CURE CITIZENS UNITED FOR RESEARCH IN EPILEPSY

CANNABIDIOL AND EPILEPSY: THE REAL RISKS AND BENEFITS (WEBINAR TRANSCRIPT)

Laura Lubbers: 00:05 Welcome everyone to today's webinar. I am Laura Lubbers, and I'm the Chief Scientific Officer for CURE. I want to thank you all for joining us today. CURE is pleased to present our leaders in epilepsy research webinar series, which consists of webinars that highlights the key research that's being done in epilepsy. Today's webinar, which is sponsored by our friends at Sunovion, will focus on cannabidiol or CBD, and the approval of the medication known as Epidiolex, and its recent impact on the treatment of epilepsy. Epidiolex which contains a highly purified CBD, cannabidiol, is approved to treat seizures associated with two rare forums of epilepsy. These are severe forms of epilepsy associated with Lennox-Gastaut syndrome and Dravet syndrome in patients that are two years of age or older. This is the first FDA approved drug that contains a purified drug substance derived from marijuana, so it truly is a remarkable addition to our cadre of medications to treat epilepsy.

Laura Lubbers: 01:16 This webinar will be presented by Dr. Anup Patel, who is associated with the trials that led to the approval of Epidiolex. CURE's mission is to find a cure for epilepsy by promoting and funding patient-focused research. This year we're celebrating 20 years of impact. Over the last 20 years CURE has been instrumental in advancing research in many areas of epilepsy, research including infantile spasms, post-traumatic epilepsy, sudden unexpected death in epilepsy or SUDEP, and genetics just to name a few. Today's webinar that is entitled Cannabidiol and Epilepsy: The Real Risks and Benefits will help you understand why CBD is effective for certain types of epilepsy and the risks that can be associated with cannabidiol, and what does FDA approval mean for the future of epilepsy research and treatment.

Laura Lubbers: 02:17 Dr. Anup Patel is a board certified in neurology with special qualifications in child neurology, epilepsy and clinical neurophysiology. He's an associate professor for neurology and pediatrics at Nationwide Children's Hospital at the Ohio State University Medical Center in Columbus, Ohio. He is also an associate medical

director for Partners for Kids, the nation's largest pediatric accountable care organization, and he's the director of the Complex Epilepsy Clinic. His publications and clinical research interests are in pediatric epilepsy, healthcare utilization and quality improvement. He's published journal articles involving medical cannabis and Cannabidiol. He's participated in many of the research trials involving CBD for use in pediatric epilepsy, and he's the lead author on the position statement for medical marijuana by the American Academy of Neurology. He's given many presentations on the topic of medical cannabis at various regional, national and international conferences.

Laura Lubbers: 03:26 Before Dr. Patel begins I'd like to encourage everyone to ask questions. You may submit your questions anytime during the presentation by typing them into the questions tab of the GoTo meeting control panel and clicking send. My colleague from CURE, Brandon Laughlin, will read them aloud during the Q&A portion of the webinar. We do 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. I also want to mention that today's webinar as well as all of our other webinars, past and future, are recorded and available on the CURE website. With that I'll turn it over to you Dr. Patel.

Dr. Anup Patel: 04:15 Thank you so much for that nice introduction Laura, and thank you Brandon for all your help so far getting us to this point. I'm really honored to be able to speak to you on this wonderful topic. Here are my disclosures. The one that I do want to point out as I have provided consulting work for Greenwich Biosciences, who are responsible for bringing this product to FDA approval. Specifically today we're going to talk about three main subjects, and I hope by the end of our time together you have a better understanding of the risks and benefits of this CBD based product Epidiolex.

Dr. Anup Patel: 04:51 But before I do that it's important that we talk about a little background as it relates to this plant and where we got to this plant. So the goal today is actually for me to tell you a story, a story of how this got started

and how we got to where we are today to get a treatment that potentially could be useful for many folks with epilepsy. But really it's important that we think of Epidiolex as just a part of the story. Cannabis sativa is the base plant, many of you know as marijuana. When it's used for medical purposes that's when we refer to it as medical cannabis or medical marijuana. But importantly, there are lots of compounds within this plant that may or may not have benefit for disease treatments, but also can have issues for side effects.

Dr. Anup Patel: 05:36 The most common ingredient, the one that people are most familiar with is this thing called THC. And THC is what binds to the part of the brain that helps you get high, and therefore is used for recreational and abuse purposes. Cannabidiol though is just one of many compounds. And we see these overlapping terms and I think it's important we have a better understanding of each of the terms so we now know how to address this and be able to differentiate one thing from another thing. The most important thing to remind you is that everything in marijuana is a chemical. So when everybody says that it's natural, that's not true. There's no such thing as natural as far as equating to safety. Everything you put in your body is a chemical structure in some form or the other and may be broken down in livers or kidneys and whatnot, and we're going to talk about that.

Dr. Anup Patel: 06:30 We know that THC binds to those areas of the brain that causes you to get high and we call that the CB1 and CB2 receptors. Cannabidiol though does not bind to that system, so it does not achieve a high. We're not quite sure why CBD works to help people with epilepsy, but here are some of the theories or processes that are involved that may lead to why it's helpful for someone who have seizures. But cannabidiol is going to be the majority of what we talk about and that is really just one of the components, and it's a cannabinoid and all of the plant compounds that have properties that may be used for disease purposes can be referred to this way. CBD or cannabidiol is non-psychoactive because again, it doesn't respond or bind to the same areas of the brain that cause you to get the high. Epidiolex is a mostly purified, the most purified plant-based CBD

product. It contains greater than 98% CBD, and it's an oil and they call it Epidiolex.

Dr. Anup Patel: 07:38

But this story didn't start with Epidiolex, the story started way back when and all the way through the dawn of time in history there've been reports even going back to Egyptian times of the potential use of marijuana or its substances to help treat disease, and specifically seizures. Only recently that there's been more public interest in this topic based on a lot of information that came forward, but ultimately I think it started really with this guy, Sanjay Gupta and his first documentary called WEED, that was broadcasted on CNN and highlighted a little girl named Charlotte, who had good responses to the CBD product she obtained out in Colorado for her Dravet syndrome. But in the background there was more that was going on to this story. This company that was previously known or continued to be known in Europe and abroad as GW Pharma, here in the United States known as Greenwich Biosciences. And other companies started to have some very big interest in the potential of these compounds potentially helping people with seizures and even other disease states that affect neurological function.

Dr. Anup Patel: 08:44

Here's a list of some that are ongoing. We're going to obviously go through some of them as it relates to the Epidiolex product. But again, by no means is this the end of the story. The story is just beginning and it's exciting. And you'll see some of these other treatments coming to fruition hopefully in the near future. The Insys product is a synthetic version of CBD. Now, it'll be 100% CBD because it's synthetic. So they took the chemical structure and replicated that for use hopefully in people. And those trials are beginning right now. Zynerba Pharmaceuticals are working on a transdermal patch and they're doing studies currently on Fragile X syndrome. And so there's a lot of excitement.

Dr. Anup Patel: 09:27

But let's talk about the effectiveness and safety of CBD. And specifically I'm going to focus on the Epidiolex trials, which I am very proud of having been able to participate, but before I do it I think it's important that we go over some basic definitions, definitions that I find to be sometimes confusing. So I

imagine there might be some who are listening feel the same way. These are the terms that are used in all medication trials when we talk about epilepsy. So this will hopefully help you with an understanding of how to address or at least interpret a lot of the studies that are coming out on this product or even others that may come out in the past or in the future. When we talk about median seizure reduction, it's the middle percent reduction number for the patients in a study. And that's what our United States FDA uses for approval.

Dr. Anup Patel: 10:18 A median is a middle of the sorted list of numbers while the mean is average, so the average is something that we're more commonly used to. However, it's not used for FDA approval process. In Europe, they talk about this thing called a responder rate. A responder rate is the percent of patients who have at least a 50% or more reduction of their seizures in the trial as it compares to their baseline when they started the trial before getting exposed to a product. And in Europe that's what they use at their European part of the FDA, they are counterpart to the FDA for approval purposes.

Dr. Anup Patel: 10:59 Now, the important thing is what the story told us. And that is that we started with an open label study and that open label study then led to this longterm data. And the reason why I want to talk about that as it compares the study that we first did in this program called the Expanded Access Program. In the Expanded Access Program all comers were enrolled but they all had to have what we call treatment resistant epilepsy, so epilepsy that unfortunately did not respond to treatments. And what we learned was that there was a lot of patients who stayed on the treatment all the way up to 96 weeks. We started this four years ago, so we now are sitting on lots of data and are continuing to analyze. And at 12 weeks about half the patients had about a 51% median seizure reduction in that study, but then we saw that maintain up to 96 weeks where we had a 48% median seizure reduction.

Dr. Anup Patel: 12:00 If you look at responder rate, which I think is really important to our patients, meaning what were the percent reductions of seizures, you could see at 96

weeks 7% of the entire patient population had no seizures while on this medication. So, that was very hopeful. Now, the downside of a trial like this is it's called open label, which means there's no placebo arm. So we weren't quite sure if there was what we call a placebo response presence. So we felt that was important to go further and try to obtain FDA approval because studies like this currently don't lead to an FDA approval, but can obviously help us in that journey towards FDA approval. Now, importantly, people ask about side effects and this is the most robust data that we have. And when we look at that, only 24% of the population withdrew. Most, 15%, came out because they weren't getting any better.

Dr. Anup Patel: 12:51 And that's important to know. Epidiolex is a good product and may be helpful for those who have epilepsy, but by no means is there a magic bullet or it will cure all your seizures. So it's important we have realistic expectations. The 5% that came out of the Expanded Access study was because of diarrhea mostly and tiredness. So that then led the story to continue, based on this we also looked at a subset of patients who had a better response or a good response. In a population that normally doesn't have a response, and that's Dravet syndrome and Lennox-Gastaut syndrome. So we thought as investigators there's worth pursuing to see if there's something more here. But to do that you have to start with why do you dose it? We made it up, we kind of figured it out, but we really wanted to test it scientifically.

Dr. Anup Patel: 13:39 In the gold standard way is to do it in this what we call randomized double blind placebo controlled studies. So we enrolled some kids into that study and we decided to see if it was safe and effective and what was the backbones of this dosing and how that meant. Now, the benefit for patients who did this study was they could go on into an open label study so they could continue to have the medication if it was felt to be helpful. But when you're in these kinds of studies you don't know if you're getting the product or what we call placebo, which is very similar but doesn't contain the CBD. And we learned a lot. We learned that this was well tolerated, that mostly the patients completed the treatment without problem, but there were some things that we had to be careful

of, that there are potential for drug-drug interaction. Not necessary with Clobazam which is called Onfi, but with when Onfi is broken down the major product that it's broken down to is called N-desmethylclobazam, or here is abbreviated as N-CLB.

Dr. Anup Patel: 14:40 And we did see an interaction with some patients with who were getting the CBD product, and therefore caused them to be more tired. So that's something that we needed to be careful of through the other studies, and what we will learn about and we'll remember when we start being able to prescribe this for all patients. And again, some of the side effects in this study were similar to what you've seen before. One of the themes you're going to hear is no matter what study we've done, we saw similar results, which is very comforting to say that it wasn't a fluke thing that we were seeing. The other thing we started to notice was that you didn't see increases in your valproate or Depakote levels, but that perhaps you had an increased risk for increases in your liver enzymes or called transaminases. And that's sometimes became problematic and had to either get off the CBD product or the Valproid product and therefore then return back to normal. And we'll talk a little bit more about that in a second.

Dr. Anup Patel: 15:39 That led to what we consider to be a hallmark study, that was luckily published in The New England Journal of Medicine. It was the first study to look at its effectiveness, Epidiolex effectiveness, in a randomized double blind placebo controlled fashion. Again, the gold standard way. And what we did in these studies was we enrolled children up between the ages of two and 18. And we saw again that this median seizure reduction was what we considered or what is considered to be statistically significant, which means it wasn't because of chance, it was related to the medication.

Dr. Anup Patel: 16:14 So it went from 39% before you got the product to 13% for the placebo product, so therefore there was a big difference between the two. And if you compare the placebo group, so again, placebo meaning the ones that didn't get the active CBD, to those who got CBD the CBD group had a 45% responder rate, which means 45% of the patients in

the study had at least a 50% or more seizure reduction. And the side effect profile was very similar to what we saw in the open label study that I mentioned before, and also very comparable to placebo, which is what we commonly see when we study a very difficult to control epilepsy population that has an increased risk for some illness. But what we really are excited about was that there were no major effects that was related to the medication. So no permanent injuries, no deaths, no significant problems that we would be concerned about. So well tolerated and safe.

Dr. Anup Patel: 17:14 Then that led to our first study in Lennox-Gastaut syndrome, another very difficult to treat epilepsy syndrome. In this study we did enroll adults as well, but the average age was 16 years. And here we decided to look at two dosing arms, a lower dosing arm of 10 milligram per kilogram per day, which I'll explain how it's going to be used in dosing once it's available commercially, and then the higher end which is the 20 milligram arm. And what we saw was again a very good difference in both groups. Now, the group that got the higher dose, the 20 milligram per kilogram per day arm, definitely had a better response than when you compare to the 10 per kilo per day arm. But it just show us there was still an effect between the lower arm, so not everybody needs the higher dose.

Dr. Anup Patel: 18:01 You could start low and you might be able to stay there. That was really exciting. That effect, meaning the difference between the placebo, happened in the first month, that's an importance in statement. So we do expect in most cases that within a month you'll know if this treatment is working if your child or your loved one gets prescribed Epidiolex, or if you're listening and have epilepsy you may be the one getting it. And again, the side effect profile was very similar to other studies. There was another study with Lennox-Gastaut that only looked at the higher arm and had a higher percentage of adult patients. And again, the same thing was seen. Even if you're an adult or a child, you tended to have a decent response and one that was significant statistically compared to the placebo. And again, very similar side effect profile, and again very similar to what we've seen in other studies.

Dr. Anup Patel: 18:55 Now what we're seeing is this study of tuberous sclerosis that just finished enrollment. My colleague and friend Elizabeth Thiele in Boston is the main leader of this study, and they're looking to see if maybe Epidiolex could be helpful for those patients who have tuberous sclerosis. So we already know it's affective for Lennox-Gastaut syndrome, Dravet syndrome, and hopefully soon we'll have the data as it relates to tuberous sclerosis as well. What did this all mean? Well, it's really exciting and I get a little emotional sometimes when I talk about it because it led to history. So the data and the studies were submitted by the company to the FDA for potential approval. Before the FDA makes a decision they always have a public advisory committee meeting, that committee voted 13 to nothing in favor of approval. And then on June 25th, 2018 history was made, FDA approved Epidiolex for seizures associated with patients greater than the age of two who had Lennox-Gastaut or have Dravet syndrome.

Dr. Anup Patel: 19:57 It was the first time in United States history that any plant based cannabis derived product was FDA approved for a disease state, and that disease was epilepsy. I was very proud of that because we've got a lot of awareness as it relates to epilepsy and that's a big thing I champion or try to champion on my local level, because I feel we need to get more awareness out there for all our patients that are in need. But that was huge and it also marked the first FDA approved treatment for Dravet syndrome. Since then, stiripentol has now been FDA approved in the United States, but still Epidiolex remains the first FDA approved treatment for Dravet syndrome. So now what's next? What happens? Well, that's what's really exciting, it's recently been rescheduled. So everyone should understand that when medication is FDA approved, that means there's potential medical benefit and not addictive harm potential when it's scheduled at a lower level.

Dr. Anup Patel: 20:54 Well, the DEA used that information to reschedule it at level five. So that's very similar to medicines like Lyrica that we use to treat seizures or codeine, which is very commonly used in public. But the DEA rescheduling had to occur because CBD marijuana and all the compounds I mentioned at the beginning of this talk

are under a class called scheduled one, which means the DEA recognizes that they are of potential harm, meaning addictive potential and have no medical benefits. Well, our studies and the studies that have been done prove that Epidiolex or purified CBD did not fit under that marker. Now, this rescheduling does not apply to what we consider to be vernacular products, meaning products that you buy from dispensaries or online or from places that sell products to have claims of CBD or other CBD type products in it. It only pertains to the Epidiolex, the purified plant based product.

Dr. Anup Patel: 21:57 What that means now is it will be available in all states very soon. The dose will be weight based, so no matter how much you weigh it's all based on your weight. That's very common for us in pediatrics, that's how we dose pretty much everything. For my adult colleagues that'll be a new endeavor that obviously I'll help them get through. It does take a calculator to calculate, but I'm sure they can do it as well as I can. But the dose will be up to 20 milligrams per kilogram per day, but as our previous study suggested, you may not need that high of a dose and you may only need a lower dose and that'll be absolutely fine.

Dr. Anup Patel: 22:35 We expect that we're going to be able to write this as a prescription. The way it's going to work is you'll write a prescription. If you're a medical provider, you'll fill out another form and you'll send or fax that form to a group or a specialty pharmacy, so a kind of a hub. And then that hub will work on you with you to get your authorization from your insurance company and potentially will then mail it to your house if approved.

Dr. Anup Patel: 22:59 You will not as a medical provider need a special license or certificate, it'll be under the guide of your current DEA license. So no matter what your state says, no law has to be changed, no rule has to be passed, the only thing that has to happen in your state is the rescheduling by the DEA. Each individual state does that, but most go with the recognition of what the federal DEA recommended, which again in this case is scheduled five. Scheduled five just so the rest of you know also means I'm now going to be allowed to prescribe this medication with up to five refills. So that'll be very helpful for those patients so

they don't have to continue to wait month to month and ask for permission to get it paid for by their insurance company. We will hopefully provide those refills on the front end.

Dr. Anup Patel: 23:48 The other benefit is to stay at the schedule and stay approved by the FDA it has to be consistent, has to be truth in labeling. So anytime it's tested, it must contain the purified CBD and it cannot change from batch to batch, product to product, bottle to bottle. And they also now recently established the price which will likely depend on how much medication you need. So for example, if you do not require a lot of CBD to get seizure freedom or optimal seizure control, then you will not have to pay as much unless you have to require more. The more medicine you use, the more expensive it will cost. The other thing we'd like to cover is can CBD make seizures worse? And unfortunately we don't have a lot of great data in our studies. We did not feel the purified CBD product led to seizure worsening.

Dr. Anup Patel: 24:36 However, there was this Israeli study. The difference here is that this Israeli study used a combination of CBD and THC in a 20 to one ratio. And in this study they didn't do a blinded phase or didn't do randomized double blind phase, but they did see 7% of the patients reported an aggravation of seizures, which led to the withdrawal of this product. It was not clear if that was because of the CBD or the THC. For years us in the scientific community feel that the THC may either be not helpful for seizures or may in some cases trigger you or make you more likely to have seizures. So that's something that we need more information on moving forward. But here is some information that perhaps helps us understand the beginning of this story.

Dr. Anup Patel: 25:29 But what's important to know about these other products is that they're not regulated. So if you've heard stories that your friend or you personally or your loved one got worse when they were given a CBD product that you currently have that you got from the internet or dispensary area or another location, the important thing to remember is we don't have a lot of safety data. We don't know how well that works because nobody's studying it in the same way. Dosing

is not established and we can't help you as medical providers because we actually really don't know how much CBD is in there, and that can change from month to month or bottle to bottle. So let's not follow the same rigorous process that the FDA approval requires, that was led to the Epidiolex product being FDA approved. So it's important to keep that in mind.

Dr. Anup Patel: 26:13 The other thing is that there's no monitoring of these products, nobody's out there doing a great job testing them. In California recently they published some data of testing and only one in five of the samples available through the state's programs in dispensaries met the grade. And that meant that there were inaccurate because of what they had as far as labeling or they were contaminated with pesticides, bacteria and chemicals. It's important to remember or know marijuana as a plant is a sponge. It gathers a lot of things up from the dirt into the plant and therefore can be seen in the product that's made if you don't control or remove those things. It's very important that people who do use CBD products understand the exact nature of where they come from to be sure that they are purified in the sense of controlling for all these factors.

Dr. Anup Patel: 27:07 It is very difficult because of that sponge factor of the plant to be able to get to that purified form that we see in the Epidiolex product, so we're very happy that that was FDA approved for that reason. The other thing that's concerning is a lot of these bottles and information that you're given can be false. They're not breaking any federal rule, they're just being unethical. But a lot of this is very similar to the movement back in the 1920s and before as it relates to alcohol, specifically whiskey when it was used for medical purposes. The proofing that is now present on liquor bottles and specifically on whiskey bottles was really in large part because of the false claims that were made.

Dr. Anup Patel: 27:48 Here's the same story that's very similar. In fact, the FDA sanctioned a study of products claiming to have some sort of CBD in them. And unfortunately only a half had any CBD, which meant 50% had no CBD when they actually said they did. Here locally in Columbus we unfortunately had a patient who

overdosed because the product that they were getting had unfortunately more THC than mother thought, and she was giving this product to her child and he ended up in our intensive care unit. So you must be careful and must be concerned over these unregulated, non truthful in some cases product.

Dr. Anup Patel: 28:29 So with that I wanted to leave plenty of time for questions. I want to first thank all the patients and families that participated in these studies. This story was won over many years in time. This story was not of one person. I am very proud to have played a very small role in it, but it's all the clinical research teams, all the patients and families that dedicated their time that led to this day. We actually hope in November we'll be able to start prescribing this medication for you if you qualify. So please talk to your provider if you feel Epidiolex would be a product that may be of benefit for you, because pretty soon we'll all be able to participate by prescribing this medication.

Dr. Anup Patel: 29:09 I also want to thank cure for allowing me this opportunity to speak to you all today. I want to thank you for the wonderful work you've done and continue to do to help those patients and families with epilepsy. And thank you to all of you for listening and watching today. I'll turn it back over to Laura and participate in some questions. Thank you for your time.

Laura Lubbers: 29:30 Thank you so much Dr. Patel. It was a terrific presentation. We can now begin the Q&A portion of the webinar. Again, if you have any questions please do submit them via the questions tab of the GoTo webinar control panel and click send, and Brandon can then go ahead and read them aloud. Brandon.

Brandon Laughlin: 29:52 Yes. Thank you Dr. Patel, you did a wonderful job. We've received many questions during the presentation, and many of those questions were actually answered later on in the presentation, so that's great. But I will start with a kind of a clarification question from a lot of the information that you provided at the beginning. How does Epidiolex differ and maybe similar from that medical marijuana that you can get from those dispensaries that you mentioned?

Dr. Anup Patel: 30:24 Yeah, that's a great question. I think the biggest difference is that the Epidiolex product must contain 98% or more CBD and very little anything else. The products you can get from dispensaries do not have that same requirement, and they may not have as much CBD and also because of that may contain other compounds from the plant or some of those chemicals I mentioned earlier. The Epidiolex product cannot have any contamination as far as bacteria. It cannot have any chemicals that aren't listed, and it cannot have a higher percentage of THC than some of the other products. So those are the main differences. The similarities though are CBD is CBD. So if these products contain a high level of CBD that is the same CBD in the Epidiolex product because that is a chemical structure. The synthetic version of CBD that's being concurrently studied is going to be a kind of laboratory made CBD based on the chemical structure. So that'll be 100% CBD and will not have anything else in it, and it's not plant-based though. So those are the major differences. I hope that makes sense.

Brandon Laughlin: 31:33 Absolutely, thank you. A kind of follow up question that just came in a few minutes ago. If you're taking a THC, CBD product purchased through a medical marijuana or dispensary, is there any way for the consumer to test or find out the ingredient accuracy of the product?

Dr. Anup Patel: 31:55 Yeah, there are some labs. It depends on where you live. There are labs now popping up that will test your product. The key thing though is to find a certified lab because unfortunately people are also saying they can test them and they're not certified, so you're not sure of the integrity of the laboratory testing process. But the danger in that is you would have to test every bottle you get because the content of CBD and THC and the other chemical compounds that are available through medical dispensaries will change from bottle to bottle and month to month. So to do it well, you must test all your products every time you get a new bottle, which is really difficult and not cost effective. But if you did want to test it, yes there are certified labs, there's a Clear certification or some sort of certification that all labs must go through, and if

you see that then you're good to go to have it being tested there.

Brandon Laughlin: 32:51 Great, thank you. Since you were actually just mentioning integrity and consistency, I'll ask this question that came in, if you have any knowledge about the integrity and consistency of the Charlotte's web product?

Dr. Anup Patel: 33:05 Yeah, unfortunately I don't. They have not produced a lot of good studies to show that. They do claim they do test it and do claim to say that they do check this from a regular basis, however, those testing sites in my knowledge are done locally and not through an outside unbiased service. So therefore it's hard to make good accurate information about it. I do hope that they will use what has happened with the Greenwich product Epidiolex and follow the same processes to hopefully go under the same idea to get their product potentially FDA approved. But to do that they're going to have to do the same tests and studies that the Epidiolex product did. But I'm hopeful that this will help spur some of that work either through them or some other similar type groups.

Brandon Laughlin: 33:55 Great, thank you. I'm going to shift the questions now. As you can imagine, I received this next question from multiple viewers, but those that have similar phenotypes to Dravet and LGS but they don't have a specific diagnosis, is there a way right now for these folks to get it and if not, will there be a way in the future?

Dr. Anup Patel: 34:23 Yeah, I think that's my most important question. I'm glad somebody asked us. And the reason behind that is we anticipated that this product or medication could be of benefit outside the actual FDA label of Dravet and Lennox-Gastaut. And to get ahead of that we did publish a lot of the data as it relates through our expanded access program. So normally when a medication is FDA approved, it's used on label and then neurologist or pediatric epileptologist and adult epileptologist will start to use it, what we call off label because we just want to help our patients, and not everything is known from studies. Then that'll lead to publications that are submitted to insurance companies that they'll use to potentially

reimburse the medication off label. In this case, we're hopeful. I cannot guarantee it, but we're more hopeful because actually the way this story got told was we got the off label studies published that led to the on-label studies.

Dr. Anup Patel: 35:20 So we're sitting on mountains of publications that I really encourage medical providers to submit to try to get this medication authorized by the individuals and patients insurance companies, which we hope will help. But unfortunately there's no guarantee. It really will depend on your specific insurance company. But please know that these manuscripts are out there and can be submitted to change their decisions if they choose not to authorize this and pay for it. We don't want patients having to be burdened by medical bills. And so this is one way we can get ahead of that and have their medical insurances pay for it. The company has promised to run and have patient assistance programs, so also look towards them to help. I don't have any details, I don't work with them on that and so I don't know what they're offering, but they have told me that they're going to have these patient assistance programs. So please if you're going to get this medication or prescription, get your insurance to pay for it the best way you can and use the resources that are available to try to get it compensated and paid for.

Brandon Laughlin: 36:23 Great, thank you. The next question or the next few questions are going to talk about the actual study that you were involved in and some other research studies that might be ongoing. Was there an interaction with those on Onfi and Valproate as part of the extension studies? Were the interactions looking at co-treatment or were the children allowed to be in the trial while on these various medications?

Dr. Anup Patel: 36:53 Yeah, great question. So in the trials we saw the same thing we saw during the Expanded Access Program trials. Where in some cases there was an interaction, not again necessarily with clobazam, but where clobazam is broken down and that caused these kids to be tired. I will tell you in a lot of cases the answer was not to get rid of the Epidiolex or CBD product, it was to actually lower your clobazam dosing. So it's important that you work with your medical provider to

either lower one or both of the products, and a lot of cases that excessive tiredness did go away. As far as the liver enzymes go, you still have a risk for increased liver enzymes with Epidiolex or CBD products in general, even if you're not on valproic acid or Depakote. The risk was more commonly seen in patients who were on both treatments, meaning they were on both the CBD and Valproate during the actual trials, the randomized double blind placebo controlled trials. And in those cases every single one of those patients had their liver enzymes returned back to normal with one of three things.

Dr. Anup Patel: 38:03 Either they got rid of the Epidiolex, they got rid of the Valproate, or they lowered either one of those medications, and in those three scenarios everybody returned back to normal. But it is going to be recommended that you get baseline liver enzymes before you get on Epidiolex. And then there will be recommendations that you get that monitored throughout the exposure while you're on this medication. Because we're not able to predict if you're going to have this interaction or not, so we just want to test everybody. If you are getting too tired because you're both Epidiolex and CBD and clobazam, so Epidiolex plus clobazam or Onfi, then again the important thing to remember is potentially either lower the clobazam or Onfi dose, or the Epidiolex dose, or even sometimes in some cases both. We do feel there may be, but more data is necessary to confirm this, a good pattern of those kids and adults who are on both Epidiolex and clobazam. But again more data is to come. So meaning that perhaps those two medicines work better in combination than either of them separately. But again more information needs to be studied with that.

Brandon Laughlin: 39:13 Great. And do you know why some are not allowed to take a THC or a CBD based product if they're participating in a drug trial, like fenfluramine for example?

Dr. Anup Patel: 39:26 Yeah, and the major reason is that those people didn't want to confound. So when you are in medical trials you want to keep everything consistent as possible. And the reason why you want to do that is

you want to be able to really safely and effectively answer the question is that medicine X safe and effective for what you're studying it for. When you're given one of these vernacular CBD products, nobody knows what's in them and therefore that can change.

Dr. Anup Patel: 39:52 So you can have a side effect one month because it was something in the bottle that you were given, and how are we going to be able to differentiate that from the medication that's in the trial like fenfluramine. And so we try to keep everything consistent and that's why we don't allow that to occur. There is going to be, no, I'm actually going to re phrase that, I believe there is actually a trial that's currently available that does allow you to be on Epidiolex at a standard and non changeable dose and still participate in fenfluramine studies. But by no means can you be on any regular vernacular product of CBD because of the inconsistency that's contained within that product.

Brandon Laughlin: 40:33 Thank you. One question regarding the actual study you were involved in. Are you following up with a longterm evaluation of side effects in your patients, especially those pediatric patients who may show some delayed side effects?

Dr. Anup Patel: 40:50 Yeah, so whoever asked that question has definitely put in a plug for my poster in American Epilepsy Society. So I'm not able to share that information with you today, but I will be presenting that information at the upcoming 2018 American Epilepsy Society meeting in New Orleans, Louisiana. So more to come, please look for that poster because I'm definitely going to be presenting that data.

Brandon Laughlin: 41:11 Thank you. The next question actually came in, in a couple of different forms, but did come in from multiple viewers. Once you are able to prescribe Epidiolex, do you anticipate being able to ween other anti epileptic drugs from patients, and if so were there any particular meds?

Dr. Anup Patel: 41:32 Yeah. That's our goal and hope. We really want to keep epilepsy treatment to a minimum while also maintaining effectiveness and safety. So we do hope that we're going to be able to wean kids off

medicines. During our trials, so the randomized double blind placebo controlled trials, when they ended we went and they're currently in what we call an open label study. And that's the data I'm going to be presenting at AES, but you'll also hear of the opportunities we had to get people off medicine. So if you were seizure-free for six months while in that "open label study" we were then able to wean some medicines back. And so we were actually able to get some kids and adults off of other medications that were on.

Dr. Anup Patel: 42:09 Personally and this is just my opinion, so that's not really reflected with the data in the studies, personally I will like you to be off Depakote or valproic acid just because I know there's a risk for that combination that's greater as it relates to liver enzymes. So I'm really working actively on trying to get people off that if possible. But it's going to be one of those things that we work with our patients and their families and really work as a team to say, "Hey, what's the least effective treatment that you're currently in on?" Many of these patients had been started on medicines and left on for years, here's an opportunity, whether it's starting Epidiolex or other new treatments, if it works then please have that conversation with your medical provider, do I still need all these other ones? Because we really do want to keep it as simple as possible.

Dr. Anup Patel: 42:53 And sometimes it's hard, right? Sometimes we get in this rut as patient and families and as medical providers where we just go. And we don't stop to say, well, shocks, does he really need Lamotrigene, do they need Levetiracetam or whatever medicine. And so we really have to have a good look at it anytime you start a new treatment. And I recommend that be done as long as you're doing it well, whether you get started on Epidiolex and do well, or if you're going to get on another treatment and do well. But you notice the biggest commonality I said there was do well. I personally don't like making too many changes at once because then it's hard for me to know if it's effective or making things worse. So I try to make only one change at a time.

Brandon Laughlin: 43:35 Great, thank you. Next question is a little off the actual research trial space and more talks about,

what if any resources or guidance materials are available or exist right now for school nurses or other personnel about CBD products being administered during school hours?

Dr. Anup Patel: 43:59

Yeah, that's a big topic that we're trying to get ahead on. So one of the roles I play is I'm the medical editor, sorry, I'm the editor for epilepsy.com as it relates to the medical cannabis content. And on that webpage we've put some information that can be helpful for schools and school nurses. We are trying to get ahead of that and get information out there because that is a topic that comes up on a regular basis. The biggest thing I would recommend and what I'm trying to get out there now is if you get on the Epidiolex product, it's just like any other medicine, it's FDA approved, it shouldn't be treated any differently, there should be no excessive or extra regulation. And so it's going to be important that we message that statement properly. And so definitely work with your local agencies and providers to get that information, but then also look at epilepsy.com as a good resource for that. It's a very important topic.

Brandon Laughlin: 44:51

Absolutely, thank you. The next question talks a little bit more about the side effects that we mentioned earlier. Somebody wrote about, they heard that there was severe nausea and weight loss in some patients as well as some memory problems. Is there any idea whether that could have been caused by the CBD itself or other factors?

Dr. Anup Patel: 45:16

Yeah. As far as the nausea and then that relates to diarrhea and also vomiting. Let me cover that side first. When we look at that side effect, it was both really high in the placebo arm as it was in the treatment arm, but higher in the treatment arm. So we thought initially that the diarrhea and the nausea and the vomiting was related, that you're asked to take oil, you're drinking oil, and that can be really difficult. Now, in a lot of cases that actually helped our patients constipation when it's not what it's used for, but we heard that's what it was helpful for. But we did see a higher percentage of those on the CBD arm have reports of nausea, vomiting and diarrhea. And

so therefore we think that might be related to the actual CBD, but is also is affected because it's an oil.

Dr. Anup Patel: 46:03 But again, it might be also related to that as well. Not everybody had that, but in those that did it was definitely something that's in some cases went away. But I'll be honest, in some other cases it didn't go away and we had to stop the treatment. And that was seen in both the expanded access studies and also our double blind placebo controlled studies and led to withdrawal in that situation as well. As far as memory loss, that was not something we saw statistical significance of to say that it's a major effect. In most cases. We actually saw cognitive benefit of those that got CBD as it compares to placebo. More studies should be done in that area to see the full benefit, but at least in epilepsy patients we did see that. And by the way, that was irrespective of seizure control, which meant it didn't matter if you had better control of your seizures, there still was a potential benefit in cognition and overall quality of life on the screening instruments that we completed or had our patients complete during the study as it compares to placebo.

Brandon Laughlin: 47:01 Great, thank you. Has there been any studies or in your particular study that look at the efficacy of Epidiolex on the different age groups, specifically adults versus the pediatric population?

Dr. Anup Patel: 47:18 Yep. That's a great question as well. And we did try to look at a sub analysis of age ranges to see if there was a particular benefit in a certain age range, and we really aren't seeing much of it. I will tell you that's a hard study to do because we just don't have a ton of subjects that we can stratify. And so there's this thing in research studies called power. So you'd have enough people in each age range to be able to see a difference, and that's called power. And unfortunately we're still learning some of that, but it does not appear to be any more beneficial or less beneficial.

Dr. Anup Patel: 47:49 It does appear as long as you're over the age of two and up to 55 which is where we have the FDA data for, that you see benefit. Now, the FDA approval is over the age of two, there is no end cap. So if you're

a 57 year old patient then you may have Lennox-Gastaut and Dravet. And if you are provider and you feel Epidiolex is for you, it's still FDA approved. So by no means don't think that just because we have most of the data up to age 55 we still have data on people older than that, and again it's awesome benefit in that age range as well.

Brandon Laughlin: 48:22 Great. You kind of addressed this question earlier, but I did receive it in multiple different ways, so I want to make sure it's answered completely. Obviously we've talked about LGS and Dravet, and you mentioned TS. Are there any studies going on that you're aware of into other syndromes such as Doose or other epilepsy specific syndromes out there that might be considered hard to treat epilepsy

Dr. Anup Patel: 48:51 Yeah. And still currently in my knowledge there's no double blind randomized placebo controlled studies. However, we have published a lot of our expanded access data because we had so many patients who had a lot of these conditions. So in Epilepsia and neurology and other medical journals there is data as it relates to the effectiveness and safety of Epidiolex for Doose, for Aicardi, for C.D. Cal. 5, for Del/Dup. So these are common but rare obviously, but common in our population that were seen in the studies, that we were able to extrapolate their data to say yes, there's still benefit and similar side effect profile as it relates to those compared to Lennox-Gastaut and Dravet. So that's not on label use nor was it randomized double blind placebo. But the thing I try to point out to folks is that when you look at the expanded data as it relates to Dravet and Lennox-Gastaut, it mirrors our randomized double blind placebo controlled studies.

Dr. Anup Patel: 49:54 So it is in my great opinion that if we're able to do those studies would see the same things as it relates to those other diseases. And I really want insurance companies to understand that by no means is this only going to potentially work for Dravet and Lennox-Gastaut. Now, obviously that's what the FDA approval says and that's what we should talk about, so this is an off label. I want to make sure I'm very clear that I'm not recommending it for off label use, but there is data as it relates to off label use and I really encourage insurance companies to look at that.

Brandon Laughlin: 50:28 Great, thank you. And kind of on that same topic a good question as we're coming towards the end of our hour here. And this was actually a two part question that was addressed by a few people. And the first part of the question I'll ask is what can people do? What can be done by the community, by all of these epilepsy advocates to really help push insurance companies to cover this?

Dr. Anup Patel: 51:00 Yeah, that would be great. What I think we need to see is the advocacy groups, the representative groups really get out there and encourage the insurance companies to look at all the data as it relates to this medication and product. Any letters of support, any advocacy that can be done on the national federal level is going to be very, very helpful in this regard. It's a really important subject and I just really encourage as many people and stakeholders to get involved and try to get that messaging out there. I do encourage that people just look at the data. They don't have to listen to what I say or opinion, because I'm not speaking opinion I'm speaking fact. And that's why they're published in the medical literature so I would recommend that. The other thing if possible, and I don't know the rules behind it, but if those advocacy groups can actually post some of these articles so people don't have to look hard to find them, or even links to them would be helpful.

Dr. Anup Patel: 51:53 Anything to make it easy for that medical provider to find it and get it, or in your case as a patient or parent or advocate to get those resources and articles. I did post a lot of this on my epilepsy.com portion of the medical cannabis side because I really feel it's important that we try to get as much information out there. I have been meeting with some payers and insurance companies to get the messaging out there, but I'm only one person, I can't meet with all of them. So the more people can actually get face to face with a lot of these insurance companies or at least high level people at these insurance companies, that's yet another way we can get the message across to hopefully get the access that's needed for any treatment, whether it's Epidiolex or anything that could be helpful for epilepsy.

Brandon Laughlin: 52:38 Great, and you kind of went into the tie of the second part of that question which Laura you may have some feedback on as well. What can people do at the national level, on Capitol Hill, things of that nature? Are there certain things that A, can be done or B, need to be done?

Dr. Anup Patel: 52:59 I think the biggest thing I would say is to really advocate for research in epilepsy. I'm a little biased because I do a lot of research, but I am more passionate about that than anything. If we don't get the answers to these questions, patients and families suffer. And there are too many unanswered questions because we don't have enough money. We need NIH dollars, we need federal support, we need people out there to get the message that epilepsy is an important disease and needs it's fair treatment or fair research. The other thing is as it relates to CBD and CBD type products, have a more open mind at the federal level as far as potential for research.

Dr. Anup Patel: 53:34 By no means do I think anything should just be reclassified and said, yeah, give it to your kid. I'm not in favor of those programs that haven't gone through the rigorous process, but what I am in favor of is making it easier for folks like us to do the research that's necessary. We had to jump through lots of hoops and lots of work to get these trials done. Now I'm very proud of that work and I would do it all over again if I had to, but I hope the next round of people don't have to do that, that they're able to get these studies done properly and effectively without as many hurdles or restrictions or barriers. So that's something that can be advocated at the federal level as well.

Laura Lubbers: 54:09 I would certainly echo that. That reaching out to your congress person, making them aware of the importance of epilepsy research. Epilepsy research is underfunded compared to other diseases that affects fewer people, so we really need to get the word out there. We as a community have been trying to increase awareness, but certainly going to your congressperson, making, developing a relationship, I've seen this be very effective ways for them to start advocating for more research dollars and improving the lives of those with epilepsy. So hopefully we can

encourage people out there. I know that there can be skepticism. I've been one of those people too, but it really can make a difference and we need your voices to be a part of this.

Dr. Anup Patel: 54:57 Yeah. I think one of the greatest things that I've seen in the last few years as it relates to the epilepsy community is the movement by the advocacy groups. You guys have such a powerful voice. The parents, the caregivers, the patients, and they're now listening to you, which they should have all along. But we need to listen to you as medical providers, the federal government needs to listen to you, these funding agencies need to listen to you, that your voice is a lot more powerful than you may think. And I know it's hard, right? You have a lot going on. You're dealing with a lot of things, but that is going to be what gets us over the hump because we still have so much work to do. The group CURE has done an amazingly great job. I don't know where our field would be without it.

Dr. Anup Patel: 55:40 I've talked to Susan Axelrod many occasions and thanked her. I'm really lucky that you guys exist. Gardener is a wonderful person, I've talked to him and he's been very supportive, Laura. It has helped us move the needle, but that needle has to be continued to be moved and there's a lot more needles that need to be moved. CURE cannot do this alone, we need other groups to be involved as well. And we need to work together. One of the other soapboxes I get on is I really want us as advocacy groups, I do a lot with Lennox-Gastaut syndrome as I said on my first slide, that I really want all of us to start working more together to come to answering these questions together. Because we can't do this on our own and we can't live in silos to get these answers or these questions answered?

Laura Lubbers: 56:27 All right. Thank you.

Brandon Laughlin: 56:29 Great, thank you so much Dr. Patel. Laura, I'll go ahead and turn it back over to you.

Laura Lubbers: 56:34 Okay. Well, thank you again Dr. Patel for presenting the real risks and benefits of CBD and providing information to our community that was very helpful to

work through how those studies were run and what the real outcomes were. I also want to thank our sponsors to Sunovion for sponsoring today's webinar. And I would of course like to thank our audience for great questions, great concern and a great opportunity to get your questions answered. If you do have more questions about this topic or any of the CURE's research programs, please feel free to visit our website. The address is on the screen, www.CUREepilepsy.org. You can always also contact us via our email address at info@cureepilepsy.org.

Laura Lubbers: 57:27 I want to thank you all again for joining us and I want to welcome you again in November, which is epilepsy awareness month, for a webinar that is just going to discuss research on the stigma behind epilepsy. Stigma as a universal challenge that impacts every generation of individuals living with this terrible disease. This webinar will be presented by Dr. Ann Jacoby, who is a member of the International League Against Epilepsy stigma task force. And will take place on a Wednesday, November 28th at noon Eastern time. So with that, I want to wish you all a great rest of your day and thanks again to Dr. Patel.