CURE Epilepsy Treatment Talk
Seizure Emergencies
(Transcript)

Dr. James Wheless: Hi, my name is Dr. Jim Wheless. I'm professor and Chief of Pediatric Neurology at the University of Tennessee Health Science Center and Director of the Le Bonheur Comprehensive Epilepsy Program at Le Bonheur Children's Hospital in Memphis, Tennessee. I'm excited today for this opportunity to update you on treatment of seizure emergencies that happen outside of the hospital setting, so at home, work, or school. And grateful for the opportunity to do this on behalf of CURE Epilepsy. I hope you'll find this information helpful to you as you help take care of your loved ones or treat your own seizures.

Let me just start with laying some groundwork because I think many may not appreciate how big a change this is and how we approach treatments for patients with epilepsy. In the past, when we would treat patients who had epilepsy, they would take medicine regularly. The ideal was that their seizures would be stopped with the medicine, they'd be seizure free, they could go about their normal activities for them. Some patients, unfortunately, could not achieve that goal. Even with best treatment, they could have intermittent seizures and sometimes have what I'll call a bad day, where they could have multiple seizures or seizures that were stronger, longer, worse than their normal seizures.

In the past, they were stuck. They either just stayed at home and kind of rode it out. Unfortunately, we had patients that did that or they went to local hospital for emergency treatment. We really did not have great at-home options that were embraced by our patients that suffered from these kinds of seizure emergencies. In the modern era, we've had intranasal treatments, and I'll talk about those that have really changed how we approach patients with epilepsy. Now we have medicines they can take daily to prevent them from having seizures, but if they happen to have an uptick in their seizures or have this bad day, they have a nasal rescue medication they can use only on those days to stop the seizures that are occurring.

And this is a huge shift in how we approach these folks. And I'll give you the example of say you drive around in your car, you have a spare tire in case you have a bad day and you have a flat. But for most of us, we hope we never use it. I would say that's the same approach here. Now, for our many patients with epilepsy, we can have a backup treatment for if they have this bad day, have a seizure emergency, and they can keep it with them. Our hope is they don't need to use it, but if they do, they have an effective treatment to stop the emergency.

With that background, let's talk a little bit about what we understand about these, maybe clarify a little bit more what I'm talking about. Then we'll quickly get into what are these new treatments. If we look at seizure emergencies, I've alluded to this a little bit. Most of our patients, they may be seizure-free or they may have an occasional seizure, but it's their typical seizure. It may last a minute, minute and a half, two minutes. It's their normal seizure. It's not longer,

it's not worse. Their recovery is the same. But we have patients that say, "I have days where I have my typical seizure, but then 30 minutes later or two hours later, I have another seizure. I know if I have two that day, if I don't do something, I'm going to have three or four. I just have a really bad day. There may be a trigger, but there may not be a trigger. I just have a bad day."

These are called seizure clusters or seizures that repeat in a day. Another term is acute repetitive seizures, but I like the term better seizure clusters or seizures that repeat close together. I think that's easier for all of us to get our head around. This is unfortunately more common than we would like. If we look in the United States, it's estimates that upwards of three and a half million people have epilepsy. Many of those can do well with current treatments, but we know a lot of people have ongoing seizures. Of those people with ongoing seizures, that's the group at higher risk to have this cluster or this bad day where they have a seizure emergency. There are estimates that up to 170,000, I think this is probably low, I think it could be upwards of a quarter billion people, have these seizure emergencies and they need something they can do without going to the hospital.

In the modern era, we have pretty good data on what these emergency looks like because patients have electronic diaries that they can keep. That helps me, when patients come to see me in clinic, to look at when their seizures are occurring. But it also helps when we look at what happens on their bad days. If we look and we count the bad days as they've had two or more seizures in a day, most patients will not do this. We know there are some, but patients that have convulsive seizures or prolonged focal seizures, but two or more in a day, how are they spread out during the day? And that's on the right side of the slide here. We see that for some of the patients, they're really close together. They're in that first hour or two. They have a seizure, they just barely recover, they have another seizure, they may recover, fall asleep, have another one.

But there are some people that have a seizure and they may have four hours, six hours, 10 hours, they'll have another one, four or six hours have another one. They have a bad day, but theirs are spread out more. When we develop kind of treatments to use at home to interrupt this, ideally we'd like it to work fast. For the people that have their seizures close together, it helps them. But we like it to last for 24 hours also in their system for the people that are spread out more. So we can use one treatment for no matter what the pattern is to your seizure cluster. That's the goal. We develop therapies to do this and where we've gone.

I mentioned in the past we were really limited with our options. Before 1997, we really had no options other than maybe take an extra dose of your medicine, try a pill form of medicine that you see in the middle of the slide here and that might work. But for the pill form to work, my patients had to recover enough between seizures to be able to swallow. If it happened in the middle of the night, they might fall back asleep. That was a problem. If they were too close together, sometimes they weren't recovered enough between seizures to be able to swallow safely. Before 1997, we were stuck with what's on the right side

of the slide here. They had to go literally to the hospital and get to intravenous drip so the tubing connected directly to the blood vessel or get a shot of medicine.

In 1997, we had approval of Diastat, diazepam rectal gel. It was a gel that was given by a large syringe. The patient bought them. That was fine for many young children, but as we got into school-aged children, adolescents and adults, it just, for many of our patients, was socially unacceptable. And because of that, if we looked at our patients with seizure clusters, at least 80% of them did not have any treatment available because they really did not want to use that treatment.

That led to, "Where do we go from here? How do we get past this point?" The medicines that we refer to as benzodiazepines is the group of medicines that we will use for rescue therapy and that all of our new rescue therapies kind of fall under this class. The reason being because they're very effective to interrupt seizure emergencies. That's what happens if you go to the hospital and you're having the worst emergency, which is status epilepticus, where you're having just one continuous seizure with no interruption, that's not stopping, that's life-threatening, that's the medicine that they give you in the emergency room or in the ambulance. These are the same type medicines that we know we'll use for seizure emergencies at home. They're our best options. They work quickly for this. We can't use them every day, but for emergencies, they work really well and we know their safety.

Diazepam is one of these medicines that we use. The rectal gel, like I said, Diastat, was available in '97, you see in the upper left here. Within a couple years of that product being on the market, we knew that there were many patients that it wasn't acceptable. And we thought the intranasal product that you see at the bottom left, that if we had a nose spray that you could hold up in just a single dose that you didn't have to breathe in, it didn't require any patient cooperation that that would be one of the ideal therapies. We'll talk about that. That's been developed and now has been in the market a couple of years.

The US military and other militaries carry with them this intramuscular diazepam. It's a shot formulation that's given much like an EpiPen. This is only for military use, not civilian use, so we don't have that available. And then we'll see, this is a product that's been tested but not in the market yet. It may or may not make it to the market, but it looks much like a Listerine film that you would put outside the teeth but in the mouth that would dissolve quickly to get the medicine in the system.

As we sit here today, the two that are available for routine use are the ones on the left side and the nose spray, obviously, is the one we're going to talk about. Let me just remind you of how we got to that point. If we look at diazepam, we know when you come to the hospital and you're having a seizure emergency, the status epilepticus is the purple dotted line. If we give it in the IV, we achieve very high levels quickly because giving it right in your blood vessel, it gets to the brain almost immediately from the bloodstream and we stop the seizures.

But we also know if we achieve these high levels almost instantaneously, like you see on the slide, that there's a chance of that interfering with breathing, which is why we only give the IV form in a hospital setting. If we give the rectal solution, the Diastat, which is this orange line here, you can see that we don't get that high peak. It's a lower and it's much smoother, so we avoid with both the nose spray and the rectal spray concerns about affecting breathing. And I can tell you the rectal dose has been given in millions of patients, the nose spray has been given to tens of thousands of patients, and we have no respiratory problems associated with it. We can feel reassured from that that it won't affect our breathing as well.

This is the injection that the military has. You can see outlined here much like an EpiPen. I'm not going to go into that in detail, because it's only military use. This is the film that we'll see if it's developed. You can see it's almost like a Listerine film. It has the chemical, in this case we'd say diazepam, embedded in this film that dissolves the soon as it hits the saliva. We'll see that product may or may not eventually be available on the market.

Let's look a little bit more why the idea of a nose spray is so attractive for seizure emergencies. The first one's the obvious one, which is that it's easy to get to everybody's nose. It's socially acceptable, if you will. And the key in what took so long to develop a nose spray is we have to give the solution in this teeny little area up here, it has to be what we call a hundred microliters. It's a teeny volume. This is the equivalent of two drops of liquid. If you take two little dropper fulls... Not dropper fulls, drops, actually. The medicine has to be contained in that teeny little amount of liquid so that when it's made into a mist, that's all the liquid this area can handle.

That was the challenge in developing a nose spray. We knew the medicine we had to get in it, but figuring out how to put that medicine into a liquid that was that teeny, so you could take it as a nose spray and be safe, was the hurdle. Thankfully, that hurdle's been overcome. We have our first intranasal diazepam product. Its brand name is VALTOCO. As we sit here today, this is approved for children, adolescents, and adults age six and above. There are ongoing studies now down to age two. Those, so far, have looked safe and promising, so I suspect in the future it will be available down to age two, but that's not there yet.

But this is the nose spray. You can see it's a very simple device. We'll walk you through how that works and how you use it. It's a single dose nose spray. The key is, I mentioned, it has diazepam in it. That's our benzodiazepine that stops the seizure. How do we get it in that teeny amount of liquid? This is very hard to put in liquid. It had to be dissolved in vitamin E, a teeny amount of vitamin E. And if you think about it, many of us use vitamin E-containing skin creams, sometimes even lip balm that have some vitamin E. Vitamin E is very safe to have on your skin or even have on your membrane the inside of your nose, teeny amounts.

And that helps us get the diazepam into that little bit of liquid. Intravail is the brand name for what allows that liquid to be so teeny that it makes a mist and gets from the nose into the bloodstream. We spray in the nose. This is what I kiddingly call the secret sauce. It's the equivalent of that in the Big Mac. It's what allows, when you get the medicine, once it's placed in the nose to go from the surface of the nose to the bloodstream and then directly to the brain. It's totally safe. There's no toxicities to this medicine, so it's an ideal way to do this.

We looked at this once the product was formed, we were allowed to give this to patients that had epilepsy that occasionally had seizure clusters as we talked about, allow them to use it and say, "Does it work as well as we wanted it to work?" Does it stop the cluster? And remember, we wanted to stop it for a full day so our patient can recover and not have the constant seizures. And what we see is when we gave a single dose, if we track folks out four hours, six hours, eight hours, 12 hours, even 24, a full day after the single dose, that a single dose, that was all that was needed. We go out 24 hours in 86% of patients.

Yes, there were a few patients that needed a second dose. They went four hours or six hours and then their cluster started back. If they needed it, that was fine. It's totally safe. But for most patients, a single dose interrupted the cluster. It worked very well. It was tolerated very well. Some folks said they got a little feeling of congestion in their nose. Some folks said they had the feeling they had to blow their nose afterwards. Some maybe had a little bit of a taste in their back of their throat. But overall, it was very well tolerated. And as I said, no problems with breathing at all.

Here are the side effects that we saw. You could see they're pretty uncommon. The nasal discomfort or congestion just from the medicine. Some folks had a little bit of, they would blow their nose afterwards and have a little bit of blood on the tissue, so that could occur. But in general, it was very well tolerated and it did what it was supposed to do.

How do we administer this drug? You can see the device here, it's very simple. It has the plunger here or what I call the trigger, whatever you want to call it. But that's what activates and delivers the drugs. You hold it up to the patient. In this cartoon, our patient's lying down, but they don't have to be. If they're sitting up like I am and they went into the seizure, you could just... Their head will be back, you could put it up to their head and just hit the plunger. As soon as you do that, it's delivered the drug into the nose. It's literally instantaneous.

The device just has to be into their nose a little bit, it doesn't have to be all the way up. The patient does not have to breathe in, so there's no requirement for the patient to help, if you will. If they're still too tired after the seizure or still in the seizure, they can get the medicine. It will work okay. It'll still get in. And what we see typically... Patients vary. We have some patients that have had a couple seizures, they take the medicine, they may take a short nap afterwards, 30 minutes, an hour, most recover by then. But I certainly have had plenty of patients that the parents say they give it and a few minutes they're up and

around back to their normal routine. There's variability in that, but it's very effective in stopping the seizures.

The other medicine that's been used as a medicine called midazolam that you may have heard of, this is the medicine that's often used. It goes by a brand name, Seizalam. If the ambulance picks you up and you're having continuous seizures and they give you a shot, this is the medicine in that shot to stop it. In Europe, they have a liquid formulation that you can see here that they give between the gum and the teeth. This is not available in the US, I just mentioned it here because you may see it online if you Google it.

Other than the shot formulation, we have a nose spray of the same medicine. It's called NAYZILAM. It also is in the same exact nasal device administer. It's the same exact plunger. You hit your finger here, you put it up to the nose and it delivers the dose. Very similar, very similar side effects to we just talked about. No respiratory, same side effects. A little bit of maybe runny nose, nose congestion. But patients that took this, if you can see, the vast majority were back to what they were doing before the seizure cluster within an hour and a half. Very quick recovery.

With all of our benzodiazepines, whether it's diazepam I talked about or midazolam, we do not combine them with patients that are on opioids. That combination can affect breathing, which is not good to do when you're at home. If they're on opioids for any kind of chronic pain condition, then obviously we're not using these type of rescues.

This comes, you can see here, same device. The box has two doses, and again, just like VALTOCO we talked about, we start off here with a single dose. For most patients, that was effective. If they give a single dose and the cluster either continues or starts back a couple hours later, they can get the second dose. It's totally safe to do that, as well. We're aware of that in many patients. The key with our benzodiazepines is to not under-dose them. We know from studies in huge number of adults, you can see in adolescents, almost 500 patients here, that when they show up to the emergency room, the biggest problem we have is was when we look at doses that are given is they're too low. The seizures continue because people don't give an adequate dose. And we know if you're having continuous seizures, the seizure itself can cause a host of medical problems. We want to make sure we give the correct dose for whichever one of these intranasal products we use, that we use it upfront when it's appropriate, and if we need to repeat it, we repeat it.

I thank you for your attention. I hope this has been helpful. In my mind, I think this has really changed how we approach treating our patients with epilepsy because now we think about what's their regular, what I would call chronic treatment. What treatment did they take every day? And then their other treatment is what's their emergency or backup treatment for when they have these bad days. And almost every patient with epilepsy, you're going to be on a regular treatment, but you also should have an emergent treatment so you have

it available when you need it. It's always better to be prepared for an emergency before it occurs, rather than be in the middle of it, trying to figure out what you're going to do. I'd encourage you to talk to your doctors to have a seizure action plan. And now you'll hear from one of my patients' mothers who will talk to you about her experience with using intranasal diazepam or VALTOCO for treatment of her daughter's seizure emergencies.

Karen Barnette: Hi, my name is Karen Barnett. My daughter Claire Barnett was diagnosed with Dravet syndrome at the age of four. And I would like to thank Dr. Wheless and CURE Epilepsy for inviting me to be a part of this talk. My daughter, Claire, she is 18 now. She is a senior at our local high school and she is going to walk at graduation in May of next year. We're very excited about that. At the age of six months, she had her first seizure. We had a normal pregnancy, we had normal delivery, and the evening of her six-month immunizations, she had a seizure. Obviously, it was very shocking to me. I was home alone, my husband was at work, and I called 911. And of course, she was out of the seizure by the time they got there. But we went to the pediatrician the next day and he said, "It's probably just a reaction to one of the immunizations."

I remember looking at him and asking, "So this isn't going to happen again?" And he was like, "No." I thought, "Ooh, okay, good. Just one of those random... It's listed in the possible side effects. And it just was one of those things that happened to us and it won't happen again." And so we carried on. A few weeks later, in October, we were at my parents' house and she had another seizure. We went to Le Bonheur, the local children's hospital in this area, and we knew we were dealing with some sort of epilepsy, some sort of seizure disorder. We got referred to the neurology department at Le Bonheur in Memphis, Tennessee. And we started seeing Dave Clark, who I've seen actually on CURE Epilepsy talks before. And he started working with us and started trying medications and different treatments.

We were not having any luck with the medications, and she would have all sorts of seizures. She would've absent seizures, she would have tonic-clonic seizures, and otherwise developing normally. But we just kept trying for probably... Let's see, we started seeing him at seven months, probably two years later. He said, "I'm Dr. Clark. I'm working with some other neurologist in..." I believe it was Australia. "On a Dravet syndrome research study." And he said, "I think she might have this genetic abnormality, this genetic mutation disorder." And because of the triggers that we were seeing in Claire... Anytime she was very excited and overstimulated, just going outside. We thought maybe it was something to do with sunlight. We noticed it a lot right after a bath. And he said, "I think one of the main triggers for Dravet is that the brain can't regulate a quick change in temperature."

So going from a warm bathroom to a cold... Maybe the air conditioning's on or the fan's running. Going from a cold inside to warm outside, or a warm bath to a cold room, she couldn't regulate. And he said, "I think she might have this genetic disorder." They tested her for it, and sure enough, hers was a

spontaneous mutation, so... Sigh of relief, it wasn't something that we passed down to her. But he said she has the SCN1A mutation, and that was just a game changer because he knew immediately what medications were going to help and which ones weren't. We started seeing much longer breaks in seizures, which allowed her to progress with things like speech and motor development.

At that point, it just took over our whole family, but she was our only child at the time. We did have a son three years later, who is a typical developing. We just had to learn how to work around what we thought would trigger her and letting her have some freedom, versus trying to want to keep her safe and seizure free. With any form of epilepsy, it can control your whole life and the life of your family. But it became our new normal was trying to keep her safe, trying to keep her in school as much as we could.

The types of seizures that Claire would have, she would have the full body, what they used to call grand mal seizures, the tonic-clonic where it just would take over her whole body. She would also have these, we called them flutters. Her eyes would just flutter. She would be playing with a toy and she would stop and her eyes would flutter and blink really fast. And then she would pick back up and keep doing what she was doing. We were dealing with all sorts of types of seizures.

At first, we would take her into the ER almost every time she had a seizure because they weren't so clustered that we were getting used to them and felt comfortable, and we didn't really know any better at that point. So we would take her to the ER at the children's hospital. And finally a doctor looked at us and I know ER doctors kind of have their own bedside manner sometimes, but he said, "You don't need to bring her in every time." We said she has a seizure disorder, she needs to be seen, or I remember us being very urgent about it. And he said, "She has a seizure disorder. She's going to have these. You don't have to bring her in every time. You can, but you don't have to."

And that's when the rescue medication topic came up, because they had prescribed rectal Diastat was what we were given. It was like a gel form of Valium, basically. And because she was a baby, you could inject it rectally and it wasn't an issue. And so figuring out when to use that versus is a seizure going to stop on its own? We don't want to just overuse this. And then when you do, you wonder is it going to be effective? But basically they said if she's having a seizure and it goes over a third minute, go ahead and administer this Diastat, and if it doesn't stop after five minutes, then call 911. They said, "You can call 911 anytime you want." But that was the blueprint we were given.

They would give us a prescription for, I think it was two rectal injection pins at a time. And in the beginning, we were burning through those things just all the time. She was having clusters of seizures. She would stop breathing, her lips would turn blue. It was just the scariest thing. We always knew she was coming out of it. She would take a deep breath in and then, I mean, she did the textbook... She was out asleep after a seizure. But we knew with that breathing

returning to normal, and the Diastat thankfully always came through. That was just part of normal life for a long time, was using that on top of all her other medications.

Dr. Clark moved to Texas. We were then shifted over to Dr. Wheless, who we still see, and that's one of his specialties. If you're going to be in that situation, we know we're in the best hands. A few years ago at an appointment with Dr. Wheless... He's always really, really good about talking things that are coming down the pipe, treatment-wise, whether it's studies that are being done, genetic therapies that are being developed. He's always looking at ways to improve Claire's quality of life, her seizure control.

A few years ago, he was discussing with me this new rescue medicine that was going to be available, and I just assumed it was going to be another rectal administration, or I didn't really know what to expect. And he said it was going to be a nasal medication. I really couldn't picture it. I didn't know what to expect. When we actually got it in hand, it's a small package and it's the rectal Diastat in this huge plastic case of medicine you have to carry around, so it is easier to just carry for the caretaker. And so at school, she has it in the little pink purse that she can wear on her at all times. It's very discreet that way and it's easy to get to.

As she gets older, having to use a rectal medication, it is difficult. Of course, she doesn't know the difference and she doesn't know obviously when it's happening, what's going on with her. But for the people around her, especially being in a high school and things, and I think it intimidates the caregivers a lot if they're not used to doing that. That's not something that everyone's comfortable doing. I'm certainly not a medical professional and I have to do these medical things with her that I just have to get comfortable with, but I'm her mom, so it's not a big deal. And so when you're leaving your child with a babysitter or at a church function or something, and you have these wonderful people that take great care of her, but you mention, "If she happens to have a seizure that goes into more than three minutes, you're going to need to have her where she's laying down and you can take off her pants and do all this with this rectal medication."

And that's a lot. It's a lot. And it's scary, anyway, when they're having a seizure. I left Claire with the babysitter just other night, and to be able to tell the sitter, "Here's rescue medication. It's on the counter. All you do is peel this back label, there's one nasal spray for each nostril. You don't have to open anything, you just pop it in and spray it up the nose and that's it. It's here if you need it. Hopefully you won't." That's always the goal, but it's very simple and it's not nearly as intimidating as someone thinking about having to use a rectal Diastat.

Since Claire's been prescribed with VALTOCO, a few years now, thankfully we've only had to use it once. Back in 2019, Claire was diagnosed with diabetes, as well. We were going through adding in insulin and dealing with some of that. Didn't impact her seizures too much, except that at the time of her diabetes

diagnosis, she was on Depakote. And it ended up we needed to take her off of that because it was really affecting her gaining and keeping weight on, which obviously is not good if you have diabetes. He said, "We need to take her off of this." And what we found was the Depakote was doing a whole lot to keep her seizures away.

We thought she had this overwhelming personality, and we found out the Depakote was even suppressing that, and so she got even sassier and had more attitude for us underneath that. Coming off of that and adding in some newer medications, she started having a lot of breakthrough seizures again, which we had not dealt with. We were going a year and a half, two years sometimes, without any... At least not any big seizures. We always say she could have little ones we don't know about, but we just don't think about those because they're not affecting her. If she can continue to progress and live a good life, we're not going to worry about little ones we may not know about.

Anyway, she started having a seizure at home and it just would not stop. And I had not been scared during a seizure in a long time. There's normally a minute or less. She'll come out of them, and she'll sleep for a little while, she'll wake up, we'll move on with life. It was just very violent jerks and tremors and shakes and not breathing and just terrible. So I went and got the VALTOCO and was watching the clock, and it hit that third minute and I popped and sprayed each nostril and just kept watching the clock. She slowly started to come out of it and take those big, deep breaths in. I started reading again, and it was... I couldn't imagine not having that rescue med, because you just never know. They tell us if the patient hasn't had a seizure in a long time and they have a big breakthrough seizure, a lot of times that's it for them. That was really scary, and I can't imagine not having a rescue med available.