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www.reachmd.com
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(866) 423-7849

The Role of CGRPs in First-Line Preventive Migraine Therapy

Dr. Turck:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the role of CGRPs in first-line preventive therapy for migraine are Drs. Richard Lipton and Hope O'Brien. Dr. Lipton is the Edwin S. Lowe Professor and Vice Chair of Neurology, a Professor of Epidemiology and Population Health, and a Professor of Psychiatry and Behavioral Sciences at the Albert Einstein College of Medicine in New York City. Dr. Lipton, thanks for being here today.

Dr. Lipton:
Great to be here with you.

Dr. Turck:
And Dr. O'Brien is the founder, CEO, and Medical Director of Headache Center of Hope, a direct-patient care and concierge neurology practice in Cincinnati. She's also the President of the National Headache Foundation. Dr. O'Brien, it's great to have you with us as well.

Dr. O'Brien:
Thank you so much. It's wonderful to be here.

Dr. Turck:
Well, starting with you, Dr. Lipton, recent data comparing CGRP-targeting therapies with traditional oral preventives showed comparable—or even greater—reductions in monthly migraine days, often with faster onset. So how do you interpret this evidence when considering first-line treatment options?

Dr. Lipton:
So I conclude that the CGRP-targeted therapies have important advantages over the more widely prescribed conventional oral generic drugs. The advantages of CGRP-targeted therapies are that their benefits often develop more quickly. They don't require weeks of dose escalation to get to an optimal dose. They, in many studies, have greater effectiveness, and they also have relatively favorable side effect profiles. So for all of those reasons, I think the CGRP-targeted therapies have important advantages.

Dr. Turck:
If we look beyond efficacy, Dr. O'Brien, studies consistently show lower discontinuation rates—often under 10 percent—with CGRP-targeting therapies compared to conventional agents. What impact do those tolerability differences have on your approach to treatment selection?

Dr. O'Brien:
Well, as you know, migraine is a progressive neurological disease, and we now have evidence that can treat and may even halt progression. We know that up to 80 percent of patients on traditional non-specific oral preventive therapies stop taking them within a year because of the adverse effects and lack of benefit. And the CGRP therapies, which are migraine specific and supported by the American Headache Society and also the European Headache Society, have been first-line treatments for migraine due to their better tolerability.

We know that tolerability differences between migraine treatments play a critical role in treatment selection. And as a clinician, we need to take time to discuss the importance of the potential side effects with patients—whether it's cognitive effects from some of the preventive treatments that are out there, sedation with certain acute treatments, or even injection site reactions with the newer biologics. Patients are better prepared and more likely to stay on their medication if there are less side effects, and they also tend to be more

satisfied with their care.

Dr. Turck:
Now, we're also seeing more emphasis on patient-reported outcomes, with CGRP therapies demonstrating meaningful improvements in MIDAS and HIT-6 scores. So if we come back to you, Dr. Lipton, would you tell us how these quality-of-life gains factor into your decision-making?

Dr. Lipton:
Sure. So there are a number of patient-reported outcome measures that are included in labeling. One of them is the Role Function-Restrictive domain of the Migraine-Specific Quality of Life Questionnaire. And then there are a couple of daily diaries that measure the life impact of headache.

And those benefits are included in the labeling of two of the monoclonal antibodies and one of the gepants, namely atogepant. And what those benefits tell us is not only is there a reduction in monthly headache days, but there's an improvement in the patient's ability to function on treatment as reflected by the patient-reported outcome measures.

And at the end of the day, talking to patients about what they hope to get from whatever preventive treatment they're taking is an important step towards selecting therapies that will help them achieve those goals, which often include improvement in function and improvement in quality of life.

Dr. Turck:
For those just tuning in, this is *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Richard Lipton and Hope O'Brien about the evolving role of CGRP-targeting therapies in first-line migraine prevention.

Now, in addition to efficacy, tolerability, and quality of life, real-world studies provide insights into treatment timing as well. In fact, emerging data suggest that earlier initiation of CGRP-targeting therapies may lead to greater reductions in migraine frequency and reduce progression to chronic migraine. Based on those findings, Dr. O'Brien, when should we consider introducing these agents?

Dr. O'Brien:
Well, as you mentioned, emerging evidence does suggest that starting therapies early will actually shift the improvement of migraine. And in fact, I think there's more of a push towards the absolute frequency reduction as opposed to the percent reduction in migraine days, which can be more meaningful.

And so we should be pushing towards headache freedom or zero headache days for optimal migraine management, so less than four headache days per month. The goal is also to reduce the disability that migraine can result in, and treating early before migraine becomes chronic may be a key factor in changing the trajectory of the disease.

Dr. Turck:
And if we put these findings into the context of the latest guidelines, the American Headache Society now recognizes CGRP-targeting therapies as appropriate first-line therapies in select patients—particularly those with frequent migraine, significant disability, or intolerance to oral preventives. So, Dr. Lipton, what does applying these guidelines in practice look like?

Dr. Lipton:
Well, it looks like having a conversation with the patient. So by the time a patient gets to a neurologist, they have almost inevitably tried other treatments—almost always over-the-counter drugs, sometimes prescription acute treatments, and, quite often in subspecialty practice, a variety of preventive treatments as well.

So it's important to know what patients had taken previously, what worked and what didn't, what side effects they have previously experienced with whatever preventives they've been on, and what side effects they're prepared to tolerate. So it turns out that obesity is a risk factor for migraine progression and often travels with depression and other migraine comorbidities. So avoiding drugs that cause weight gain can be important. Offering treatments that promote weight loss can be important, and that's been demonstrated both for topiramate and atogepant, and then selecting treatments that avoid the side effects the patients have prioritized to avoid in selecting treatments most likely to work can be quite important.

I wanted to add that longitudinal epidemiologic studies show that of people with episodic migraine, a few percent per year develop chronic migraine, meaning that they make the transition from having fewer than 15 monthly headache days to 15 or more monthly headache days, and the more frequent your headache, the more likely you are to progress. That's led to the expectation that if we can effectively reduce monthly headache day frequency and severity, one of the benefits of early prevention could be reducing the risk of progression as well, and the common experience in subspecialty practice is that once patients have evolved to chronic migraine, it's harder to treat them than if treatment had been initiated earlier.

Dr. Turck:
So let's bring all this together before we close. Dr. O'Brien, when integrating CGRP-targeting therapies into first-line strategies, how do you balance the data and guideline recommendations with other factors, like route of administration, patient preference, and patient access?

Dr. O'Brien:
The science is clear that CGRP-targeting therapies are among the most effective and best-tolerated migraine preventive treatments that we have, and the American Headache Society now recommends them as first-line options, but having great treatment isn't enough if patients can't access it. And today, we have insurance step therapy requirements that still force most patients to try and fail medications before they get to some of the newer agents. And there was a recent analysis of nearly seven million patients that found that the recommendation or the publication from the American Headache Society hasn't really changed their access despite the updated guideline. At the same time, we know that patient preference matters and that roughly 85 percent of patients prefer a pill over an injection, and we now have oral CGRP options that can meet that need.

I think it's also important that we are addressing the patient's specific needs. There may be patients who prefer a non-oral and may want something like a device, which can be used to not just treat, but also prevent migraine. But in general, I think the goal is to match the right therapy to the right patients by considering what works best, what they're willing to take consistently, and what they can actually get. We also need payers to catch up with the science so that access reflects the evidence and not outdated restrictions.

Dr. Turck:
Well, as those key strategies bring us to the end of today's program, I want to thank my guests, Drs. Richard Lipton and Hope O'Brien, for joining me to share these considerations for integrating CGRP-targeting therapies into preventive plans for migraine. Dr. Lipton, Dr. O'Brien, it was great having you both on the program.

Dr. Lipton:
Thanks so much.

Dr. O'Brien:
Thank you so much for having us.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Neurofrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.