter kind of hinted to, can be a bit overwhelming in clinic. So how do you between a tried and true and maybe a newer medication for a patient?

Jessica Ailani:

So they are some consensus statements that can help us think through when is it time to pull out a new treatment option for a patient in clinic versus using something that's been around a little bit longer. Of course, in the end, the decision should always be the right decision for you and your a patient in front of you. But this is something that we will use sometimes to kind of get us through clinic. You want to take a look at an adult patient because these newer treatments at this time have only been FDA approved and are indicated for adults. There are studies ongoing in pediatric populations, but they aren't completed or really close to completion at this time. You want to think about out them in patients who with contraindications or intolerance to triptans, and you want to think about them in patients, who've tried two or more oral triptans and have found them to be not working well.

Jessica Ailani:

And this is either they've told you and you've documented that, or you had them do some kind of validated treatment questionnaire, like the mTalk, which can be found online. I usually find just asking the patient in clinical practice, was it effective and if not, why? Did you have side effects? Did it take too long to work? Did the attack come back? Were you just not satisfied with the treatment? Simple enough things that you can jot down in the clinical note and that serves as purpose for deciding to move on to a different treatment option. So now let's move on to our final learning objective, where we're going to think about implementing patient-centered approaches to individualized treatment strategies for patients with migraine. So Peter, could you tell us a little bit more about patient reported outcomes or what are known as PRO questionnaires?

Peter Goadsby:

Yes. Some of them listed, some of the more popular ones are listed on this slide, the idea the patient reported outcome is what it says on the jar patients report the outcome, which is pretty much everything that's going on in migraine. The mTalk one that Richard Lipton developed was listed first and I have to say, if I have to use one, it's the one that I use migraine assessment of current therapies, what you might expect patient perception of migraine questionnaire and a functional impairment scale. I ask patients when they come back more or less, how's it going? Is it useful or not... I try to get some global impression of what's going on? And patient global impressions actually track very well with any of the PROs that I'm talking about.

Peter Goadsby:

Some of the utility of this can be to document what's going on if you are getting a little bit of a rough ride from insurance companies, for example, having something that's validated, published and says what it does on the jar, how to optimize migraine treatment can be useful when you're trying to support an app support getting a new medicine and sometimes say useful in terms of communications.

Jessica Ailani:

Yeah, I have to agree with that. I think in clinical practice the one thing we don't want to come across is saying that you have to use all these questionnaires which can overwhelm a clinical practice, but I simply just ask the patient how you're doing and do you think your migraine treatment is working satisfactorily for you? And I find that elite gets me to the root of the answer very, very quickly, but say you really don't have any time at all. Some of these questionnaires can be done in the waiting room before you even enter and that can be very nice and easy for you, or you're getting trouble with the insurance company then having one of these scales can be helpful, kind of getting that next step treatment for your patients. So we usually rarely will use one of these scales but it is really nice to know they exist and they're starting to make their way onto labels for patient medications, which I think is really important.

Jessica Ailani:

So Gretchen I'd wonder if you could quickly take us through treatment considerations that you might be making with patients when it comes to perhaps not necessarily using me pharmacological treatments, but also when you would consider non-pharmacological treatments.

Gretchen Tietjen:

Well, I think with a patient and you could take the patient Laura, for instance, I mean she's just using acute therapy and if that's all a person needs, that's great. But the question sometimes becomes if they come in and they want something different or something that works better, it may be that they're starting to take too much of it. So I think the first thing you want to address with somebody on an as needed medicine is how often are you needing it? Because sometimes people skip over that thinking that they're taking it exactly as prescribed and not realizing that the headaches are getting more frequent and they're taking more of it. So I think trying to avoid medication overused by keeping track of how much the patient is taking and asking them if it's effective.

Gretchen Tietjen:

And I think then the next thing would be is if they are taking it quite frequently, is it just because it doesn't work or do they actually need to have a preventive added to their regimen? And preventive could be a preventive medication because there's certainly a number of those but it could also be another type of non-pharmacologic therapy, for instance cognitive behavioral therapy. Some of these behavioral therapies have been good for prevention and changing lifestyle and some of the other non-pharmacologic things can help both acutely and also as preventive for patients in trying to keep the number of headaches down. And I think the hardest thing about migraine in general is when it comes to their medications or other therapies, how people respond to drugs and how many of them... what they can tolerate before they really want to go to a preventive just varies a lot from person to person.

Gretchen Tietjen:

It's great when we have meds that are efficacious because I think people feel less like a guinea pig and there's less trial and error with finding something that works for them hopefully with more and more effective medications. But I think keeping track of how much they're taking is really, probably the first question I would address in somebody who's just on an acute medication.

Jessica Ailani:

I will say, as we're going to talk a little bit about lifestyle changes before getting to that one unique thing about the gepants that has been really nice is not having to necessarily track and sometimes being able to allow the patient to even flex up how often they're using a gepant now that rimegepant is used for acute treatment of migraine but also recently has received FDA approval for preventive treatment of migraine. And some of these patients that fall on that cusp of having enough migraines that they need prevention but are hesitant about starting a medication for prevention are happy to take their rimegepant for acute treatment, allowing them to take it more often and then starting to abroach the idea of every other day use. I find that the patients, some particular patients, are very comfortable with this because they know that medicine that they've been using for as needed and feel comfortable with it whereas others are very comfortable with neuromodulation, not thinking of it as a preventive treatment option.

Jessica Ailani:

So sometimes it's also phrasing and just changing their perspective but I agree a lot of it is their comfort with something and side effects. It really shows us how much harm has been done from some of the prior treatments and a lot of the side effects, even though they could have been very beneficial for patients. So Gretchen, you briefly mentioned non-pharmacological and I wonder if you could just very quickly mention what are top line, what do we do for nonpharmacological treatments for patients? What are some of the lifestyle modifications we might mention to patients who have migraine?

Gretchen Tietjen:

Yes, I think that given that there is certainly a connection between sleep and migraine and we know acutely that sleeping or taking a nap can sometimes actually even turn off the migraine mechanism and being tired or oversleeping can trigger a migraine. I think that going through sleeping, eating, exercise, having them keep a diary of the things that they need to track and get stress controlled are some of the things that we can start to look at. So dietary triggers can be different for everyone. Some people can never identify any one, some people have many but things like alcohol I think is probably the best known one, many people with migraine don't drink at all because they find it triggers headaches. Caffeine is a harder one because in some of the medications that are over the counter, caffeine is in them, the acetaminophen, aspirin and caffeine is widely used and it's been in some of the migraine medicines, like the caffeine and ergotamine.

Gretchen Tietjen:

But it can help acutely, but can sometimes trigger attacks in people if they overuse it and so that's something that sometimes has to be discussed with a patient. MSG, which there are fewer and fewer things containing it now are people watching for it. Aspertame, which is in a lot of diet products including diet, as for some people they're very sensitive to those and skipping meals, something as simple as skipping meal can sometimes trigger headaches. And then there are other things that are less easy to control, menstrual periods being subjected to odors that trigger headaches. Sometimes they're noxious fume, but other times I've had patients where they just smell citrus and they'll get a headache. So that can vary from person to person weather changes certainly have been associated with triggering migraine for some people.

Gretchen Tietjen:

Sleep, having sleep apnea or insomnia can be a detriment in a person with migraine headaches. Exercise, they may not feel like exercising when they have a headache that might make it worse or in some cases triggers. But when people get regular exercise, that can oftentimes make them feel better, sleep better and have fewer migraines. And then I think the one that is really very important is stress and there's a lot of stressors people have in their lives and they can't always get rid of all of those but if they can learn techniques to control their stress to manage their stress so that it doesn't have a detrimental effect as such as triggering headaches, I think that's very important. And that's where things like exercise or meditation, yoga, Tai Chi, the cognitive behavioral therapies all these things have sort of been related to decreasing stress and potentially that maybe the mechanism by which they decrease migraine.

Jessica Ailani:

Yeah. So we talked a lot about triggers. There's only a few ways to capture triggers. Peter, why don't you talk to us a bit about headache diaries.

Peter Goadsby:

And diaries can be, as you said, use to capture... try to capture triggers. Diaries are probably... they've become more important as if you talk about if you're talking about prevention because it's very... for many patients it's important to be able to document what's going on. Patients can use diaries at a paper base as an illustration of one and it can be as simple as marking whether you have a headache or not. And a sort of when you have a headache and a zero, when you took something or simple things like that, the degree to which they keep the diaries is a little bit a personal thing. I don't like to make diaries a form of punishment for patients or a Drudge and of course there are the apps like Migraine Buddies is one that I'm pretty familiar with, some patients like those.

Peter Goadsby:

I think it's useful to know, as Gretchen said, particularly for people who are taking... particularly in the acute side, how often they're using acute medicines to have some sort of diary for that. I find it useful to get an overall impression and I really think that it's important that you let the diary, you tailor the diary little bit to the individual sitting in front of you. There are people sitting in front of you who want to write down 10 things about their headache every day, let them, and there are people who don't want to write too much, let them do that as well. So long as you get the overall load and the overall impression of what's going on, how they respond and so forth. I think one needs to be flexible and listen to sort of feel what's useful to the individual sitting in front of you.

Jessica Ailani:

This is very good point. So now we have covered quite a lot of round and we're going to get to the last question to all of you before you get to ask us more questions. So let's ask how you guys have been doing here, which of the following is the primary endpoint, oh, you've had to be paying attention here, of the phase three clinical trials for recently approved lasmiditan, rimegepant and ubrogepants, sorry. All right.

Gretchen Tietjen:

I did my job.

Jessica Ailani:

I'm so proud of us and of all of you guys.

Peter Goadsby:

It looks like we emphasized that enough, very good.

Jessica Ailani:

All right. So yes, the correct answer is freedom from pain and most bothersome symptom to hours and Peter had been talking to you about the two new primary endpoint, just to quickly mention resolution of photophobia. Photophobia of close, those were most bothersome symptoms photophobia, actually just as a side note turns out to be the most common, most bothersome symptom, but the patient got to choose only one. So it's not quite answer and it wasn't one hour, it was two hours. Freedom from pain and nausea, similar reason that it wasn't just nausea. It was most bothersome symptom. Patients chose one of three photophobia, photophobia, or nausea and four hours was a little bit too long, one hour was a little bit short, two hours is the key answer.

Jessica Ailani:

So I'm going to wrap this program out by talking to you about SMART goals. These are specific, measurable, attainable, relevant, and timely goals. Ensure that you are making accurate assessments and diagnosis in patient histories are included in the management of its acute migraine. Implement patient education on the frequency of use of preventive and acute medications that include lifestyle modifications for acute migraine and try to avoid medication overuse headache in patients, especially when utilizing some of our older treatments like triptan. Individualized treatment plans for acute migraine, with patient reported outcomes, such as migraine specific quality of life questionnaires, or just asking them simply, "Are you satisfied with your current acute treatment?" This can really help monitor the patient's treatment response. So we are up to our question part, let's get through some questions. So, the first... we actually have quite a lot of questions about medication overuse headaches. I might try to put some of these questions together.

Jessica Ailani:

So one of the questions that's coming up is, can you have rebound headaches or medication overuse headache if a patient is using ditans or if they're using a gepant? So Peter or Gretchen, either of you want to answer that?

Gretchen Tietjen:

I don't know specifically but I would assume that we didn't think when triptans first came out, we didn't realize the propensity for overuse headache that we later found. And one of the things that was interesting, the different than other medications, sometimes that were overused, if a person stopped the medication pulled Turkey, it took a shorter period of time to kind of reset and then they could start it again. But I don't know that there's a reason to think from a pharmacologic perspective that you couldn't get an overused headache with these new agents. What do you think Peter?

Peter Goadsby:

I think that the ditans, it's likely that it's... I think it's possible then we've got some good... both Frank PERA's group and Phil Holland and Kings has got some nice preclinical evidence that ditans can cause sensitization inappropriate animal model. So I think we should be wary of that and I think broadly speaking that's an agonist bashing the receptor too much, bash a triptan, or a bash with a ditan and it creates some sensitization. I think that with gepants, the likelihood is that given the... basically the more you take the better you get in the sense that if you take Rimegepant second daily, then you get reduction in headache frequency and if you take a to pant every day, you get a reduction in headache, frequency as well.

Peter Goadsby:

It seems to me lightly that for the vast majority of people, the GPS are not going to cause medication overuse. As you say, fast forward five years and I'll have egg on my face.

Gretchen Tietjen:

Yeah.

Peter Goadsby:

I'm happy to do that but I am struck by the fact that all that the clinical trials with all the Gepants, and of course the monoclonal antibodies at CGRP monoclonal prevention, all are at the same pathway and-

Gretchen Tietjen:

Yeah.

Peter Goadsby:

People don't get it worse, they get better or nothing happens. I'm optimistic about gepants. It's pretty exciting. It has to be said that we could have a conversation where we seriously think it's possible that you could have an acute medicine that also acts as a preventive and doesn't cause a problem.

Gretchen Tietjen:

Yeah, of course we did have that a little bit with folk prophylaxis with the triptans around the menstrual cycle, for instance. And some people, and I know cluster headache patients found that they could take a lot of them and wouldn't get the rebound headache, but that's good to know if pharmacologically, it looks like from preclinical data, the gepants that's not going to the issue that we have to wrestle with.

Jessica Ailani:

So there are some... just to stay around that topic of gepants and prevention, medication overuse. So the theory clinically has been so far is that as some of the blocking of CGRP receptors, like the CGRP monoclonal antibody, and then coming further with the data on rimegepant from their long term safety study, where they were using up to 15 doses a month. There was suggestion that rimegepant didn't cause medication overuse headache and perhaps this was class effect. There are older trials from telcagepant where use frequently reduced migraine instead of, and did not cause medication overuse, headache, and then rimegepant was studied and found to be effective as a preventive treatment. There's a question of if rimegepants approved as a preventive and acute, do we think other gepants with work as a preventive and any information we can share about atogepant?

Jessica Ailani:

I would say just to add on that, just to make the picture complete, if we know atogepant works as preventive, do we think you ubrogepant could work as a preventive. And then there is someone asking, well, if atogepant works as a preventive, can it work as an acute? So we have an extremely intelligent audience members, I have to say, because they already got their self thinking about, "This class can work as both, so can we just throw them all in there?" So Peter, I'd love to hear your comments on this.

Peter Goadsby:

Well, I'm taking calls to Newcastle as they say, in some parts of the world to tell you is first author of the primary of the largest paper on Atogepant is a preventive that it works as a preventive. So you could comment, I'll throw that back to you at some point. I think it is, the audience is right. There's a very disruptive class of medicines where it's probably true that you gave ubrogepant at the appropriate interval, and I'm not recommending this it's not part of the... this is not in the-

Jessica Ailani:

This is off label.

Peter Goadsby:

This is very off label.

Jessica Ailani:

This is not FDA approved.

Peter Goadsby:

But you're asking a mechanistic question. If you gave the intervals appropriately for its half-life, I'd expect it to have a preventative effect. And if atogepant was absorbed fast enough, I'd expect it to have an acute effect. I think the way that the gepants are used is really driven by their pharmacokinetics. So what's their half-life and how rapidly are they absorbed? And that's really atogepant is 11 hour half-life you can do if it once a day, that makes it really useful for prevention, ubrogepants is shorter. I think we're going to see the really troublesome development of... I need to think about these things flexibly as time goes on.

Jessica Ailani:

Yeah. And I think that can be troublesome in sense that we have very rigid ideas right now.

Peter Goadsby:

Yes.

Jessica Ailani:

And so we're going to have to rethink our ideas but I do think that is beautiful for the patients and actually much easier for your primary care providers and your general neurologist because at some point, the hope is this keeps going some of these lines can be blurred and much easier conversation. So again, sticking to medication, overuse headache, because we didn't quite finish the answer there because the truth is who knows you're on the right track with your thought process and there isn't data to quite is atogepant also useful as an acute treatment? We don't know the trial shows us that it can be effective as soon as the first day. Does that mean that's preventive effect or acute treatment effect? We don't really know and just like Peter said, ubrogepant has never been looked at as a preventive treatment but who knows if it could be effective if used very frequently. But I think dose regimen wise would be difficult for a patient. Now let's talk about-

Peter Goadsby:

A small thing, I mean there's a study published in JAMA recently Paul Winner the first author of the relief study of eptinezumab.

Jessica Ailani:

Yes.

Peter Goadsby:

Given intravenously as an acute treatment and it hit those two end points that we had the test on-

Jessica Ailani:

Yeah.

Peter Goadsby:

Pain free at two hours and most bothersome symptom beating placebo. So if you took that data and you just applied the FDA standard, it's not got a license for this but if you just applied the FDA standard, you would say it could be used for acute treatment.

Jessica Ailani:

One time every three months.

Peter Goadsby:

Yeah, I mean it's but it's licensed as a preventive. So I don't think we are drinking from the Kool-Aid to say that this is a... there's a lot of broad... this is very broad and it's the data all the data coming out is supporting what we're saying.

Jessica Ailani:

Yeah, and it's super exciting. The relief study was a very good thing to bring up is very exciting just to show preventive treatment can work as soon as a few hours during a migraine attack because someone who's experiencing a migraine could get better immediately and then have benefit because some of the subgroup analysis they're going to be looking at is how long does that benefit last but potentially could have benefit lasting out for three months. That is pretty spectacular. So let's talk about risk factors for medication overuse, headache, a question from the audience. Are there any particular risk factors for medication overuse, headache and another, I think a risk factor, but a question is why not Butalbital why isn't no longer considered a good option for treatment for migraine? So I think those two go together. I don't know Gretchen, if you wanted to talk about this a bit.

Gretchen Tietjen:

Well, for medication overuse the thing that is... some of the risk factors are the things some of them are obvious things such as the medication the acute medications are ineffective and so people take more of them, but they did I think the HUNT study, Norwegians did, where they followed patients for like 11 years looking at development of medication, overuse, headache, they found some things such as higher levels of depression and anxiety. I know I've had patients that are anxious and they take the medicine even before they need it because they're worried that they're going to get a headache. There's a lot of symptoms people get in between headaches and also when they had muscle skeletal complaints or other pain conditions, they tended to have a higher risk of overusing medications.

Gretchen Tietjen:

I think the other things are in that study it was something like physical inactivity and smoking and some other things that aren't really very healthy habits to have put them at higher risk and it's not necessarily causation but those were things that were associated with it. So maybe some of these are just people that are less healthy to begin with that are higher risk of overusing medication. But particularly when they have other pain conditions or anxiety, I think those are certainly things that put people at risk of overusing medicine. With regards to butalbital, I mean we know it's not very specific. It can be somewhat sedating. It does have a tendency to get overused. I mean I would say that if there was any medication I hated to see a patient come in on, it was one of these butalbital combination drugs because they were frequently taking way too many and it's not always easy to get off of it.

Gretchen Tietjen:

That has some addictive potential and people can sometimes have some withdrawal side effects from it. So it's not that it has no benefit, but in some countries, like I believe in Germany and stuff, they've totally like taken it off the market. It's still available in the US and it has been used here certainly, primarily in primary care clinics, I think more than now than in specialty clinics because we do have a lot of other options, but that drug does have some problematic side effects to it.

Jessica Ailani:

Yeah, thank you.

Peter Goadsby:

When you look at the population, the work that Lipton did some years ago the frequency of intake of [inaudible 01:19:29] compared to anything else, including opioids is about a third. So it's about after once you get to about four days... well, once you get to four days a month, that that predicts the increased frequency in the following year compared to 10 days for an opioid. So you've got a much narrower margin of safety if you want to think about it that way, in terms of promoting worsening of headache, they're difficult drugs to use in any way you look at them and they're said 80.

Gretchen Tietjen:

Yeah, they're difficult to stop using patients... some patients have a lot of problems with it. You have to be more careful than you would even probably with an opiate and just stopping it.

Peter Goadsby:

Yes.

Gretchen Tietjen:

Because of the potential for seizures and stuff during withdrawals. So I don't like them too much.

Jessica Ailani:

All right. Great. Thank you both for your answers. I wanted to quickly take us to have two of the questions to answer them before handing you guys off one more question. There's a quick question about these new therapies, gepants and ditans and women who are pregnant and currently they're not recommended because of potential safety pregnancy in pregnancy and in lactations so we will usually hold off on these medications. Another question that too, that are linked are asking about newer options and insurance coverage and do we usually start with triptans first. Most insurance policies will require that patients have tried at least two, sometimes three triptans before moving on to newer treatment options like gepants and ditans. So we do... I would recommend checking in with insurance policies but most of these treatments are now on insurance coverage for most commercial and mostly for Medicare as well.

Jessica Ailani:

Important thing to note for some government plans that one insurance does vary from state to state so you have to check in with your local policies and two, that with government plans, sometimes if the patient doesn't have a secondary insurance, even though it might be covered, there might be a high copay and they can't use these coupons. So that can definitely be an issue and then one quick thing, someone asked if you can overuse the device and that can cause a problem. I would say no, except I did have patient once overuse the super orbital nerve stimulator which is a question that's come up and they did develop a little bit more frequent migraines. So I always tell them use it as it's directed and try not to use it more often than that. And so the last question.

Peter Goadsby:

Just before... would it be fair to say that, I think we are not trying to trash triptans because they're good drugs, they're being used in tens of millions of people. We know what their problems are because we know what their problems are and they've been used for 30 years. What I think we are trying to emphasize is that we have now choices when there are problems, choices and options. So it's not like it's triptan trash time, it's expansion and options for therapy and it's good for patients. So I wouldn't want people to walk away the questions thinking that we think that triptan should be thrown out. I don't think that for a moment.

Jessica Ailani:

No, no, it's actually... yes, Peter, excellent point and thank you for bringing that up. They're still a first line because they're effective but another question was, is it required also, so by insurance and it is a requirement as well.

Gretchen Tietjen:

Yeah. And the American Headache Society, they had recently published a paper mentioning using starting with things like migraine specific drugs, like the triptans before going on to the other ones and it's always a question of, is that just purely based on economics of it since the newer drugs work very well as well and it is really a balancing act in part. But I think it's more than just the economics of starting with the triptan in that there is a long term safety data on those and I think there's nothing wrong with trying them first because in many cases they are very effective.

Jessica Ailani:

Yeah. So last question I wanted to throw to both of you before we end the program is comment on gepant dosing and I will say this is very specific to ubrogepant as rimegepant pant only has a single dose of 75 milligrams, one tablet once in a day. So for Ubrogepant there's two dose options, which dose do you start at? If the migraine pain is not resolved, do you increase the dose or do you change out of the class or swap to a different medication? And how long do you wait before changing the treatment option? I'm going to guess that means how many migraine attacks do you treat before changing to a different treatment? So Peter, if you wanted to take this first.

Peter Goadsby:

Yeah, so thanks. I think cause migraine treatment is the long game. So I start with the lowest dose I can and if I get an effect I'm happy and if I don't I'll raise it. So ubrogepant comes in 1,500, I'll start with 50. I'll give them two attacks, three, if they're not too sure and then ask and then ask the question whether it's useful or not. And if it's not useful, I'd increase to a hundred. I wouldn't get into a pitch battle with someone who wants to start with a hundred and see what happens. It's just little bit's a question of who's sitting in front of you. There are patients who want to run over the road before they look both ways and then there are people who want to look ways five times before they cross the road.

Peter Goadsby:

And I think one of the nice things about having those choices is you can have that discussion with the person what are you really? What's the thing that worries you the most about the next thing I'm about to do? So if you make that connection, you don't really have to take this decision. The person will take it for you, and then it will be the right decision because it's the thing that they want to do. So while I'm a low dose person, if someone wants to run it straight up the mass pole, they particularly bad. I don't think that's a bad thing.

Jessica Ailani:

All right. So I think we're pretty much out of time. I wanted to encourage our audience members to visit the Migraine Education Hub for additional information, clinical guidance, clinical guidelines, resources and patient education about migraine. And to receive CME credit for today's activities, participants must complete the post test and evaluation online. So you want to click on the request credit tab to complete the process and print your certificate. So thank you again for participating and for providing the best care that you can for your patients with migraine, and to think about acute treatment options. I'd also like to thank both Peter and Gretchen for joining me today and this absolutely fantastic discussion that we've been having.

