CURE Epilepsy Webinar
Focal Onset Seizures: From Causes to Care to Potential Cures
Presenter: Dr. Pavel Klein
(Transcript)

Dr. Laura Lubbers: Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer of CURE Epilepsy and I'm delighted to have you join us today. CURE Epilepsy is the largest non-governmental funder of epilepsy research. Since our founding in 1998, we've raised millions of dollars to fund epilepsy research. With these generously donated dollars, we've provided grants that support novel research projects and advance the search for cures and more effective treatments for epilepsy. We also provide educational opportunities such as this webinar to highlight some of the critical research that's being done on epilepsy. Today's webinar is entitled Focal Onset Seizures from Causes to Care to Potential Cures, a topic that has potential implications whether you have focal or generalized epilepsy. Focal onset seizures, also known as partial onset seizures, are a type of seizure that occurs when there's abnormal electrical activity on one side of the brain. They may be classified as focal onset aware seizures, which were formerly known as simple partial seizures. A person experiencing focal onset aware seizures is aware of the seizure and their consciousness is not altered.

Alternatively, focal seizures may impair awareness and these of course are called focal onset impaired awareness seizures, and they've been referred to previously as complex partial seizures. A person experiencing this seizure type may be unaware of the seizure. While these seizures generally occur in the temporal lobe of the brain, they may originate in other regions as well, and their symptoms vary from repetitive involuntary motor movements to confusion and memory loss. This type of seizure can be due to head injuries, genetic mutations, infections, or metabolic disorders among other causes. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website. You can also download transcripts of all of our webinars for reading. This webinar is presented by Dr. Pavel Klein, the director of the Mid-Atlantic Sleep and Epilepsy Center in Bethesda, Maryland. He's also an adjunct associate professor of neurology at George Washington University.

Dr. Klein's clinical research includes prevention of epilepsy after traumatic brain injury, the effect of hormones on epilepsy, and epilepsy in women. He's also been a lead contributor to many clinical studies on new therapies. Before I turn it over to Dr. Klein, I'd like to encourage everyone to ask questions. We'll address the questions during the Q&A portion of the webinar, and keep in mind you can add your questions into the Q&A tab located at your Webex panel at any time. We'll do our best to get through as many of the questions as we can. We do want this webinar to be as informative and interactive 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'll turn it over to Dr. Klein. Welcome.

Dr. Pavel Klein: Thank you Laura, and thank you for that introduction and thank you CURE for everything that you're doing. Above all, thank you all in the audience who've

come far to spend an hour of your day with us today. I hope that this will be a worthwhile hour and that we'll be able to have a dialogue during the talk. So I was charged to talk about focal onset seizures from causes to potential cures. Brandon, if I could have the next slide, please. These are my disclosures. Next slide, please. This is the outline of the talk. So I'll talk about focal seizures definition, how it happens, about the symptoms, about the diagnostic criteria for focal aware and unaware seizures, about the causes and triggers for focal seizures, current treatments, treatment options, and I will wind up with discussing one particular medication called Cenobamate. If I could have the next slide, please. So how do we define a seizure? A seizures? The formal definition of a seizure is that it is a sudden uncontrolled electrical disturbance in the brain, which can cause changes in behavior, movements, sensations, and consciousness.

Seizures may vary in intensity and duration. They can be brief lapses of attention and they can be severe convulsions and anything in between. They may occur once off as a one-time event or they may occur spontaneously, and if they do, the condition is called epilepsy. There are different types of seizures, focal seizures, previously known as Laura said, partial seizures, which affect only one part of the brain that hence partial seizures or focal part of the brain, hence focal seizures. They include generalized seizures which involve the whole brain, and then specific types of generalized seizures such as absence seizures that are characterized by brief lapses of awareness, myoclonic seizures where you have sudden jerks of an extremity or other part of the body, drop seizures when you lose suddenly the tone and you may drop either the whole body or your head and fall. Brandon, if I could have the next slide, please.

What is a focal seizure? Focal seizure is occurs when abnormal electrical activity starts in one specific localized area of the brain. The effects of the focal seizure depend on the part of the brain that is affected, either initially or subsequently in the course of the spread of the seizure. The symptoms vary depending on which part of the brain is affected by the seizures. As Laura said, there are two main types of seizures, focal aware seizures, previously known as simple partial seizures, which are primarily distinguished by the fact that the patient retains consciousness. They may have symptoms that they cannot control, but they are conscious and they can interact with the world in a normal way. The focal impaired awareness seizures, previously known as complex partial seizures, on the other hand are seizures that may also have focal symptoms, but the patient is not in command of their full consciousness. Now, they may appear conscious, but they may not respond, they may appear confused, they may be doing things that they wouldn't otherwise do without being aware of it.

So there's a disconnect between the appearance of the patient and their processing of the information around them. If I could have the next slide, please. So how do seizures happen? Seizures occur when part or all of the brain

acts together in unison when it normally doesn't. So the brain consists of neurons which generate electrical discharges that come on and off, on and off, here and there depending on which part of the brain is active in which particular task. You can think of it as lights in a city at dusk time coming on one at a time, then somebody leaves the office, the light goes off and you've got flickering on off, on off, here and there all over the city. During a seizure, all lights come on at the same time. There's a massive electrical surge, everything acts together and there is an electrical shortcut. For that to happen, you need two basic changes in the way neurons work from the normal. One, as I mentioned, the basic activity of neurons is electrical activity when a electrical impulse called action potential is generated and then passed onto the next neuron.

The electrical impulse action potential is generated as a result of excitation of the neuron. In patients with seizures, and for that matter, animals with seizures, neurons are more excitable, so it takes a little less for that action potential, the electrical impulse to be generated. The second component of seizures is that the neurons fire together, just like I mentioned now, they are more synchronized than normal, all of them, they are abnormally linked to each other. That allows for that large number of neurons to fire together. You have to have these two components, two or both to generate a seizure, increased excitability of neurons, and increased synchronization of neurons. If I could have the next slide, please. So this is just a slide for illustration that shows different mechanisms by which anti-seizure medications work. You're looking at a neuron which releases chemical from the green blob. The chemical crosses the space that's called synapse to the next neuron, and then you've got that pink stuff, which is the membrane of the next neuron and the chemical acts on it.

This is a really complicated slide. I'm showing it just to show that there are many different ways how the excitability can be altered by chemicals and many different ways how anti-seizure medications can act to reduce that excitability. If I could have the next slide, please. So what are the causes of focal seizures? Broadly speaking, they can be genetic, they can be acquired, they can be both, or in a very significant proportion of patients we do not know. That unknown proportion of patients is estimated somewhere between quarter and half of all patients with epilepsy. Next slide, please, Brandon. So the genetic causes include some relatively common epilepsy such as juvenile myoclonic epilepsy, which has a bunch of genetic abnormalities associated with it, another epilepsy of adult called generalized epilepsy with febrile seizures. Plus, most commonly you've got single gene changes that lead to diseases with epilepsy that are relatively uncommon. They're referred to as rare diseases. They include tuberose sclerosis, that may be the commonest of the rare diseases, Dravet syndrome and other rare syndromes of which there are many.

There have been over a thousand genes identified to be associated with epilepsy, and a significant number of them are affected as a single gene effect

producing disease. We don't know exactly what proportion of all epilepsy is genetic because we think that there's a large number of epilepsy causes that have not been discovered yet that may be genetic, but let's say that it's maybe between a third and a half of patients with epilepsy. Then you've got the other bracket, which is I think more commonly of which there's a greater awareness and that's acquired epilepsy. The acquired epilepsy happens when in the course of life something happens that alters the brain. That something maybe an acute injury, head injury, sudden destruction of part of the brain resulting to reformatting of the brain in such a way that there's increased excitability and hypersynchronization resulting in seizures. Same with a stroke, part of the brain dies during stroke, you've got reformatting of the brain with the same outcome. And the same after infections like encephalitis, meningitis, abscess. Between these three things, you've got about 20% of all epilepsy caused by these three acutely acquired injuries to the brain.

I'm dwelling on this for a reason, namely, you've got a situation where you've got a previously normal person who has an acute injury, and as a consequence of the injury somewhere down the line they develop epilepsy. And because epilepsy develops somewhere down the line, not at the time of the injury, it allows us to try to figure out how we could prevent it. That's a major direction of research in epilepsy today. So you've got other changes to the brain that happened in the course of life that are not as acute but maybe more chronic, for instance, tumors. Epilepsy is associated with a number of tumors, both primary brain tumors and tumors that secondarily involve the brain. Alzheimer's disease, so patients with Alzheimer's and degenerative dementia of other causes have an increased risk of epilepsy, and then there are others. Brandon, if I could have the next slide, please. So what are the symptoms of focal seizures? Can we flip through this slide, the next slide and then land on the third slide? Yep. One more. Yeah. So the symptoms of ... back please, Brandon? Yeah, thank you.

The symptoms of focal seizures depend on the part of the brain that is involved. And so here you're looking at the brain, looking at the left top part, you're looking at it from outside, from the side. Look at the yellow area. The yellow area is the area that controls the primary movements. So let us say that I have a tumor up at the top near the number three. That part of the brain may control, let us say movement of the shoulder and I'll start having jerks of the shoulder. If they have focal aware seizures, I'll have jerks of the shoulder, on the contralateral side. So we're looking at the left side of the brain, if the number three is affected, I'll start jerking my right shoulder and I may be completely aware. If on the other hand, we move to number nine in the blue area, that is an area that's responsible for sensation, touching, scratching, pain. So if I have, let's say, an infection, abscess in this area, I will start having abnormal sensation, let us say tingling in the right shoulder again.

The symptoms depend on the part of the brain that's affected. It can be motor, it can be twitching of the thumb, it can be sensory, it can be tingling in the thumb, it can be further forward in the frontal part of the brain that controls more complex movements. So let's say I have had head trauma and I have had injury to the red part of the brain that says frontal lobe. Well, that part of the brain controls complex movements and I may start having bicycling movements of my legs, having strange movements and maybe hollering, having strange symptoms. Or let us say that I have had head injury or stroke in this back part of the brain called occipital lobe. Well, that's responsible for vision. So I may see flashing lights, or I may see zigzag lines, or I may see formed images. As Laura said, a common site of seizures is the temporal lobe. Here is the outside of the temporal lobe and it does a number of things. It processes speech, hearing, and a number of other things.

As it happens, in the area that's marked number two is where you process hearing. I may start hearing unusual things if I have, let us say again a tumor, in this part of area labeled number two, I may hear ringing in my ear or I may hear voices. These are the symptoms that come from here. If on the other hand, if you go to the right bottom part and you look at the green part, that is the temporal lobe from below. The inside of the temporal lobe is here and that is involved in memory, for instance, so I may suddenly lose memory. It's also involved in processing of emotions and matching those emotions to memory. So commonly, if I have, let us say, trauma to this part of the brain, again, I may have seizures that may start with a feeling of sudden deep depression, doom and gloom. Everything turns black, not because I have depression in general, but because the part of the brain that is responsible for processing emotion suddenly goes haywire.

You can see this yellow string here in the red, that's the olfactory bulb, that's responsible for carrying information about smell. A common symptom in this part of the brain, again, the inside of the green, the inside of the temporal lobe is olfactory hallucinations. When you smell things that are not there, commonly unpleasant smells, burning rubber rancid butter, and that again is because of involvement of the inside of the temporal lobe, the green part of the brain we're looking at. So these symptoms depend on the part of the brain that's involved. In focal aware seizures, you will be completely aware. In temporal lobes that's relatively uncommon, and you'll often have impairment of consciousness and that will also happen more likely if you've got both hemispheres involved, for instance, in the parietal lobes. In both instances, the seizure which may start in, let us say, that number three that I've talked about earlier may spread. It may then spread to affect either adjacent part of the brain, let us say, area number nine or number nine.

In which case I go from jerking of the thumb to tingling of the thumb, or it may spread all over, in which case I'll lose consciousness and I may have convulsion.

If we could go to the next slide, Brandon, please. The duration of the seizures may last from seconds to minutes. Commonly after focal seizures the patient may feel tired, exhausted, may sleep, sometimes may have a headache. Sometimes after the seizure, the part of the brain that was involved most in the seizure maybe temporarily dysfunctional. So let us say that we started with the twitching of the right thumb. If that twitching is long, after the seizure, I may for a short time have weakness in that right thumb. As I mentioned before, the focal seizures may spread to affect all of the brain and become generalized. Next slide, Brandon, please. What are the triggers of focal seizures? This is an important point because while we may have causes for epilepsy, such as genetic alteration, or such as head trauma, not everybody with epilepsy has seizures all the time.

There are certain things that may further make it easier for that excitation of neurons to happen and lower the threshold for seizures. For reasons that we don't understand, all mammals have the capability to have seizures and it's a matter of threshold. If I have a rat and I put a rat in a chamber that I heat up to 109 degrees Fahrenheit, that rat will likely to have a seizure. If I, myself, put myself in that chamber and I turn the heat up to 112, I'll probably have a seizure also, I've never had a seizure before. If a patient with epilepsy goes into a heated area, they may have the seizure not at 112 or 109 degrees Fahrenheit, but at 101, so they have lowered seizure threshold. That's important in the way, we as patients with epilepsy, can regulate the danger for seizures because there are certain things that are predictable that can lower seizure threshold. They include stress, both emotional and less so physical. They include lack of sleep. Sleep deprivation is very important. Between these two things, they impact roughly half of all seizures.

So not half of epilepsy, they're not a cause of epilepsy. But in patients with epilepsy, when these things are active, when you're under stress, when you're sleep deprived, the threshold for seizures is lower and you're more likely to have seizures. Fever and illness that I mentioned before, hormonal changes, for reasons that are not perfectly understood, there is an increased risk for seizures in certain situations, particularly in women. Those situations may include for the initiation of reproductive life, menarche, much of epilepsy in women with epilepsy starts at menarche, disproportionately so. You may have seizures clustered, round menstrual cycle, not only but maybe more commonly around certain parts of the cycle, most commonly per menstruation. And you may have alteration of seizures both during pregnancy and during menopause. Alcohol and drug use are common triggers of seizures. So if I have epilepsy, I've had no seizures for two years and I go and have a pint of bourbon tonight, I have a much higher risk of having seizures tomorrow morning than if I either don't drink or if I have one beer. And then really importantly, missing medications.

Not taking medications is something that's not unique to patients with epilepsy, it goes across all diseases, all patients, all parts of the world. When you take all diseases, all patients, all parts of the world, roughly a quarter to a third of lack of control of a disease comes down to not taking medications, not necessarily because of patient's fault. Let's say the pharmacy doesn't have it, or let's say the doctor doesn't prescribe it on time, or the patient travels and doesn't take it with them. This is a really important thing that both the healthcare providers and the patients can work on to minimize the seizures that may occur as a result of this. In every clinic that I have, there is one, two, three, four patients whom I'm seeing emergently because they've had a seizure because something happened with medications. That's an important aspect that we can control. Next slide please, Brandon. And then there are others. Certain medications can lower seizure threshold, notoriously for psychiatric diseases, Wellbutrin is one of them. Certain antibiotics can do it and some over-rhe-counter medications that the doctor may not know about can do it.

Most notoriously medications such as Benadryl or Dramamine, so the antihistaminergics, Robitussin for cough and some of the decongestants like pseudofed or ephedra. And then in patients with diabetes, low blood sugar can trigger seizures as can severe high blood sugar. Dehydration can do so, low sodium. If you've got epilepsy and you're running a marathon, make sure that you drink plenty of Gatorade and get enough sodium so that your sodium doesn't get low and you're not at risk for having seizures from that. And then a minor head trauma in somebody who's got epilepsy can also trigger seizures. Brandon, next slide, please. This is a graph showing the proportion of seizures that were related to specific triggers in two studies, one done at Yale back in the 1980s and one done by our group in 2000. It shows you that roughly 25%, the red column on the left, of seizures are triggered by missed medications. The most common cause is stress. In these two studies, up to 80% of all seizures were related to stress. Sleep loss over 50%, and then menstruation and alcohol that I mentioned before.

These are things that are important to bear in mind. I've spent quite some time on it because we are in charge of our lives to a certain degree and some of these things are potentially avoidable. Next slide, Brandon, please. What are the goals of treatment of focal seizures? They are two, no seizures and no side effects. If you've got a cause that you can treat, then treat the cause also. Next slide, please. The treatment options include anti-seizure medications. They include surgery where you remove the seizure focus. Let's say you've got a brain tumor that's causing the seizures, you remove the brain tumor, the seizures may stop, or you may have a seizure focus without an obvious cause. If you know where it is and you can remove it, the seizures may then stop. You may have other surgical treatment with neurostimulation devices such as vagal nerve stimulation, such as D brain stimulation where you put up an electrode inside

part of the brain called thalamus, or responsive neurostimulation where that acts very much like a cardiac pacemaker.

You find where the seizure focus is coming from, then you put a sensor on that part of the brain which senses the seizure very early, within seconds, and then stimulates that part of the brain, again, very early to stop the seizure before it spreads and becomes symptomatic. Ketogenic dietary treatment has been of interest. Ketogenic diets can be very helpful in controlling seizures and there's a number of them. And then lifestyle, which means modifying those seizures triggers that I mentioned before. Next slide, please. So non-drug treatments, again, to go back to the triggers that I mentioned, sleep deprivation. So how can you modify seizures by focusing on sleep deprivation? Sometimes it's very difficult. You may have insomnia. The insomnia is hard to treat and you are sleep deprived. You're stress because of any number of reasons, including seizures and you can't sleep because of that. But sometimes it can be dealt with relatively simply. Think of somebody who works night shift, typically a nurse and when she or he works at night shift, they don't get enough sleep. Furthermore, if the night shift alternates with day shift, the sleep pattern may be totally irregular.

If that person is sensitive to sleep deprivation with their seizures, then you may have seizures simply because of the work conditions. A simple solution there is to have the employer allow that particular person not to work night shift, but just work a day shift. I've taken nurses as an example because it's an obvious example, but you may have the same thing with other professions. Stress, a little more difficult to control, but I think it's worth dwelling on. Trying to steer your life so as to reduce stress, external stress is number one, and to find a way of coping with them internally number two. Stress is a composition of two things, it's the external environment pressing on us, number one, and it's the way we cope with that pressure, number two. Insofar as we can alter our way of reacting to the external environment that can help and insofar as we can alter the external environment, that can also help. Think of another situation with stress at work because of an unpleasant boss and how much stress that leads to seizure exacerbation.

Well, change your job or change the boss and you may improve your seizures. Fever, so I suggest to patients with epilepsy to take fever-lowering medications, most typically Tylenol, around the clock when they have an infection. We mentioned alcohol and recreational drugs and we mentioned menstruation. Next slide, please. Moving on to seizure medications. This is the development of anti-seizure medications starting in 1858 with bromides. You can see that starting in 1980 when everything turns green, there's been a huge number of new medications, over 20 new medications since 1990. So one new medication every 18 months or so. It said we have a large number of medications to choose from and that is a great thing. Next slide, please. The commonly used

medications for focal seizures include Levetiracetam and it's second generation follow up, brivaracetam, lamotrigine, lacosamide, Oxcarbazepine, eslicarbazepine, and Carbamazepine. Those are medications that belong to the same family. Topiramate, zonisamide, perampanel, clobazam, a large number of other medications. Next slide, please.

By and large, when you use any of these medications as the first medication in somebody who has just started to have epilepsy, they are very similar in their efficacy and in the rate of side effects. Although, we tend to use some medications rather than others, really most of the medications are similarly effective in bringing about freedom from seizures when they are used as a first medication. That's shown in this slide just as an illustration. The left side part of the slide shows you the efficacy of the medications in terms of seizure freedom after use for one year and the right side shows you the side effects. You can see that different medications carbamazepine in red, gabapentin, yellow, lamotrigine, Topiramate, Oxcarbazepine in orange, they all have similar efficacy. Next slide, please. So how do we choose anti-seizure medications? There's a large number of things that factor into the choice, but I'm going to dwell just on a couple of them.

Comorbidity, because we have such a large number of medications to choose from ... next slide, please, Brandon ... we can tailor the potential benefits and side effects of a medication to a patient's particular profile. If you've got somebody who's completely healthy, they have no other diseases, then it doesn't matter. But let's say that you've got somebody who already has another condition, let's say migraines. It so happens that some medications have dual efficacy, both against seizures and against migraines. So in that patient those medications would be good to choose. Those two medications are topiramate and valproate. Let us say that somebody's got depression, medications that affect both mood and seizures include valproate, lamotrigine, carbamazepine, oxcarbazepine. So you might want to use those medications in somebody who's depressed. Or obesity, so there's a number of medications that can lead to weight loss. The two more commonly used ones are topiramate and zonisamide. So in somebody who has a weight problem, these two medications may be worth thinking about. I mentioned insomnia already, very common in the society, no less common amongst patients with epilepsy, roughly a quarter to third of all patients.

There are some medications that act as partial or complete hypnotics. They include the old fashioned anti-seizure medications, phenobarbital, pregabalin, gabapentin, perampanel amongst others. In the elderly you want to have medications that don't interact with other medications because elderly patients often have other diseases and other medications and you want to have medications that have the minimal possible side effects to affect other potential diseases of older age. These medications may include lamotrigine,

levetiracetam, oxycarbazepine. You have some other conditions that may be addressed by anti-seizure medications, another example of this is restless leg syndrome, which is well-treated with pregabalin and gabapentin. Another one is fibromyalgia, which is well-treated with pregabalin. If I could have the next slide please. And then you've got the side effect profile. Most anti-seizure medications have the propensity to cause certain side effects. These include tiredness, sleepiness, and dizziness. These are the three common side effects that every anti-seizure medication has the potential to induce. There isn't one that doesn't.

On top of that, you may have medications that may have specific side effects and then you want to select that medication to tailor the patient who has the potential for those side effects so that you avoid that medication. If I could to the next slide, Brandon, please. I mentioned behavioral abnormalities. Well, certain medications can make depression or anxiety worse, levetiracetam is one of them, perampanel is another, so you might want to avoid those medications in somebody who has got depression or anxiety. I mentioned obesity. Well, certain medications make you not lose weight but gain weight, Depakote, valproate, pregabalin and gabapentin. So if you've got somebody who is overweight or obese and if they have conditions related to obesity, you don't really want to start one of these medications for use of seizures. Some medications can cause renal stones like topiramate and zonisamide. So in patients who are risk for kidney stones, you want to avoid those. Osteoporosis is a common concern because you're taking the medications for a long time when you have epilepsy and some medications make thinning of bones more likely to happen. Thinning of bones is what osteoporosis is.

Those include the old-fashioned medications, phenobarbital, primidone, carbamazepine, phenytoin and Depakote. Diabetes, Depakote can make it worse so avoid it. Hyponatremia can be made worse in patients who have hypertension and are on certain medications and are then treated with oxcarbazepine, carbamazepine or eslicarbazepine, so avoid those. Next slide, please. So we use that first medication and as I told you, there's a similar likelihood of patient responding to that first medication. What happens if that first medication fails? Well, you can try a second medication, either adding it to the first medication or replacing the first medication. Next slide, please. So there have now been a number of sequences of one large study started in Scotland back in 1982 that has looked at the outcomes of patients who are newly diagnosed with epilepsy and are treated with anti-seizure medications. The researchers looked at the proportion of patients who become seizure-free with treatment. Seizure freedom was defined in this study as no seizures for one year or longer. They've done this study now for 35 years and they looked at proportion of patients who become seizure-free were the first medication. That's the blue part of the pie.

On the left side you've got the patients who were evaluated between 1982 and 1997 and 47% of those patients became seizure-free were the first anti-seizure medications. On the right side you've got patients evaluated between 1982 and 2014, so another 20 years, and you can see that the proportion of patients, blue part of the chart, who are seizure-free after the first medication is almost the same 46%. So if you've no change with all these 20 new medications in the proportion of patients who become free of seizures after the first medication, about 45%. Now, the orange part of both pies shows you the proportion of patients who become seizure-free with a second medication, which is roughly 11 to 13%. And then you've got a third medication in gray, 1 to 4%. And after that any number of medication has a reducing likelihood of becoming seizure-free. So the slide and the study shows you that if you fail the first medication there is a reasonable chance, but much decreased, that you'll have control of the seizures with the second medication, but if you fail two medications, it becomes a struggle.

Next slide please. This is an elaboration on that theme. There is a difference in the likelihood of you becoming seizure-free after the first medications failed. Depending on whether the medication failed because of side effects, when you still got about 40% likelihood of becoming seizure-free with the next medication, the second medication, or if the first medication failed because it was just not effective. In which case you've got a roughly 11% likelihood of becoming free of seizures with subsequent medications. Next slide, Brandon, please. So what happens if two medications fail? If you've failed two medications, you really should see an epilepsy specialist. Why? Because there may be things that may have been missed and there may be things that may need different treatment. So things that may have been missed, maybe the diagnosis is wrong, maybe these spells are not seizures. How do you find out? You do long-term EEG monitoring with video to put together the behavior and the electrical activity of the brain and you confirm the diagnosis or not.

This evaluation is done only by specialist centers, or if you've confirmed the diagnosis and the patient has not responded to medications, you want to know whether the seizures are in a part of the brain that could be treated surgically by removing the focus of the seizures. In which case with some parts of the brain there is a relatively high rate of curing epilepsy. If you've got seizures coming from temporal lobe that don't impair other functioning of the brain and you remove that part of the brain, you may have 60, 70% likelihood of becoming free of seizures. That's something very well worth knowing and it's better to evaluate this early in the disease than later. Next slide, please. This brings us to the drug-resistant epilepsy. The definition of drug-resistant epilepsy is failure of an adequate trial of two tolerated appropriately chosen and used anti-seizure medications either as monotherapy or in combination to achieve sustained seizure freedom, which is defined usually as 12 months or longer. Next slide

please. The mechanisms of drug-resistant epilepsy are unknown. That's the large print. You don't need to read the small print.

We don't know what causes it, which makes it difficult to treat. Next slide, please. Before 2020, the options for treatment of drug-resistant epilepsy were as follows. Next, if you could run through the slide, Brandon, please. So more anti-seizure medications than evaluation in epilepsy monitoring unit, pre-surgical evaluation and treating the triggers, neurostimulation, diet, and then participation in new treatment studies. Next slide, please. In 2020, there were two medications that were approved that have really changed the responsiveness of patients with certain types of seizures that have previously been refractory to treatment. For focal seizures, that medication is Cenobamate. For a group of patients with a genetic disease called Dravet disease, that medication is Fenfluramine. Next slide, please. So a few words about Cenobamate. This is a slide from a study that was done to evaluate the efficacy of Cenobamate in patients with focal seizures who did not respond to other medications and were treated with other medications at the same time.

The way these studies are done is that you have patients who have uncontrolled seizures, they're on certain medications, you count the seizures over a period of four to eight weeks as baseline, and then the patient is randomized to get either placebo or the new medication in a way that neither the patient nor the investigator knows. So it's blinded. And then you treat the patient with either the placebo or the medication in dose A or B or C for a certain period of time, typically 16 weeks, and you compare seizure frequency on the new treatment versus placebo compared to the baseline. This slide shows you what happened with Cenobamate. I'd like you to look at just the right end where the blue arrow is. It shows you seizure-freedom during 12 weeks of treatment with full dose of Cenobamate. Patients who are in the placebo arm are blue and 1% of those patients became seizure-free, which is pretty interesting. Orange shows you patients who are treated with 100 milligrams per day of Cenobamate, gray, 200 milligrams, and pale orange or yellow, patients who are treated with 400 milligrams of Cenobamate per day.

You see that about 20% of patients treated with 400 milligrams per day become seizure-free. When you move to the red arrow, you're looking at 90% seizure frequency reduction and almost 30% of patients have that degree of seizure frequency reduction. Next part of the slide. This has been compared, not head-to-head, but historically with other medications that were evaluated in similar studies, so placebo randomized controlled studies. The response of seizure-freedom with Cenobamate, which is to the right side of the slide, is significantly higher in this indirect comparison then response to other medications that have been approved since 1990. Next slide, please. The effect is long-standing. We did a study that looked at the efficacy over a period of up to four and a half years, and looking at the last year of the study, 10% of patients were still

seizure-free, so that's roughly four years after they started Cenobamate. On the right side of the slide, about 24% of patients had 90% seizure frequency reduction over that period of time during the last year of the study. 90% seizure frequency reduction includes both patients who have real bona fide seizures.

It also includes people who may not have taken the medication because of any number of reasons, and it may include patients who are exposed to seizure triggers such as alcohol and drugs. These results are long-lasting for most patients. Next slide, please. Next slide, please. Next slide, please. What are the side effects of Cenobamate? The common ones are the three that I mentioned before, so tiredness, dizziness, sleepiness. You may then have medications that there's side effects that are also relatively common, double vision, unsteadiness, poor balance, nausea. These occur in roughly 10 to 15% of patients. In all instances, the higher the dose of Cenobamate, the more likely it is to have the side effects, particularly when you increase the dose from 200 to 400 milligrams per day, less so when you increase the dose from a 100 to 200 milligrams per day dose. In the first roughly 1,000 individuals that were exposed to the drug, there was a side effect called drug reaction with eosinophilia and systemic symptoms.

That is a severe condition that can be associated with death, and in fact, one individual did die, that led to a reevaluation of the whole program. Next slide please. All these patients were studied at a relatively high dose of Cenobamate 50 milligrams and the dose was increased fast every week. A different approach was taken where in the next large study that looked at this issue and safety in general, the starting dose was much lower, 12.5 milligrams, and the increase in the dose was much slower, every two weeks. In that study, which had just under 1,400 patients, there were no further cases of [inaudible 00:45:43]. The side effects were similar. Roughly 11% of patients stopped the medication because of side effects. The side effects that we did see were similar to the ones I just showed you, so the commonest ones were sleepiness, dizziness and tiredness followed by some of the others. Next slide, please. So interestingly, amongst all the patients that were evaluated in the program that led to approval of Cenobamate in the clinical development, there was a study that looked at the rate of sudden unexplained death in epilepsy.

As you know, this is a condition of great concern where a patient with epilepsy may die because of causes that are not related to anything other than epilepsy. It may happen at the end of a seizure, it may happen in unknown circumstances, but there's no other explanation of death. It is a condition that increases in its incidence with severity of epilepsy, particularly with severity of the generalized seizures that may start as focal seizures. Well, in the study that the company did with Cenobamate, SUDEP rates where at the same rate as amongst patients who have controlled epilepsy. So if you take patients who have badly uncontrolled epilepsy, the rate of SUDEP may be 10 or 15 in 1,000 patient years.

So think of it as, yeah, 1 in 100 patients that use [inaudible 00:47:28] in a number of years. So Cenobamate appears to reduce that risk. If this turns out to be true, it's a major new improvement in treatment of epilepsy. Next slide, please.

One reason for that may be because Cenobamate was particularly effective in controlling the that are focal to start with and then generalize. Those are the seizures that carry the highest risk of SUDEP. In a study that evaluated seizures by the seizure type, there was a 90% reduction in the seizures with secondary generalization. So focal seizures that became bilateral tonic-clonic seizures in patients who are treated with Cenobamate. I think we'll skip the rest of the slides and just go to the answer that we have time for questions. I think I've ran over my time a little bit, so I apologize for that. But thank you for listening.

Dr. Laura Lubbers: Thank you so much, Pavel. Thank you, that was a very rich presentation. It was great to hear about how seizures evolve and how they impact a person based on where in the brain they're starting. So thank you so much for all of that information. I know we already have a couple of questions in the Q&A. We can start there. If others have questions, please go ahead and put them in the Q&A panel and click send and we will get them. So we will start with Juan. The question is, "Are there any things to consider for a female who is planning pregnancy and is currently on Felbamate and Clobazam medications?"

Dr. Pavel Klein: Gosh, that's a very tough question. So the question, if I understand it correctly, is really asking what is the danger of number one, Felbamate and Clobazam to the baby, number two, of stopping those medications to the mother? The answer is very difficult, basically not known. So for Felbamate, we really do not have enough information to say whether it has the potential to damage the baby or not. For Clobazam, the data so far doesn't show any red flags. So for Clobazam it's not extensive data, but there is data and it has shown no red flags. Generally speaking, if you've had epilepsy that has been uncontrolled and has required medications that have not so commonly used like Felbamate, then the most important consideration is what would happen to your epilepsy if you change the medications. If there's a possibility that your epilepsy would get worse, then my advice would be not to change the medications.

It's a very difficult question, but we think that there are certain medications where we know there is a potential for risk to the fetus. These medications are valproate or Depakote, two names for the same medication, phenobarbital, and then to a lesser degree some other medications like Topiramate and others. With the exception of these two medications, valproate and phenobarbital, the most important consideration is still the control of seizures during pregnancy because if you have a generalized seizure during pregnancy, there is potential for harm to both yourself and the baby. That is of paramount importance. The other thing to consider is to plan for the pregnancy well in advance and consult

with your doctor, whoever he or she is, a healthcare provider, but do it in advance so that you're not caught unawares.

Dr. Laura Lubbers: Thank you. Pavel, we've got a few other questions that have come in. I know we've only got a couple more minutes and some of these are complex. They're always interesting questions. Here's one, and we may or may not know anything about this, but, "What are your thoughts on cord blood stem cells as an experimental treatment for epilepsy?"

Dr. Pavel Klein: Really exciting and really unknown. There is a number of studies that are looking at this in animals as [inaudible 00:52:25]. There's a large number of studies. There's one human study that's not looking at directly at stem cells, but is looking at taking cells, manipulating them to become new neurons with specific function and then injecting those neurons in part of the brain to see whether they could modify seizures. It's a very exciting area and there really isn't any information at the moment.

Dr. Laura Lubbers: Right, but exciting things ahead. I think there's really novel things out there. Again, there are other questions. I'm going to skip a couple of questions and go to one, because I know it's in your sweet spot. "After a traumatic brain injury that causes focal motor seizures, is it common for a person to develop additional types of focal seizures decades later?"

Dr. Pavel Klein: Yes, it can. I don't know whether I would say common because it hasn't been mapped out, but can it occur, it can. So when you have the injury, I mentioned before that the brain adapts. The primary purpose of brain adaptation is to clear the debris and repurpose the brain to take over the functions of the part of the brain that was destroyed. In the plastic changes, there may be missteps that may lead to seizures. If those seizures happen, the seizures themselves, as well as adaptation to the injury, may alter other parts of the brain remote from the area where the seizures occurred. So not uncommonly, you may start with an injury in frontal or parietal lobe and just like you said, decades later, have seizures that are occurring in both there and in temporal lobe.

Dr. Laura Lubbers: Thank you, Pavel. So I think we're going to wrap it up. I know that there's some additional questions and we'll see if we can get those addressed in other ways, have to do with metabolic disorders, and the fundamental question of how do seizures start. I think that is still an open question in many cases. But I want to thank you Pavel, Dr. Klein, you're always informative, gave a lot of information to our audience today. Thank you so much for that. And thank you to our audience members for attending and always asking great questions. If anybody has additional questions on the topic or wants to learn more about any of the CURE Epilepsy research programs or webinars, please visit our website or email us at research@cureepilepsy.org. Please go to our website at cureepilepsy.org to learn more. You'll probably get an email informing you of this opportunity as

well. So please keep a lookout for that. Once again, thank you all. Have a wonderful day and weekend. And once again, Pavel, thank you.

Dr. Pavel Klein: Thank you everybody for joining us this afternoon and thank you, Laura.