CURE Epilepsy Webinar
Pipeline of Progress: Epilepsy Medications on the Horizon
with Dr. Nathan Fountain, MD
April 8, 2026
(Transcript)

Dr. Laura Lubbers:

Welcome, everyone, to today's webinar, entitled Pipeline of Progress: Epilepsy Medications on the Horizon. I am Laura Lubbers, and I am the chief scientific officer for CURE Epilepsy, and I want to thank you for joining us today. We would love to learn more about each and every one of you, so I encourage you to put your name and the type of epilepsy that is of most interest to you into the chat so that we can offer learnings opportunities that suit your needs.

I also want to thank our webinar sponsors, Lundbeck, Stoke, and Xenon. These sponsors are helping us bring you information about the pipeline of promising medications, devices, and novel treatments for epilepsy, which will be our theme in 2026.

Each of these broad approaches are unique ways to reduce seizures and improve the lives of those living with epilepsy.

Our mission at CURE Epilepsy is to fund breakthrough research that will transform the lives of those living with the disorder as we lead the search for cures.

We fund inspiring new ideas that will help us understand and more effectively treat epilepsy. In fact, CURE Epilepsy has played a role in funding critical steps that have helped advance some of these new approaches that we'll be talking about this year.

Today, Dr. Nathan Fountain, who is the Thomas E. Worrell, Jr. Professor of Neurology and Epileptology at the University of Virginia School of Medicine. We'll talk about promising drugs that are on the horizon. He will first describe the steps that are necessary to test potential new treatments and then share details on specific new medications that are being tested.

And then we'll have time for Q&A. I encourage everyone to ask questions. You can submit your questions anytime during the presentation by typing them into the Q&A tab located on your Zoom panel. We want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy.

So with that, I'm delighted to turn it over to Dr. Fountain.

Dr Nathan Fountain:

Thank you very much, Laura, and thank you, CURE Epilepsy, for inviting me to talk, and, mostly, I thank all of you for joining us. We have a big crew, and we're excited to talk to you about this today. I don't find there are very many venues for this kind of topic of discussion for experimental therapies or clinical trials or research in epilepsy, so I'm delighted to talk about it.

To start, I have some disclosures. I don't think any are very relevant. I have executive leadership in these companies over here on the left. I'm not going to talk about anything from that. The University of Virginia, where I'm a faculty member, gets grants for clinical trials that I'm the principal investigator for from Xenon and Biohaven, I'm going to talk about those a little bit, and Neurona and NaviFUS that I'm not going to talk about.

Before we talk about the specific clinical trials, I want to take a step back and talk about some clinical trial basics, something that's true across clinical trials. And then we'll launch into the landscape of clinical trials today. The foundation for what we're going to talk about is the phases of clinical development or clinical trials. It comes in three phases, phase 1, 2, and 3.

Phase 1 studies, you can think of as safety studies. These will determined if a drug is safe, and find maybe not the best dosage that I've written here, but instead maybe the best tolerated dosage, and to identify side effects. That's given to a small group of healthy volunteers typically, so people that don't have epilepsy, but sometimes also people with epilepsy, in our case, as the medical condition. These have typically maybe 15 or 20 people per treatment arm, so it might be a total of 30 or 45 people or sometimes a few more. They're small studies that help us learn some basic things about the drugs.

Phase 2, which is really when we sort of come to learn about them, because that's the first time it's used in people that have the condition, people with epilepsy, are proof of principle studies. So they aren't really to demonstrate effectiveness or efficacies we'll talk about, but really to see if it's safe in people who have epilepsy and give a clue about effectiveness. Sometimes they actually help to prove effectiveness, but in general their idea is to give an idea about whether they could be effective, but also to see if they're safe. These are moderate sized groups of patients. Typically, in epilepsy studies, it might be 50 people, occasionally 100, but more like 50 people per treatment group. So if you have two or three groups, it might be 150 people participating, for example.

And phase 3 studies are the ones that really we're going to focus on today and what we kind of all focus on because those are studies that prove effectiveness, also called efficacy. These are the final large-scale testing that have to be done to determine a drug's effect to be submitted to the FDA for approval. In epilepsy and in most conditions, typically you're comparing the drug to a placebo or control group. A placebo or control group means they're taking something that looks and tastes and smells and, for all purposes, seems just like the study drug, but is instead might be a sugar pill or something like that. So you're comparing the study drug to placebo, and that's an important concept we'll come back to that probably most people are familiar with.

For FDA purposes, this usually requires two phase 3 studies. There are some exceptions to that, and maybe we'll come back around to that. But for what you might call garden variety of epilepsy, for focal seizures, the most kind of epilepsy that exists, it typically requires two phase 3 studies to demonstrate efficacy or effectiveness. The way we measure this is often by measuring the reduction of seizures, that makes sense, and that's compared in the treatment arm to the placebo arm. Instead of comparing it overall, it compares the reduction between a certain baseline phase to a treatment phase when they get either drug or placebo, and I'll come back to that.

Just for a general concept, it typically takes one or two years to do the phase 1 study. The phase 1 studies are brief, but it takes a while to get it off the ground and to wrap it up. Phase 2 studies typically take a couple of years. I've written one to two years, but in reality it's typically more like two years. And phase 3 studies typically take five years, and it takes two of them. So if you add all that up, the typical time between drug discovery, so when it comes out of the laboratory and first goes into people, until it's approved by the FDA, it's typically 10 years. It could be shorter. There's a few that have done it a little quicker, many are longer, but what that means is it takes longer than you'd think from drug discovery until actually it's approved to be available to take from the pharmacy.

There we go. This is a diagram of a typical phase 3 epilepsy clinical trial for refractory focal seizures, and you'll see that there's an initial one-month period called the screening. In the screening phase, that's when you'd come to the research clinic and see if you're eligible to be in the study, if you have the right qualifications. But the important part about that is the investigators and study team would tell you everything there is to know about the study, and that would be communicated through a consent form that might be 20 or 30 pages long. It really does contain almost everything that you'd need to know about the study. After you have a chance to ask questions and understand what's going on, if you decide to participate, then you'd sign the consent form and be enrolled in the study. Typically, blood work and

an EKG and some things like that would be done, and those things are collected together to make sure it's safe for you to be in the study and you're eligible depending on the study.

You'd return sometime in a month or maybe less than that for the baseline visit. The importance there is, the baseline visits, when you really start to count things and keep track of them. For the next two months typically, so you'll see in this diagram this sort of brown box, it's two months, that's the baseline. The only thing we do during that time is count seizures, so you kind of sit on your hands. Typically, the other medications you're taking aren't changed because you want to establish a baseline. You're not taking the study drug yet. You're just counting the number of seizures you have per month is the way we typically think about it. And it could be any number of seizures, but most common paradigm has four to maybe eight seizures per month as the minimum criteria, typically four for the kind of studies I'm talking about.

And then, at month two, after you do that for two months, then randomization occurs. That means you're randomized, either you get study drug or placebo. Typically, in these phase 3 studies, you as a participant are blinded to whether you take study drug or placebo, and so are the investigators. You start to take a pill, but you don't know whether it's drug or placebo, that's the sugar pill, and the investigators don't know that. The reason is so that the participants and the investigators can't subconsciously influence the outcome of the study, so it's truly double-blind. Typically, we'd count seizures for the next three months. Between months two and five, we just count the frequency of seizures.

At the end of those five months, then everybody goes into the open-label study. Typically, under most circumstances, if all goes well, you'd roll over whether you're on placebo or on study drug to be a known on the drug, so now you know you're taking the drug. Once you're in that part, the investigational part to determine if it affects seizure frequency is over, but it's still a research study and it still comes through the research clinic. But as far as whether or not the drug is figured out to be effective, that comes from looking at the people that got study drug compared to those who got placebo and looking at the seizure frequency compared to the baseline rate, and this is why the baseline phase is just as important as the treatment phase.

And the open label goes on for as long as it's necessary. That might be until the drug's approved, if all goes well, or until it's no longer being developed. I wrote down here 36 months, so three years, but I just said it could take five years. We have patients sprint some clinical trials that this is year seven. 2019 is when they first enrolled in this clinical trial for the randomized controlled phase 3 trial, and now they've been in the open-label trial for seven years. Hopefully, it'll be approved soon.

Today, we're not going to focus on everything in phase 3 trials, but we're just going to focus on small molecule medications. We're doing that really just to limit the scope of it, but also because it is a theme. Small molecule drugs are small exactly when compared to biologics. Biologics are things like antibodies or proteins or genetic treatments. And if you look over here on the left side of the slide, you can see at the top it's actually glucose, so it's the sugar that's in your blood. It's just this tiny little molecule compared to what the bottom is a protein. You can see the protein is giant compared to this one small molecule.

If you were to look at these proportional in size, this whole glucose molecule would fit right onto the tip of that arrow. The large molecule is not just a little bit larger, they're much larger, and that's important because small molecules have a simple chemical structure and they typically work on channels at the surface of cells. That's important because that's where neurons or brain cells communicate one to another, called the synapse, and so the molecules can go to the surface of it and trick the cell into thinking that one neuron's communicating with another, either block that transmission or promote that

transmission of information. In general, small molecules are easier to manufacture than biologics, and that has some other practical importance.

Compared to biologic, which are much larger, typical small molecules can usually be taken in a pill form, so that's great, you don't have to take a shot like you might with certain biologics, and they can cross the blood-brain barrier more easily because they're so small. They're often simple to manufacture, that is synthetically manufactured rather than derived from nature or have cells produce it. So we're focusing on small molecules.

And if we take a step back for just a minute to put these research drugs into perspective with the drugs that are available today, you can think about anti-seizure medications as coming in generations. So first, we have here the first generation of drugs, and this is admittedly a bit arbitrary. Some of it is just based on time, and some of it has a certain logic that I'll refer to. The first generation was 1920 to 1990. I've put, at the top, carbamazepine, whose brand name was Tegretol, and so you might be familiar with that. It was the most commonly prescribed drug for focal seizures for many years. I have it at the top for other reasons, but the first drug approved was phenobarbital and then phenytoin. I should say used because it was before there was any approval, but it was used.

The second generation starts in about 1990 and goes till about 2000, and the second generation conceptually was derived from the first generation. Carbamazepine tended to cause double vision and dizziness because it's metabolized to a certain drug, a component of it. Oxcarbazepine, known as Trileptal by the brand name previously, it's constructed in a way that doesn't allow it to be metabolized to that compound that causes the dizziness and double vision. So that was an advancement, a second generation. That was also the time that a number of these other drugs were derived, including levetiracetam, known as Keppra, gabapentin known as Neurontin, and these others, some of which are very popular.

The third generation starts in about 2000 through 2026, through today, and eslicarbazepine was derived from oxcarbazepine, so the next generation you might say. Eslicarbazepine is a metabolite of oxcarbazepine, but only has to be taken once a day and may cause less of certain side effects than oxcarbazepine. Brivaracetam known as Briviact was derived from levetiracetam, so yet another generation. And then pregabalin was derived from gabapentin, or at least the cousin, I guess you'd say of it. So that's the idea.

Many of these just came about based on their timing, but some were derived one from another. So that's kind of the perspective to think about the drugs as they exist today, and that takes us to the next generation. Beginning at each one of these generations, drugs became more and more designer-based, but the new drugs are very specifically designer-based. Some of these third-generation drugs were derived just based on serendipity or coincidence or chance, but all of the drugs that are now in development were very specifically designed for a purpose, and we'll talk about that.

We're going to limit our discussion to phase 3 drugs, meaning drugs that already made it to people, but also to this stage where they're going to be tested for effectiveness, and there's a bunch of them here. There's 34 or so drugs that already exist, which is now a bunch of them, and we're just going to talk about certain components of the next generation.

What we're really going to talk about is the small molecule drugs kind of divide into those that are for medication-resistant focal seizures. They're being developed, as I'll talk about for other things, but the most common form of epilepsy is medication-resistant focal seizures. We'll talk about... I'll just say them now to get the names out there, which are a mouthful sometimes. XEN1101 is also called azetukalner, PRAX-628 is called vormatrigine, and BHV-7000 is called opakalim, and you can see why we sometimes just use their other names, and then RAP-219 doesn't have another name yet as far as I know.

Just as a point of reference, when drugs are derived, not just for epilepsy, but for other things, they typically have some abbreviation first that stands for the company that developed them followed by a number. And the number might logically be which compound they were developing by the companies who might think, "This is the 1,101st compound," but my experience is that this is kind of arbitrary. Nobody wants to think it's the first drugs. There's no such thing as number one typically. For example, I'm involved in a company where we're developing a drug we called 021, because it was found in 2021. Nevertheless, this name and number is how we keep track of them, and it's unique to it. And then, eventually, they get a chemical name, which is what's listed here. That's different from the brand name. The brand name is something that comes after commercial developments. These are their chemical names that were assigned after the compound was found.

We're also going to talk briefly about some drugs that are being studied for developmental and epileptic encephalopathies or DEE, and we're going to just discuss DEEs intermittently, so I bring it up here. The specific drugs we're going to talk about is PRAX-562, otherwise known as relutrigine, LP352, bexicaserin, and then EPX-100, clemizole. Here's what we're not going to talk about. We're not going to talk about gene or cell-based therapies from Stoke, Praxis, and Neurona because those are topic for another webinar, another day. The things we're going to talk about now is enough of a mouthful, so we're going to stick with what we're talking about today. Everything we're talking about is an investigational treatment, so not approved by the FDA and not available for commercial use. You can't go get it at the pharmacy.

The mechanism for the drugs we're going to talk about are mostly ion channel-based or use ion channel modulation, and this cartoon over here is supposed to represent a channel. This is the cell membrane, the thing that covers a cell, like a nerve cell in your brain, and this purple part is supposed to be a hole in there, and this is the protein that's the channel that ions flow through. Ions are charged small molecules. In this case, it's supposed to be sodium flowing into or out of the cell. Each one of these channels that allow charged ions to flow in or out has other subcomponents, and that's important because of how the drugs may work.

The whole concept or core idea is that seizures are an electrical storm in the brain, and that electrical storm is conducted through abnormal electro activity that comes from these ions flowing in and out of the cells. The small molecules then either block or promote flow of these ions, these things like sodium and potassium, through the channel. By adjusting the flow of the sodium or potassium or calcium, these ions, you can change how excitable the cell is and you can stop the electrical storm is the idea.

New investigational drugs are intended to be more selective. So if this is a sodium channel, it's intended to just affect certain kinds of sodium channels or certain kinds of potassium channels. The idea is that by just affecting the channels that are involved in seizures and not the other channels that are like it but not involved in seizures, it should reduce some off-target effects, and so it should be better tolerated. In general, the most common ones block sodium channels or open potassium channels, or we'll also talk about some ones that augment or open serotonin channels.

Basically, the ones that are sodium channel blockers is kind of the vernacular, the way we commonly refer to it, are illustrated here. The drug would come here and conceptually block sodium from flowing in, and that would be important because sodium conducts that electrical storm I was talking about. Or they'd open up the potassium channel, and that's important because, when potassium flows out of your cells, it makes them more stable, makes them less likely to have that electrical storm. So that's the most common mechanisms we're going to talk about, and I'll refer to them here again in a minute.

So, now, let's talk about some specific drugs. That stuff was all background, it's true kind of across the board, and now you can kind of focus on the specific things we're talking about.

The first drug we're going to talk about is azetukalner or Xenon 1101 developed by Xenon pharmaceuticals. It's completed phase 3 trials, although the phase 3 trial's not published yet, but has completed a phase 2b trial that is published, I'll talk about. This is the one furthest along in development for focal onset seizures. Indeed, we'll talk about those completed trials, and it's also being studied for primary generalized tonic-clonic seizures. It works as a potassium channel opener, so it opens the potassium channel I just talked about on the previous slide, and it's selected for a specific subtype, and the name of the subtype is Kv7.2/7.3. That's kind of a mouthful and has a lot to do with the physiology, the specific makeup of the channel, but basically K stands for potassium, V stands for voltage-gated, so it's affected by the electrical current around it, and the 7.2 and 7.3 are the subtypes that are determined by the proteins inside of that.

The idea here is that the drug will open the potassium channel, and not just any potassium channel, but those are the specific subtype. The hope is that then it wouldn't have any off-target effects and affect the other kind of potassium channels that might be someplace else in the body. And that's important because other potassium channel openers in the past that seem to be effective for seizures caused other problems either in the retina, so in the eye, or changes in skin or in urinary retention. So the hope is that this would prevent those kinds of things, and that's true across the board here. This is specifically for potassium channel openers. It's dosed once a day, so that's great, you want to take it once, and it's a pill, so that's good.

I'm going to talk about the published phase 2b trial. One thing I want to stop and mention here is that following this is very difficult, following this whole area. And the reason it's difficult is because it moves quickly. Across the rest of science, we would typically talk about things in the medical literature because after, say, a study's completed and it's submitted to a journal for publication, then the people who review that, people like me or people that work in the field, would go through all the details of that study and vet it. They'd look at it and see where it could be a problem or why it's good, and that's called peer review. So it'd be under peer review. I'm only going to talk about data that's been published under peer review.

Now, the FDA scrutinizes it probably even more than that. Once the FDA's looked at it, it probably has even more scrutiny. But in between, when the study's done, the FDA's reviewed it in peer review, all we know is what's published on, say, a company website. I have no reason to think that's not accurate and complete, but it doesn't have all the information that a final journal article does. That's why I'm going to talk about, for instance, this phase 2b trial that's like a phase 3 trial, and not necessarily about the phase 3 trial, even though the results are very similar. One thing about this drug is it didn't have any of the safety concerns I mentioned before, so that's great. Really importantly, I think Xenon anticipates submitting a new drug application. That's an NDA, that's what's submitted to the FDA to have the drug approved for commercial sale this year. That seems very good.

These are the results from the first phase 2b, which for our purpose, like a phase 3 study, it's just the terminology used. This is the example of how really all of these studies look at seizure frequency and reduction, how you might interpret what comes in the medical literature on a website or when you're trying to think about what it means. This bar graph here has median percent change. This over here is percent, 10%, 20%, 30%, et cetera, and that's change from baseline. Listed over here in the bars are the different treatment groups. This one's placebo, the people got essentially sugar pill. That's the control. These are people that took 10 milligrams a day, and these took 20 milligrams a day, and these took 25 milligrams a day.

What you can see is that, for instance, in this highest group, let's start kind of with the biggest group, in the 25 milligram group, there's a more than 50% seizure reduction, and that's really great. More than 50% seizure reduction on average as just a number is greater than has been previously reported in the

literature for most studies, so that's great. At the lower dose of 20 milligrams, you can see it's in the range of around 45%, and at 10 milligrams is just over 30%. Then placebo here is about 18%, and so you're probably thinking, "Wait a minute, you're telling me that who got placebo had a reduction in their seizure frequency?" Yep, that's the case. People who just took a sugar pill also had some improvement in seizures. On average, in this study, for instance, around... you can see just less than 20%. A typical placebo rate would be around this range.

In the latest studies, which are doing better, you might say, have a lower placebo rates, around 15%. In some studies, it's 25%. This is an important topic, both to understand when you compare the effectiveness of drug, but also as we design better ways to do the trials. In my view, there are better ways to do this now, even though they're not very popular. The point of all this is that the highest dose reduced seizure frequency by more than 50% compared to placebo, which did it by less than 20%.

Another way you'll see it displayed is the percent seizure reduction week by week. Here at week 0 is when they started the drug, and this goes all the way out to eight weeks. And if you look first, let's say, at the placebo group, that's this one at the top, so here's that drop of almost 20% in seizure frequency, then you can see it hangs out around there, maybe goes down a little more. On average, that's only about 18%. Those who got 10 milligrams also hung out near placebo. Those who've got 20 milligrams and 25 milligrams, you can see week by week improved with a big improvement in the first few weeks. That tells us a lot about how the drug acts. It's out here at the end that we're most interested, how did you do after you were on at the end of the whole treatment phase or even longer, beyond eight weeks. But the idea is to think about how it goes over time. There are two ways to look at the trials. This is a specific trial, but you'll find this presentation for almost all clinical trials.

Now, we can talk a little bit... That's the one with the most data. So, now, let's progress to some that have a little less data available. Vormatrigine is sponsored by Praxis Precision's medicine as a phase 3 clinical trial that's ongoing for focal onset seizures and also being developed for generalized seizures. It's a voltage-gated sodium channel blocker that's selective for persistent sodium currents. The same concept that I mentioned before is true. If you think of it just as a sodium channel, it's blocking it, and it's blocking just specific channels in a specific way, and so it hopefully will avoid some of the side effect that sodium channel blockers traditionally had. Sodium channel blocking is important because that's the mechanism that phenytoin uses, or Dilantin. Dilantin, historically, which was synthesized in the 1920. It's been one of the more effective drugs we've had, but has lots of side effects. So this hopefully is something more than a better version of that.

It's designed as once daily dosing, that's great. In phase 2 studies being completed, it's more than 50% seizure reduction. I just mentioned for azetukalner that there's a more than 50% seizure reductions, that's also true for vormatrigine. But really, we have to wait for the phase 3 study. Phase 2 studies are almost as good as the phase 3 nowadays because they have a placebo control group. But the phase 3 study, particularly in this case, is really what we're after. Importantly, there's no specific safety concerns. That doesn't mean nobody had side effects. Safety concerns, I mean end organ toxicities, so it didn't have any significant effect on the liver or the lungs or the brain or anything like that. When you see safety, I mean literal safety. But tolerability is different, how many people felt dizzy or sleepy. Across all the drugs, some proportion did. In phase 2 studies, that's a little harder to derive because there are fewer patients in them than in phase 3 studies, so it's phase 3 studies we're really looking after to find out the tolerability. And there's a phase 3 study that's currently enrolling.

That takes the opakalim or BHV7000 from Biohaven. There's also a phase 3 clinical trial ongoing, and this will sound very, very familiar in the big picture because it's also for focal onset seizures and for generalized seizures. It's a potassium channel activator or opener. Opener is not quite right for some of these, so I put an activator, but you can think of them as openers, and it's again selective for the

Kv7.2/7.3. You can see the theme here is trying to not affect those other potassium channels that we're not interested in, and instead just affect the potassium channels that might help avoid seizures. It's also once-a-day medication that comes in a pill form.

As far as I know, we don't have any published phase 2 data in people with epilepsy like we do for the others, but instead an EEG-based study in healthy subject is showing it increased the EEG spectral power. What that means is they did an EEG brainwave test, gave people the drug, and saw that the EEG kind of calmed down, you might interpret it as. The hope is that that also will affect seizures. There have been no safety concerns raised yet. In the phase 1 trial, it was very well tolerated at the highest doses. There's an ongoing phase 3 enrolling trial that hopefully will tell us more about the effectiveness of it.

RAP-219 is the last one in this category we're going to talk about. It's being developed by Rapport Therapeutics. They just completed a phase 2 clinical trial, and phase 3 is initiating for focal onset seizures and generalized seizures. This works differently. This blocks glutamate selected for a particular kind of glutamate receptor. Glutamate's the most common way that one neuron talks to another in the brain, and this is selective for a particular kind of communication that blocks it. It's designed for once-daily dosing. The phase 2 design was really novel. It wasn't like the others. Instead of counting seizures in people with epilepsy, it took people with epilepsy that had a device implanted in their brain, called responsive neurostimulation, that detects things that are like seizures as a marker of seizures and saw a vast reduction in these markers, a more than 80% reduction in the marker. And that is really a novel design, but kind of a profound response. We'll see how that plays out in phase 3 studies. There were no specific safety concerns. It's not enrolling yet, but I'd anticipate a phase 3 clinical trial will be coming next.

That reminds me to say that, for all of these, I'm kind of zipping right through them, but if you want to know more about it, we'll talk about at the end. The website for each one of these companies or if you simply Google search or any kind of search the name of any one of these drugs, you'll easily find the sites enrolling. We'll talk about ClinicalTrials.gov, a website that's particularly good for that.

So, now, let's shift gears a little bit in the next few minutes and talk about investigational drugs for developmental epileptic encephalopathies or DEEs. I imagine everybody here is familiar with seizures and epilepsy and focal seizures, which are when they affect just one spot in the brain and spread. In many people, most people, with epilepsy or otherwise don't have any other medical or neurological problems, whereas people with developmental epileptic encephalopathies always have, to some degree, some other problems because it affects their development. That's why it's called developmental epileptic encephalopathy. It starts in childhood. The easiest way to understand it is a genetic condition, and that genetic condition affects development, typically starting in childhood. Sometimes there's a specific known cause, like a genetic cause. We'll talk about some of them. Most often, the cause isn't known though, and that leaves a lot of people that don't have a specific cause, and that's relevant for the trials we're going to talk about.

The first drug we're going to talk about is relutrigine, also from Praxis also called PRAX-562, and this is already completed phase 3 trials for specific DEEs. SCN2A, sorry, I've written it down here wrong, and SCN8A, these are genetic conditions which are sodium channel, that's the SC part, sodium channel, and N is the... NA is the abbreviation for sodium, so it's a sodium channel 8A or sodium channel 2A. These are kids, or could be adults, but typically diagnosed in childhood, that have a severe form of epilepsy, SCN2As, also called Dravet syndrome, have a specific kind of genetic syndrome or condition. In this condition, they may have overactivity of the sodium channel or, in some cases, underactivity.

There have been studies already completed, phase 3, for these conditions and phase 3 studies for more broader DEEs, which is many more people. In this case, it's seizures due to the specific sodium channel disease we talked about. It's a voltage gated sodium channel blocker. Imagine you have a condition

where your sodium channels, let's say, are stuck open, in the easiest concept, and specific sodium channels, a specific type is the 2A and 8A, they're stuck open. So if you have a drug that works right there and blocks just that channel, it should work especially well for that. That's the concept. It's designed for once-daily dosing. In the phase 3 clinical trial of the SCN2A and SCN8A, kids, there was a 46% seizure reduction. For these conditions, that's a big seizure reduction. These are kids that have severe, or could be adults, but typically kids that have severe epilepsy and frequent seizures. There have been no specific safety concerns, so that's great.

And the phase 3 data is currently under review by the FDA for these two conditions. So that means that hopefully we'll hear pretty soon [inaudible 00:34:53] the FDA has adequate data to decide to approve these for these conditions. Remember, you can't get it in the pharmacy and it's not available for commercial use until it's been approved by the FDA and then marketed and so forth, although it could be available through clinical trials.

The next condition is bexicaserin or LP352 being developed by Lundbeck, and it's in a phase 3 trial for developmental epileptic encephalopathies. This is kind of the opposite. We said before that the Praxis compound was specifically for those genetic conditions. And then, additionally, for a larger trial here, very clever and kind of near to my heart, is the basket trial that included these other syndromes, like Dravet and Lennox-Gastaut, that we talked about, but also other rare childhood onset epilepsy with treatment-resistant seizures, so it's kind of a broader indication.

This drug enhances the activity of serotonin receptors, very selective for the 5-HT2C subtype, so a specific subtype, and that's important because other serotonin drugs caused heart valve effects, if you think back to the old Fen-Phen diet drugs, for instance. It's hoped that by having this subtype-specific drug that it'll avoid those effects on the heart. So far for many drugs in this class for epilepsy, there hasn't been substantial heart effects. This drug use an oral formulation that can be given through a G-tube or a PEG tube, so that's great. Those are tubes into the stomach that some kids with severe neurological conditions have to have, or adults.

The phase 2 study's being completed as really the novel basket trial I talked about, so a collection of kids with DEEs. And that's really great if we can find something to help even more people than specific conditions. There's no phase 3 safety data available yet, and we'll be looking for that, but there hasn't been any safety problems so far. The phase 3 study is estimated to complete in October, so we'll see if that turns out.

This is the study that has been studied. This is the PACIFIC study, so the one I mentioned, the phase 2 trial, and this is similar to the graph I showed before, although upside down. This is the seizure reduction. That's why it's upside down. You could just flip it over. It'll be just like the other one we saw. This is the percent seizure reduction, just like the other graph, except going downward. This is in Dravet syndrome, and the first group's supposed to be placebo, and then the treated group. You can see these are small numbers. It was a small study.

But in the three kids with Dravet syndrome, you can see it reduced the seizure frequency by 74%, which is quite a lot in this condition. In Lennox-Gastaut, it reduced it by 50%, and, in all the others, it reduced it by 65%. Those are all big numbers, but look here at the gray bars. Even in the placebo group, it was reduced by 32% for Lennox-Gastaut syndrome... or sorry, for all the other developmental epileptic encephalopathies, and that's a pretty big reduction for placebo. That's why it's important to have a placebo group. There are times when it's not appropriate to have a placebo. But in this context, when you do, it really gives you a frame of reference.

The last one I want to talk about in this group is clemizole or EPX-100 from Harmony Biosciences. There's an ongoing phase 3 trial for LGS, which is Lennox-Gastaut syndrome. This is a particular kind of DEE, and for Dravet syndrome, that's what I mentioned before, the SCN2A syndrome. It enhances

activity at the serotonin receptor as well, and it's taken also as a liquid twice per day. Liquid's important for going through a G-tube or PEG tube also. There's a phase 3 study that's ongoing separately for LGS and Dravet, so two different studies, and we don't really have safety data available yet from the phase 3 study. It's currently enrolling.

So we've kind of zipped through all those, and that was kind of on purpose. I wanted to give you a big picture of the whole concept, some specific aspects of drugs for you to think about, make sure you've at least heard those names and words so you can think more about it. But really, if you're interested in specific things, you'll need to learn more, and the way to do that is through these websites. The most important one is ClinicalTrials.gov. That's sponsored by the federal government through the National Library of Medicine, and there you can go and search by anything you want. You can search epilepsy to find clinical trials, you can search DEE, you can search a specific condition, and that's the one that is required for clinical trials to post their clinical trial to and then required to post the results of the clinical trial eventually within a year of completion of the study.

Of course, you can also look at cureepilepsy.org on the CURE website, the pharmaceutical-sponsored website. So if you've heard something we've talked about you have a specific interest in, you can look there. Advocacy and research group webinars, there are a few of those, that's hopefully we're remedying, and talking with your neurologist or epileptologist, of course, because they would be able to give you the most relevant information specific to you, and then the medical literature. Everyone has access to the medical literature now, so you can search things on your own.

Great. Thank you.

Dr. Laura Lubbers:

Fantastic. Thank you, Dr. Fountain. What a great presentation, and it has inspired a lot of questions here. We do have some time. I think one of the big themes you had was around sodium and potassium channels. One question is, "Can neurologists tell whether you need potassium channel or sodium channel medications? And if so, how?"

Dr Nathan Fountain:

The only way to tell is if you have a specific genetic condition, which we know that you have abnormal sodium or potassium channels. For people with, for instance, SCN2A or SCN8A, those genetic conditions, we know they have abnormal sodium channels. Not only that, we know if they're up-regulated or down-regulated. Some drugs might be more or less appropriate depending on whether it's up-regulated or down-regulated, meaning you have overactivity or underactivity. Through genetic testing is the only way you can tell that. For people with what you might call garden variety epilepsy, so refractory focal seizures, or if you don't know the cause, then we don't know anything about sodium channels or potassium channels that would make one or another better, that is modulating one or another better.

I guess the fundamental question is, is one drug targeting potassium channels better than another drug that targets sodium channels? In general, unless we know a specific mechanism, then we don't know which is better. Not only that, we don't know which one is better among the drugs that exist today. We don't have any randomized controlled trials. I listed 34, we didn't talk about them all of course, 34 drugs approved for epilepsy and I think 10 or 12 in development. So not only do we not have comparisons among that, we don't have comparisons among any of those in a randomized controlled trial, with just a few exceptions, and we don't have controls among any of the most commonly used drugs. We don't know for those.

Dr. Laura Lubbers:

Right, so we need more comparative effectiveness trials perhaps to sort some of that out. Okay. I know we've got a lot of folks with kids on this webinar, so there were some questions related to that. Are children included in trials like this?

Dr Nathan Fountain:

Yeah, there's two answers to that. For conditions that are common in adults, the standard approach is to do trials in adults first to see that it's safe and effective before exposing children, and the concept is children can't quite consent for themselves. They can ascent if they're old enough and can understand, but you're putting them in a research study in which they might not know the consequences. So we start with adults and see it's safe and effective, then move to children. That would be true for things like focal epilepsy.

But are there any common focal epilepsies that exist that are different in adults and children? The answer is no. A few years ago, as a result of some efforts from the community, actually, the FDA now allows extrapolation from adults to children. Once a drug is developed in adults for what I'm calling garden variety epilepsies, so meaning refractory focal seizures, the drug doesn't have to have placebo-controlled studies in children. Instead, they can take that effectiveness research and just extrapolate and think it's going to be good in children down to age one now. It requires other research to show it's safe in children and to know the dosing and how it's metabolized in children, but those aren't typically placebo-controlled studies. For refractory focal seizures, it's done in adults and typically doesn't have to be done in children for efficacy studies, although others do.

Now, on the other hand, if something doesn't exist in adults or starts in early childhood, then those studies are done in children. For genetic conditions that begin in childhood, the research is done in children. Often, adults are included, but it's a bit uncommon for adults to be in a position to be in those clinical trials. They can, but often they're so far advanced down the pathway that it doesn't make as much sense or is much more complicated than enrolling children who are at the beginning of the whole process. For example, in the DEEs, commonly that would be in children.

Dr. Laura Lubbers:

Okay. Complicated.

Dr Nathan Fountain:

Yeah.

Dr. Laura Lubbers:

Yes. You did answer a question about how do these drugs get used in toddlers, and there is this extrapolation that can be done.

Dr Nathan Fountain:

Yeah. Babies and toddlers are an issue, babies in particular. Babies, we don't have a good answer for. It's complicated and difficult. We need more drugs to treat babies in the neonatal ICU right after they're born, even in the first year of life, and we don't have a good solution for that at the moment, although we're working on that, because that might be a little different thing if you have seizures in those right after being born or even in the first year of life. But for toddlers, they can be in studies. Typically, for focal epilepsy to be extrapolated downwards, they wouldn't be in a clinical trial. You typically have access to the commercially available drug. For research studies for the developmental epileptic

encephalopathy, those typically severe conditions, then they'd be enrolled down to age one or sometimes two, depending on the condition.

Dr. Laura Lubbers:

Great. With thinking about the moms on the call, there was a question, "How are medications determined to be safe or not during pregnancy?"

Dr Nathan Fountain:

That's a tough one. We don't have a way to prospectively give people the medicine. Typically, we'd say, "We're going to give half of you placebo and half of you drug. We're going to see who has problems and did more people on drug than placebo have the problem." But we can't do that for pregnant women because we'd be exposing it to them, so instead we have pregnancy registries, which we ask people with epilepsy who are taking these drugs, once they're pregnant or becoming pregnant, ask them to register in the registry and then follow them prospectively over time. That's kind of the best we can do. Pregnancy registries then look backwards to see if it caused problems. That sort of two or three kind of problems you might think of is, did they have a problem during pregnancy? Did the baby have a problem right after it was born? Birth defect, for instance, is what we tend to focus on. We can count that and understand it. There's some drugs that cause that and some that don't seem to.

And then third that's harder to figure out is, did it cause a problem later in development? We're just now having research emerge from that. So that's how we figure it out. Not surprisingly, that means we have to have a lot of women register in the registries to determine this, and that means we only know it for the most common drugs. For example, for lamotrigine, we have a lot of information. It's been around a long time. A lot of young women take it, so a lot of information. It seems like there's no greater rate of birth defects, for instance. For valproate, which is Depakote, also been around a long time, a lot of young women used to take it, we know that it has an increased risk of birth defect. We discourage women from taking it when there's an alternative, although they might need to take it.

For a lot of drugs in between, we don't know. For these brand new drugs, which I think maybe is the nature of the question, we exclude pregnant women from clinical trials. We say, "You can't be in the trial if you're pregnant. Not only that, if you get pregnant during the trial, you have to leave the trial," and that's because we don't know if it's safe for the baby. But then of course, we also don't know if it's going to affect pregnancy. So you have to wait quite a while after approval to figure that out.

Dr. Laura Lubbers:

Okay, lots to do. This question relates to the origin of the seizure. "Does it matter where in the brain the seizures comes from in terms of the efficacy of these drugs, especially for focal seizure medications?"

Dr Nathan Fountain:

It really does make sense that you might think that. That's a perfectly reasonable question. The most commonplace seizures come from in the brain is the temporal lobe. The temporal lobes behind the temples are particularly ticklish. They tend to have the electrical storm. About half of all epilepsy or maybe more is from the temporal lobes among focal epilepsy. The next most common site is the frontal lobe, and that's about another 25%. Then the whole rest of the brain is the rest of them. We know a lot about temporal lobe epilepsy, less about the others. But if you take those cells out and put them in a dish, so to speak, and look at their physiology, what happens when they have a seizure? We, overall, don't know any difference between a neuron having a seizure in the temporal lobe and frontal lobe.

They're undoubtedly different, but we don't know enough about them to help us understand if one drug is better than another. In the future, we might very well, but at the moment I'd say we don't.

Dr. Laura Lubbers:

More research.

Dr Nathan Fountain:

Yes, definitely.

Dr. Laura Lubbers:

"Is there a specific genetic test series you would recommend these days for people with refractory focal epilepsy?"

Dr Nathan Fountain:

Yeah, I'd recommend... In the whole field, there's standard recommendations as a standard of care that, if you have refractory seizures, whether they're focal or generalized, genetic testing, and there's sort of three kinds of genetic testing. To cut to the chase, the important part is that most people would have what's generally called whole-exome or whole genome-sequencing. The idea there is that, from a sample of blood, you could sequence someone's entire DNA, all their whole DNA, and then compare it to another group of people who don't have epilepsy and look at the differences. You'd say, "Ah, this group of people without epilepsy doesn't have these particular genetic changes, and you do, as a person with epilepsy, have it." And if it's in a gene that we know causes epilepsy and if it's a variant in that gene that we know is in a whole family of people that causes epilepsy, we say, "Aha, that's the cause."

If you are identical to that group of other people that don't have epilepsy, we say, "Well, we didn't find anything."The dilemma is that, very often, we find someone who has a genetic change that's different from these other people, but we don't know if it's causing their problem or not. And the more genes you look at, the more you're going to find that in a way. The short answer is I'd recommend whole exome or whole genome, which are kind of similar sorts of things. Whole genome's the biggest test you can do to look for causes of epilepsy.

There's another test that's actually much easier to get, easier to interpret. That's an epilepsy panel. It's a genetic test that just looks at the specific genes. That would be the most popular probably, maybe even still, but was definitely, just a few years ago, most popular. And then after that, there are other genetic tests you can get. So if those are negative... For people who have more than epilepsy, so if they also have, let's say, some developmental problems or particularly things you can see, changes in their face or in their arm to their legs, that kind of thing, then there's another genetic test that looks at how the chromosomes or genetic materials rearranged, chromosomal microarray it's called, or CMA sometimes.

But I think the answer to the nature of the question is, in my view, well, I guess in the whole field's view, you should have genetic testing if you persist in having seizures because you might first find out something you can treat one way or another. If you're an adult with focal epilepsy, we're probably not going to find something we can dramatically treat, but it might help guide us in the future. The second is because it might alter the kind of treatments you do. For example, surgery might not be a good idea if you have focal seizures and have genetic cause sometimes. I think genetic testing is definitely the way to go.

Dr. Laura Lubbers:

Okay. Well, I appreciate you bringing up the issue of adult genetic testing because this is a question we all forget and in a population that's often overlooked when it comes to genetic testing. So thank you for adding that.

Dr Nathan Fountain:

Yeah, I think there's kind of a history of reluctance on the medical community to get the genetic testing. I would say, in my experience, this reluctance from patients, from people with epilepsy, they say, "Well, it's not going to change anything tomorrow." We have this whole discussion I just had, and a lot of people decide not to do it, which is... I'm sort of surprised at that. I think that's changing over time, of course, but I'm still surprised at that.

Dr. Laura Lubbers:

Okay. There was a new question that was submitted that sort of aligns with the question around pregnancy, but for males, "Do drugs, particularly Depakote, impact male physiology?"

Dr Nathan Fountain:

Yeah, we typically focus on female physiology on how drugs affect menstrual periods or fertility or pregnancy, but there's also evidence that they affect men as well. They typically don't affect fertility in a substantial way, so we don't have a lot of research about that. They may change the patterns that men have. As a practical aspect, it's infrequent for drugs to affect male fertility in a substantial way, but it's possible.

Dr. Laura Lubbers:

Okay, okay. I had a couple of questions related to epilepsy as a result of TBI. "Is there anything in the pipeline for partial motor focal epilepsy caused by scar tissue as a result of traumatic brain injury?"

Dr Nathan Fountain:

I'm sorry, on my end, you cut out a little bit there.

Dr. Laura Lubbers:

I'm sorry. The question leads to post-traumatic epilepsy. "Are there any new treatments in the pipeline for partial motor focal epilepsy caused by scar tissue as a result of TBI?"

Dr Nathan Fountain:

That is a question kind of dear to me. CURE sponsored a study I was an investigator in, along with the principal investigator Pavel Klein, looking for markers that might help us understand who would develop post-traumatic epilepsy. It's a vitally important thing. It's very common. When we think about epilepsy, we tend to think about everybody that epilepsy and seizures are main problem. So if you have post-traumatic epilepsy and you have a bunch of other problems, you have a big head injury, you kind of get... The epilepsy almost gets neglected, but that's a big group of people who we really should help. The answer is no. I'm not aware of anything far along the pipeline. I will say that there is a group I know about that's developed... There are two groups that are developing drugs that we hope will help prevent post-traumatic epilepsy, something I'm involved with that seems to dramatically help brain injury after trauma, but nothing near the phases that we're talking about and nothing I'm aware of in clinical trials.

Dr. Laura Lubbers:

Okay, great. Thank you. This question relates to nocturnal seizures. "Is there anything that is particularly helpful for somebody with nocturnal seizures or any different treatment paradigms that would be helpful?"

Dr Nathan Fountain:

In general, no. But if we kind of drill down on some specifics, nocturnal seizures are often due to frontal lobe epilepsy. Frontal lobe epilepsy, depending on its cause, might be amenable to surgery, for instance, but yet is often neglected. Nocturnal seizures can be particularly bad because, if you have a seizure at night while you're asleep, it might increase your risk of SUDEPs, a unexplained death in epilepsy. SUDEP is uncommon, but a horrible thing when it does happen, and so there's kind of a greater motivation to think about seizures at night, even if we don't have something exactly directed at that to treat it. So we'd think about frontal lobe epilepsy in terms of doing more diagnostic things and more workup, and at least, in my case, being a bit more aggressive about the workup, trying to find it in case it is amenable to surgery. Along there would be certainly genetic testing because there are certainly some genetic causes of frontal lobe epilepsy, and that might influence that surgical workup, for instance.

This is a great time, not exactly talking about drugs, but devices to detect seizures that might help detect seizures at night that would help prevent SUDEP. We don't know that's the case, but it's logical that would be the case. So we hope that we, right now, have devices that can detect seizures, particularly at night. I would definitely advocate for that. It's not quite the same as treating them, but at least they'd be identified so someone could come and intervene and you'd know you're having them. So that's a whole nother issue. Regardless of how bad they are, if you don't know you're having them, then we can't go tell your doctor to change your treatment.

I don't think that was the nature of the question. I think the nature of the question probably was... There's something about frontal lobe seizures you could pinpoint with a specific drug. There are drugs in development for specific causes of frontal lobe seizures, so something that was called autosomal dominant nocturnal frontal lobe epilepsy, so genetic cause, that is kind of a prototype or an example of a specific receptor, the acetylcholine receptor. There's some drugs that have been thought about that might work specifically in that receptor. That goes back to figuring out what's causing it. And if you figure out what causes something treatable, then you might have a specific treatment for it. That might be the nature of the question you're asking about this particular type of epilepsy. But as a location, we don't have a treatment.

Dr. Laura Lubbers:

Thank you. I think we have time for one more question, although there are so many questions in front of me right now, including in my lap. "Would you say that this generation, this new generation, of treatments will have a better side effect profile than past medications?"

Dr Nathan Fountain:

We certainly hope so. Among those generations, the first generation not just had annoying side effects, they had toxic end organ bad things that could happen to people. The second generation of drugs did a little better, but you still kind of felt miserable. The third generation, some of them have very few side effects and are very well tolerated. So I think the expectation is that the drugs under investigation now will have to at least do that well, probably do better than that. And the theory is that by being selective, they'll have fewer side effects.

There's an idea they'd also be more effective, and the great thing is that, you can probably tell I'm a bit of a skeptic. "In God, we trust to always bring data," is what I might say, but the data we have so far shows the seizure reduction is substantially more than we've seen in the past, and the tolerability is very good. It looks like they'll be more effective and more tolerable, but I'd say we're not really going to know that until they're sort of out in the wild, until we can give them to people and see how they feel in a regular home environment.

Dr. Laura Lubbers:

Great. Thank you so much for the tour to force in answering these questions.

Dr Nathan Fountain:

Thank you for tolerating-

Dr. Laura Lubbers:

Not an easy challenge.

Dr Nathan Fountain:

... the fast talk and for inviting me.

Dr. Laura Lubbers:

Well, thank you so much, and I want to also thank our sponsors once again, and thank the audience. Again, so engaged, so interested. We'll have to figure out how to do this again so that more people can come and learn and ask more questions.

If you do have any more questions, please we'll do our best to see if we can get some answers. If you have questions about CURE Epilepsy and our research programs, please feel free to visit our website or email us at research@cureepilepsy.org.

Today's webinar was recorded. So if you'd like to listen again or share it with others, please go to our website. It should be available in the next couple of days. You can also download transcripts of the webinar for reading, and we'll also circulate an email to all attendees with a link to help guide you to where it is located.

Finally, please keep your eyes open for our next webinar later this year that will focus on new devices for epilepsy.

Thanks again, Dr. Fountain and everyone for joining us.

Dr Nathan Fountain:

Thank you.