Episode 222: Prescribing Medications Off-Label for Kids

Lindsay Weitzel, PhD:
Hello and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I'm the founder of Migraine Nation and I have a history of chronic and daily migraine that began at the age of four. I have a super exciting topic today, especially for people who have children with migraine. I am here with Dr. Amy Gelfand. Hi, Dr. Gelfand, how are you today?

Amy Gelfand, MD:
Hello. Thanks for having me.

Lindsay Weitzel, PhD:
Thank you for being here. Dr. Gelfand is a board-certified neurologist and the Director of Pediatric Headache at the UCSF Benioff Children's Hospital. She's also the editor in chief of *Headache: The Journal of Head and Facial Pain*. I asked Dr. Gelfand to talk to us today because our topic is prescribing off-label medications for kids with migraine and other headache disorders, not just migraine.

This is such an important topic. I know that probably just about anyone out there who has children with migraine or other head pain and they're on medicines is always just wondering about this whole off-label prescribing process. Why is it off-label. What does it mean. Should we be worried about anything. And we're going to talk about all of that today.

Dr. Gelfand, let's just start by learning a little bit about you. Why don't you tell us why you work in this field and why you like it? If you do, we assume you do.

Amy Gelfand, MD:
I do. I love it. When I was a child neurology resident, I realized that unfortunately migraine and other headache disorders are quite common in children and adolescents and can cause quite a bit of disability, missed activities. All kinds of childhood things that we want kids to be doing can be impacted by these diseases. And there were not nearly enough clinicians focusing on this area, especially at the time. They're more now, but I realized that this is a very common problem. The need was incredibly great, and the degree of disability, unfortunately, can be quite significant as well. Yet these are treatable disorders. And so, I was drawn to the field to try to make a difference in the lives of these young people and their families in trying to give them effective treatment so that they can get back to doing the things that children and teenagers should be doing.

Lindsay Weitzel, PhD:
I love that. We love hearing a little bit about anyone who talks to us on our podcast, so thank you for letting us get to know a bit about you. Let's just start by talking about what it means to prescribe a medication off label.

Amy Gelfand, MD:
Prescribing off-label can mean one of two things. It might mean that it's a medication that's labeled for treating one disease, but you're using it to treat a different disease. That's one example of using something off-label. Another might be using it in a different population than it's labeled for, which comes up a lot here in this discussion, which is a treatment might be labeled for treating migraine or other headache disorders in adults. But now if we're trying to extrapolate that to adolescents or children, that is an off-label use because we're going below the age of 18. And sometimes both might be true. You might be trying to use it for a different disorder in a different population.

Lindsay Weitzel, PhD:
Can you talk to us about the difficulties of conducting clinical trials in children and why we have so few approved medications for kids?

Amy Gelfand, MD:
Yeah, this is a this is a good question. So generally speaking, new treatments get studied in adults first. And there are a number of good reasons for that in terms of making sure that we have more safety data before we're exposing young people to a new treatment. Once a product is approved in adults, companies can do a study in pediatrics, and they're often motivated to do that because they can get a patent extension.

However, usually those studies don't get started until a couple of years after the new treatment has already come to market. Those studies take typically years to do. They're very expensive. They might have particularly restrictive inclusion criteria that can make it hard for them to enroll and meet their enrollment targets. And so sometimes those trials don't necessarily get completed, or they take years before we get the results. And sometimes we're just left in limbo for the better part of a decade maybe, waiting to see if we're going to get trial results from a pediatric trial.

Lindsay Weitzel, PhD:
As a mother of a child with chronic migraine and a formal clinical researcher, I did used to work in academia. I think something I always wonder is, are these medications, these ones for migraine, like some of the newer ones, the monoclonal antibodies related to the CGRP pathway, the gepants, etc., likely to always be considered off-label in kids? Or are there plans to study them in children? And not only that, but what about the ones that have been given to kids for years for a migraine, but maybe have never been formally studied in kids?

Amy Gelfand, MD:
Starting with that second part for some of these older medications like propranolol, amitriptyline, they are not labeled for migraine prevention in children and adolescents. The only medication that's labeled is topiramate for migraine prevention in 12 to 17 year olds. Everything else that we're using for prevention is an off-label use, and it's unlikely, I think, that those older medications will ever get labeled for use in children and adolescents.

Once a treatment is off patent like these older generic medicines are, there's not a lot of incentive for a company to pay those millions of dollars that it can take to conduct a clinical trial. Clinical researchers could do it, this so-called investigator-initiated research. But it's very hard to get grant funding in migraine and other headache disorders. The NIH underfunds migraine compared to how much disability it causes in the United States. So it's very difficult to get those grants. And one of the things that grants are scored on to help determine whether they'll be funded is innovation, something new. And so grant reviewers might not think that it's very innovative to conduct a trial of an older medicine for migraine prevention in young people. They might say, why aren't you studying something new like a gepant.

And I myself have received such critiques on grants trying to study something that works in adults now in kids and adolescents. So it can be really tricky to get that kind of funding secured. So I think that most of the medications that are older that we do use off-label to treat migraine and other headache disorders in kids and teenagers are going to remain off-label. This is a common situation in pediatrics. This is not just something happening in pediatric headache. This happens in many pediatric fields. As for the newer medicines that you mentioned, the CGRP monoclonal antibodies, the gepants, there are trials going in children and adolescents. And so hopefully those will complete and lead to FDA indications in those populations. But it's going to take a little bit of time.

Lindsay Weitzel, PhD:
Let's ask another question. What should parents be concerned about if anything once their child is on, let's say, 1 to 3 or more medications that are being prescribed off-label?

Amy Gelfand, MD:
That first example, maybe it's a medicine that is on-label for a different condition now being pulled over to migraine. And it's an older medicine. So, one thing that's important to remember is that just because it's off-label for migraine, it might have been formally studied in kids for something else. So propranolol is an example of that. That's an older medicine. It has been formally studied for treating infantile hemangioma. That's a skin condition in babies. And so, we have really good dosing and safety information on how to use that medicine even in very young patients like infants. And I think that is very reassuring when we're now applying that to using it to treat migraine in kids and adolescents.

So, in that sort of situation, I think that can be really reassuring for clinicians and families that the medication has been formally studied in kids for different condition. Also, those older medicines have a lot of benefit just from having been around for a while. When they've been around for decades, generally speaking, the medical community has figured out what are the common side effects.

What are the rare side effects. What are we looking for. It's not perfect, but it's pretty good. Something that's been around for decades, usually there aren't surprises. And we have observational research. Maybe somebody did chart review research of kids with migraine, and they published their outcomes with propranolol, amitriptyline, etc. So, we often have some real-world evidence about efficacy and safety of those older medicines.

Newer medicines are a little bit trickier since they do have potential unknown. So this is a little bit of a different situation. Certainly, everything that's on the market was first studied in adults. That's something. And those trials do often go down to age 18. And given the epidemiology of migraine and

headache disorders, often at least in a pediatric headache program, we're treating 16, 17-year-olds. And so I don't think there's a big biologic difference between treating a 17-year-old versus treating an 18-year-old. So, I find it reassuring when we're treating older adolescents. It's a little bit trickier when you're treating prepubertal children. And I do personally try to avoid using brand new things in that population unless we've tried several things already that are more traditionally used and the patient is still experiencing quite a high symptom burden. Then we have to have a conversation.

It's always a shared decision-making process with the family. I do think if you're in that situation, that it can be helpful to be treated at a subspecialty program like a pediatric headache center, because we are using the newer medicines in these younger patients more commonly. And so we have the potential to start to see safety signals if they're there earlier. And so if you are, particularly with a younger child needing multiple newer medications, if at all possible I would recommend trying to be treated by a pediatric headache specialist.

Lindsay Weitzel, PhD:
That was a lot of great information. Thank you for that. When kids are prescribed medications off label, it is often difficult to get insurance companies to cover those medicines. Can you comment on that for us?

Amy Gelfand, MD:
Yeah. This this can be fairly frustrating. And I think really often boils down to being about money. We never have a problem getting off-label coverage for older medicines. Never. Propranolol, amitriptyline, that always is covered. It's really only the newer medicines which are more expensive where we have big challenges and need to do prior authorizations appeals. We have literally multiple staff members who do this for hours and hours a day, every day, trying to get through this process. And sometimes it works and sometimes it doesn't. And patients aren't able to access a treatment that I, as their treating neurologist, really think they need. Or there's a significant treatment delay in getting them access to that treatment while we go through this very time-consuming process. And that is very frustrating for everyone involved, the clinicians, the families, the patients, everyone. It's really hard.

Lindsay Weitzel, PhD:
It just occurred to me that I just recently, because it is time for people to change insurance companies if they choose to, as I'm going through this with my son who's on off-label medicines for migraine. And I'm wondering, do you know, is there any indication that if an insurance company does cover some of these newer medicines for adults, are they often the companies that also you're going to have the most luck with them covering it for children?

Amy Gelfand, MD:
I don't know. To be honest with you, I don't know. But I do recommend especially at this time of year, if you're picking your new insurance company for your family, you might want to call the ones that you're considering and ask which of these medicines do you have on your formulary, which ones will be approved. And what is your approach taken to under 18 use of these medicines. What kind of requirements might need to be met, or is it going to always be an outright no.

It puts a lot of burden, I think, on families to have to make these calls. It's very time consuming. You got to go through the phone tree. It's awful. But I think at least you can get a little bit more information. It's tricky because also each insurance company seems from my perspective, to renegotiate these things each year. So something that this plan covered in 2024, are they going to make a change in 2025. That can be really hard to navigate, but at least you can go in with as much information as possible if you do give them a call.

Lindsay Weitzel, PhD:
Many parents of children with migraine are also headache advocates. Some even participate in lobbying events like Headache on the Hill, where we work at the federal level for legislation that's fair and helpful to people with headache disorders. Is there any way you see that parents can help improve research for pediatric migraine and headache medicines, or even help improve insurance coverage?

Amy Gelfand, MD:
Well, first of all, I just commend you and all the other families for doing this advocacy work. It's so important. I think policymakers really need to hear what it's like being a child or a teenager experiencing chronic migraine or other disabling headache disorders, and what it's like for their families to see their childhoods being lost by the impact of these diseases. So thank you.

In terms of improving insurance coverage, I think we need to somehow help insurance companies understand that by delaying and repeatedly denying outpatient treatment, sometimes they're setting up a worsening of the condition, and it might result in even more expensive treatment needs. For example, the patient might need to get admitted to the hospital for I.V. infusions for several days, and that's much more involved than outpatient therapy.

I think we also need to revamp this so-called peer-to-peer process. So, this process is what happens when I, as the treating neurologist, need to get on the phone with the doctor working for the insurance company to advocate for why I think my patient needs coverage for a certain treatment that has been denied. And this is after sending in all the notes, the clinic notes, by the way, saying what's going on and what we've tried. All that has already been communicated.

So, I get on the phone, I talk to this person. But in all the times that I have done this, I have never spoken to another child neurologist, let alone another pediatric headache specialist. The vast majority of the time I'm not talking to another pediatrician or neurologist. It might be an internist, it might be a retired OB-GYN. I mean, they're a physician, but they really don't have necessarily any experience in treating children, treating children with headache disorders, and certainly not in treating children with refractory headache disorders that have not responded to initial therapies.

And so, I would like the option to be able to talk to another pediatric headache specialist or another child neurologist and have a true peer-to-peer discussion with someone who treats patients in this situation so that we can really be having a peer-to-peer call. In California, if the insurance company still denies the coverage after this whole appeal process and we've exhausted the peer-to-peer, families can take the situation to the state insurance board. And then it usually goes to a panel of independent child neurologists. And most of the time in that situation, it does get covered, because I think they can see the logic of how we've gotten to this advanced sort of therapy. But that's incredibly time consuming

and burdensome and a lot to put on families. So, I think we really need to revamp this so-called peer-to-peer process and make it an actual peer-to-peer discussion.

Lindsay Weitzel, PhD:
That is a very good point. I've actually never heard anyone say that, so I'm glad I asked you that question. That is something that I hope someday we will be able to lobby for. So thank you for saying that. Is there anything else you'd like to add that perhaps we didn't cover today before we go?

Amy Gelfand, MD:
I think you were really thorough in the questions. It's a hard topic. There's a lot going on here. I think I'm so lucky. I have the most incredible team of nurses, medical assistants, admins. But even with that incredible support, these insurance authorization processes can be very time consuming and very frustrating. So, I guess just asking all of us involved to take a deep breath and try to be patient with each other, but it's a very hard situation.

Lindsay Weitzel, PhD:
Well, thank you so much for being with us today and answering our questions. And thank you everyone for listening in. Please join us again for our next episode of HeadWise. Bye bye.