CURE Epilepsy Webinar
*The Role of Medicinal Cannabis and Cannabidiol in the Treatment of Epilepsy*
(Transcript)

Dr. Laura Lubbers: Welcome everyone to today's webinar. I'm Laura Lubbers, and I'm the Chief Scientific Officer of Cure Epilepsy. I want to thank you for joining us today.

Today's webinar is entitled, The Role of Medicinal Cannabis and Cannabidiol in the Treatment of Epilepsy, and it's brought to you through our generous support of Jazz Pharmaceuticals.

Medicinal cannabis has been of interest to the epilepsy community for quite some time, with greater interest fueled by the Food and Drug Administration's approval of the cannabidiol, or CBD extract, called Epidiolex. The marijuana, or cannabis plant, actually contains hundreds of different substances, two of which, specifically CBD and tetrahydrocannabinol, or THC, has been widely studied to understand their effects in the brain. Unlike CBD, THC is the major chemical compound found in marijuana that creates the psychoactive effect when it binds to receptors in the brain. CBD, on the other hand, binds to a different set of receptors and is not psychoactive.

Epidiolex is a purified plant-based CBD extract used to treat seizures associated with rare genetic epilepsies. Because of its effectiveness, there's great interest in further understanding how CBD acts in the brain, and also, if other cannabinoids might be useful in the treatment of seizures.

In contrast, Epidiolex, marijuana products sold in dispensaries and online, are not approved or regulated by the FDA. Those products can vary significantly in quality, the dosage needed to treat seizures, and their safety. In some cases, commercial non-prescription cannabis products are thought to increase seizures.

This webinar is the third installment of the 2023 Cure Epilepsy Webinar series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the Cure Epilepsy website, and you can also download transcripts of all of our webinars for reading.

Cure Epilepsy is proud to celebrate our 25th anniversary this year. Since our founding in 1998, we raised millions of dollars to fund epilepsy research that supports our mission, which is to find a cure for epilepsy by promoting and funding patient-focused research. Cure Epilepsy provides grants that support novel research projects, that advance the search for cures and more effective treatments.

Today's webinar will review the basics of cannabis biology, and the differences between cannabis strains. It will also explain the medical uses for medical marijuana, and the use of Epidiolex, to treat specific types of epilepsy. This webinar is presented by Dr. Eric Marsh, who is an Associate Professor of Neurology at the University of Pennsylvania Perelman School of Medicine, and
the Children's Hospital of Philadelphia, or CHOP. He is the Clinical Director of the Penn Orphan Disease Center, and the Director of the CHOP, Rett and related disorders clinic.

Dr. Marsh's clinical interests include developmental and epileptic encephalopathies, neuro developmental disabilities, and cortical malformations. His research interests have focused on analysis of intracranial EEG recordings, to better understand where seizures start, and performing natural history in biomarker studies. In addition, he has studied the role of mutations of specific genes related to epilepsy. Dr. Marsh has been involved in a number of clinical trials for pediatric epilepsies, including Dravet, Lennox-Gastaut, and Rett syndromes.

Before Dr. Marsh begins, I'd like to encourage everyone to ask questions. We'll address the questions during the Q&A portion of the webinar. Please keep in mind, you may submit your questions any time during the presentation, by typing them into the Q&A tab located on your Zoom panel, and click send. We'll do our very best to get through as many questions as we can. 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 loved one's epilepsy.

So with that, I'll turn it over to Dr. Marsh.

Dr. Eric Marsh: Thank you, Laura, very much for inviting me to give this seminar, and for that wonderful introduction. Switch there. And just a few disclosures. So I have been involved in studies about cannabidiol with GW Pharma, Greenwich Pharma, which is now Jazz Pharmaceuticals, including studies with the State of Pennsylvania. I'm an advisory board member for Acadia Pharmaceuticals, and have been a site PI of clinical trials from a number of different companies.

So what I'm going to discuss today, is kind of a general introduction of medical marijuana and kind of how we've gotten to where we are. Then go over a little bit about the plant and the biology, and try to explain the different aspects of the cannabinoids that Laura mentioned in her introduction, and then dive into the clinical data. What we know about pure cannabidiol for epilepsy and the studies that have been done by GW Pharma, Jazz Pharma, and others. And then, go into a little bit of data for other disorders that are highly related, and often coexist with individuals with epilepsy. And at the end, I'll wrap it up by discussing a little bit of what the state regulations are, and what the current status of the law is for epilepsy.

So kind of how did we get where we are now, with a lot of people interested in using medical marijuana for people with epilepsy? Because cannabis has been around forever, and people have been using pot recreationally, religiously, in a number of different places in the country for a long time. So why recently has this become such a big issue? And you could kind of focus this on the story that
came out of Colorado, of a girl with Dravet syndrome, who had a dramatic response to a medical marijuana product that was high in CBD.

Dr. Sanjay Gupta of CNN heard the story, and he proceeded to produce a one-hour documentary, focused primarily around her story, about the potential medical uses of marijuana. And this was a shift from him, because prior to this story, he had been somewhat against medical marijuana use. But him airing this, and the story of Charlotte Figi, that was available on YouTube, really made child neurologists and pediatric epileptologists, like myself, inundated with questions about the use of medical marijuana.

So what is medical marijuana? Well, it has a lot of names, recreationally, pot, hashish, hemp, marijuana, cannabis, et cetera. It is a plant that grows indigenously in South and Central Asia. The cannabis sativa plant is a fibrous plant that can be used for a number of different things, including making rope, for clothes. And it's also, the fibers of the sativa plant are being considered for a lot of different things, and there's a lot of work on engineering this, because it's a very reusable, renewable, resource that people can use.

And then, cannabis indica has more of a resin in the plant, and that is the strain that is used for extracting the cannabinoids that can be used both recreationally and therapeutically. And what's important to note, that these are strains of the same plant. So this is kind of similar to the difference between a golden retriever and a laboratory retriever, right? They're both dogs, they're just different strains of the same plant.

So cannabis use has been around for a long time. And in the 1960s, it was discovered that the major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol, or THC. And THC can have many effects in the body. It can modulate your hunger, anxiety, learning, memory, sleep, and these can all be used for varying different purposes.

Marijuana that is out, and produced and sold recreationally, is often high in THC, and very low in CBD. Because, as Laura mentioned in the introduction, the THC is the psychoactive component and the CBD is not. And there are reports that the DEA has found plants and products that are being sold out in the community, of super high doses of THC, with up to 37% of the cannabinoids being enriched in THC.

So the cannabis plant, the marijuana plant, is a complex, naturally occurring plant, that has many different compounds in it. The most distinctive class of compounds that are found primarily, almost exclusively in the cannabis plant, are the cannabinoids. And there's at least 70 of these known. And though there is debate about the exact number of cannabinoids that exist, because many of them exist transiently in the biology of the plant, there are a bunch of other compounds that people think have potential medicinal use within the plant, such as the terpenes, the flavonoids, or the phenols, that can have potential other biologic activity.
So CBD is the component that seemed, or cannabidiol, is the component that seems to lower seizures. That original strain of Charlotte's Web, that was used by Charlotte Figi in that original report that got a lot of the epilepsy community excited about this, was very high in CBD. 17% in CBD, and very low in THC. It has low or no psychoactive effects. It's generally well tolerated. And there are reports of many other things it can do besides treating seizures, though the data for some of this, needs to be improved over time.

So how does one plant produce two different compounds? Well, it turns out, that the plant has a number of enzymes that exist that metabolize this olivetolic acid, which is like a cholesterol-like molecule, that gets metabolized into either the THC pathway, or the CBD pathway. And this is why any given plant is not going to be high in both, because the plant chooses the direction in which it synthesizes, either high in THC or high in CBD, and this is likely due to the genetics of the plant.

The overall chemistry of these cannabinoids is very complex, where there's a lot of different varieties of these exist in the metabolic pathway. And what I'm showing you here, is a very, very simplified diagram of the pathway that exists to produce, eventually, THC or CBD. As part of this metabolism, there are secondary metaboloids, called the flavonoids and the terpenoids, that are produced as well. And what's important to note is that the concentrations of these metabolites depend on a variety of conditions, particularly within the extraction process. So one of the things that Laura mentioned in her introduction is that, products that are obtained from dispensaries are very variable, because how the cannabis plant has grown, how it is harvested, extracted, et cetera, all change the potential amount of cannabinoids that exist within the plant. So you really have to have a very, very highly regulated process like GW Pharma or Jazz Pharma does to produce their plant, in order to get a very reproducible product.

So one of the questions that you want to ask is, so why does the marijuana work? Why do these cannabinoids work? And we still have a lot to learn about how cannabinoids work in the body, but much of what we know comes from work that's been going on since the 1960s and '70s about an endogenous system called the endocannabinoid system. And it's called the endocannabinoid system because it has the structure of the endogenous cannabinoids, is very similar to the structure of THC. And there are two major endogenous cannabinoids, which is the one here on the left, 2-Arachidonoyl glycerol, and the one on the right anandamide. And these are produced by metabolism of cholesterol moieties within the cell surface. And as the cholesterol is metabolized, it produces these molecules, which then act on receptors within cells to modulate activity. And these cannabinoids are often released by synapses in response to electrical or neurologic activity.

So THC binds to the CB1 receptor, with what's called a moderate affinity, so it binds pretty well, and it turns on that receptor. And that receptor then alters synaptic function, which changes neuronal activity. And that change in brain...
activity gives you the symptoms that one expects with using marijuana. That includes the high, reduction in pain sensation, reducing spasticity, enhancing appetite. And that's because these CB1 receptors are expressed throughout the brain, but in higher regions, in particular parts of brain, that gives the cannabis plant these psychoactive effects.

CBD, on the other hand, does not seem to bind to either the CB1 receptors that are in the brain, or the CB2 receptors that exist out in the periphery, particularly on your immune system. And some people think that CBD might actually block CB1 receptors, having an anti-psychoactive property by blocking those CB1 receptors. CBD changes neural singling, and how it does that is still being sorted out. There was just recently a really interesting paper published, talking about its role in antagonizing a receptor in the cell called the GPR55 receptor, but it's thought to have potential, multiple potential effects, that modulate neuronal activity, and would give the anti-seizure effects of cannabidiol.

So as I've already mentioned, but cannabis, the naturally occurring plant that's high in THC, has a number of psychoactive effects that many people are aware of, because people have used marijuana in the past. And if you haven't, they're listed here. But one of the things to note is that, smoking marijuana actually does have associated health problems. And there's a little bit of misconception in the community that, oh, smoking marijuana is completely healthy and it's not a problem, but that's not really true. In people who are chronic users of marijuana by smoking, that they can have respiratory problems, including bronchitis and large airway obstruction. They can develop addiction. So people can become addicted to marijuana that's high in THC. And some people think, up to 10% of adult users can get addicted to marijuana, high in THC marijuana, and that this might be higher in children.

And for people who are chronic users of THC, there are some potential long-term issues with cognition, and potentially increasing the risk of developing schizophrenia. This data and this concept is a little bit still debated, though most of the evidence that's emerging, really falls on the fact that chronic long-term use of marijuana high in THC does give you long-term impact on your cognition, and potentially increases the risk of developing schizophrenia in teenagers and young adults.

One of the things I skipped over here, is the association of smoking marijuana and cancer is lacking, and that's probably mostly due to the smaller numbers of individuals that smoke marijuana compared to cigarettes, in order to make that association.

So what do we know clinically? So as a pediatric epileptologist, I like to make many of my decisions based upon clinical data that has emerged in established well set up trials. So what do we know about the data for medicinal marijuana for epilepsy in general? And so, prior to Sanjay Gupta, and to GW Pharma, now Jazz Pharma, generating a series of studies to test purified cannabidiol, we didn't know very much about how the cannabinoids affected seizures. So this is
from a review from the Cochrane Reviews database, which is a well established program that reviews different clinical features. And this was published, I believe in like two, I can't remember now, sorry. But this was published before the surge of studies. And what you see is that, there was very few studies that actually tested the use of marijuana, and they were all tiny little studies, with nine people or 15 people. So prior to this study of Epidiolex, there was little that we actually knew about this.

And then, because of a bunch of cases and case reports, GW Pharma decided to move forward with developing a clinical program for their highly purified version of CBD. And the first thing they did, was actually start an expanded access program, which gave people who had severe epilepsy, kids with severe epilepsy, access to this purified cannabidiol before it was FDA approved. And so myself, along with a number of other sites around the country, enrolled people in this open label, what we call expanded access, program, to look at really the safety of cannabidiol in kids with epilepsy. And this was primarily a safety study, and this is showing you who was enrolled across the country, and the different types of syndromes that they hear with Dravet syndrome, Lennox-Gastaut syndrome, CDKL5 deficiency disorder, tuberous sclerosis, and the number of patients that were recruited in these conditions.

And what we found, and I'm starting with efficacy, and like I said, this was primarily a safety study, but everyone wants to know, get to the punchline of whether it worked or not. And what we found was that, overall, there was a almost 38% reduction in all motor seizures. And the graphs I'm showing you here are what are called waterfall plots, where everything above the zero are individuals who had worsening of their seizures, and everything below the zero are individuals who had improvement of their seizures. And you could see, if you look at monthly motor seizure numbers, which is this figure up here in A, that there is more people to the right which are below zero than are above zero. So the majority of people had an improvement, though some were very small improvement. And the red line is when you take away the dose escalation period, and you only look at the stable end part of it. And you see that there is this overall 37, 38% reduction, and a small number of people who became seizure free.

And if you break this down into the different groups of patients, the patients with Dravet syndrome, almost 50% of them had a 50% reduction, whereas, the Lennox-Gastaut syndrome patient, 40% had a 50% reduction. We didn't break down the smaller groups, because the numbers of patients in each of the other groups was kind of too small to really make a definitive interpretation about.

And one of the things that immediately became clear, is that people who are on clobazam, or Onfi, would get sedated with this. And it was known that CBD inhibits a system in the liver that metabolizes benzodiazepines. So what this means is that, the CBD blocks the enzyme that breaks down your clobazam, which means that you have for the same dose of clobazam, you have more of
that drug in your body. So then the question was, well, are we only seeing effect because you're increasing the level of Onfi or clobazam in the system?

So we had 65 patients who were on clobazam, and if you look at their reduction in seizures, 52% had a greater than 50% reduction if they were on clobazam. But 26%, who weren't on clobazam, had a reduction in their seizures. Suggesting that without clobazam, you still had an anti-seizure effect, but you definitely had a positive interaction with clobazam. And the same thing was true with valproate, or Depakote, that those who were on valproate did better than those who were not on valproate, though not on valproate still responded.

So if you try to analyze this all together, we saw that there was an independent effect of CBD in reducing seizures, but that only clobazam independently predicted whether you'd have a better response. And this is something that clinically, that we've learned through all these trials, but also just from personal use, that sometimes, adding a little bit of clobazam to Epidiolex can give you some added benefit. That there's some synergistic effect that we don't understand very well, that is either dependent upon just this metabolism issue, or independent of the metabolism issue, but more research is needed to really figure this out.

So with this data in hand, GW was able to move forward with the definitive type of trials that myself, as a pediatric epileptologist, want to learn about, to know whether a drug really works. And that is a Phase III placebo controlled study. So this is the type of study where half the group gets placebo, half the group gets the drug. You follow them along without doing anything else for 16 weeks. And then you see who responded better, those on placebo or those on the drug. And for Epidiolex, or CBD, they actually carried out five different studies of different groups of pediatric epilepsy patients, including Dravet syndrome patients, LGS patients, and tuberous sclerosis patients. They did two parallel studies of Dravet, two of LGS, and a single study of tuberous sclerosis. And these have all been published, and this is just listing some of the publications that have come out from this work.

So I'm not going to go over all these studies. I can spend a full hour just going over these studies, but I'm just highlighting one study in brief to show you kind of how this was done, and how we've learned about the efficacy and the safety of cannabidiol. So this is a very classic epilepsy study design, where individuals, in this case with Lennox-Gastaut, are screened for whether they have LGS or not, and whether they have enough seizures to go on into the trial. And then they're randomized into being treated with CBD or placebo. And it was a one-to-one randomization, meaning, half the patients got placebo, and half the patients got CBD. And then there were followed for their 16 weeks, with the first four weeks being dose escalation, and then 12 weeks of steady state. And in this process, 14 patients in the CBD arm with Dravet, and one patient in the placebo arm with Dravet.
But remember, when you start a process like this, you're blind. You don't know whether you're in the CBD group or the placebo group. But after the fact, in looking at it, this were the numbers that moved forward. And then everyone went on to an open label extension file, so that everyone was able to get the drug. This year, the characteristics of the individuals who came into the trial on the right, and you see the mean age was about 15 years old for these studies, though most were in the two to 17 year group. And these kids had frequent seizures, with an average of 70 drop seizures per month in these kids. So this is, these kids have a lot of seizures, because they have Lennox-Gastaut syndrome, and we know kids with Lennox-Gastaut syndrome, unfortunately, have a lot of seizures.

So what was found? Well, what was found was that, I'm going to just focus here on the maintenance period, so this is not including the dose escalation part, that there was a 45% reduction in those people who took CBD, and only a 15% reduction in those people on placebo. So there was a statistically significant difference between treatment with CBD versus placebo. So this is the type of evidence, as a clinician, that we want to see, that CBD really does work to lower your seizure frequency.

And the other thing you could ask families who are in a trial like this is, kind of overall, how do you feel your child's doing? Do you think they're better, worse, the same? And so this is what we call the caregiver global impression of change. And you see that in the slightly improved, much improved, or very improved group, the CBD group, the blue bars, are much higher than the green bars. And that 58% of people on CBD said their child was improved, where only 34% of people on placebo. So this is not just seizures, it's kind of overall how did they feel? And there was a real statistically significant difference between the two.

Now, one of the important things when you do a trial like this, is to look at what are the side effect profiles that you see? So these are what are called treatment emergent adverse events. And what we saw was that there was, if you look at CBD or placebo, the major one was diarrhea that occurred. And we think this is due, because the Epidiolex is in an oil, and it's in sesame oil. And if anyone starts to just drink eight mls of sesame oil every day, you're probably going to get loose stools, so it's probably independent of the CBD. There was increase in being tired. There was temperature changes. There was decreased appetite and vomiting as the major side effects.

And so, oops, I can go back one. So you know what we learned from all these, and remarkably, I should say, that all five clinical trials had a very similar results. So there was remarkable consistency that CBD lowers seizures by 30 to 45%, and that the side effects were pretty consistent across, but it was generally a very well tolerated new drug to add on to people with intractable epilepsy.

So this then raises the question of going back to, we started talking about medical marijuana more broadly. And so, what about just medical marijuana you'd get from a dispensary that could be higher in THC, lower in THC, what is
the effect of medical marijuana more broadly? So unfortunately, no one has done a Phase III clinical trial for kind of the more artisanal preparations of medical marijuana that exist. This is actually from a very recent, it was just published in February of this year, review in the Frontiers of Neurology, which looked at, looked throughout the literature and said, who’s done studies on medical marijuana and what was in that medical marijuana, et cetera?

And so, this is a figure from that paper, and a number of the studies are listed down below. And these are things that they looked at in the studies. And the reason I chose to show this is that, even though a lot of people have looked at studies, no one has consistently looked at the same thing. So what we end up with is a lot of anecdotal data, suggesting that medical marijuana as a whole, and not purified CBD, might be good for certain things versus other things. But even something as simple as age, is not always reported in some studies, which tells us some of the studies are not very well done. But, there is a lot we still need to learn about using medical marijuana more broadly.

And then, another recent study from Dr. Devinsky’s group at NYU, where they actually just observed patients who were getting medical marijuana from a dispensary. And it was from a dispensary that they had conversations with, so they trusted the product in this dispensary, and they just observed what happened to their seizures. They asked them to track seizures before and after. And so they observed 29 patients. And this is the same waterfall plot that I showed you with our original expanded access data. And you see here now that, those above the zero and those below the zero are very similar, but four of these 29 patients became seizure free on this product. And so, four out of 30, for people with intractable epilepsy to become seizure free, is high. But overall, there were many of those who did not respond for medical marijuana. What we really do need is a Phase III type of trial for a product that isn’t just purified CBD, but has other cannabinoids in it, or different levels of THC, to see whether adding THC makes things better or worse for your seizures, but also other symptoms.

And that takes me to the next part of the talk, where one of the things that people have told me a lot when they are placed on Epidiolex, or they take a product from a dispensary, is that it helps with the seizures, but it also helps with sleep, and behavior, and this and that. And so, what’s the data that we have for its use in other symptoms? And these are the symptoms I’m choosing are those that people with epilepsy, and particularly kids with epilepsy, often have. So these are abnormal behaviors. So this again, is a review of a number of different small studies, little anecdotal studies, that were pulled from the literature. And these are different sources to pull from the literature. And they said, that at the end of this, there was really only a few studies that were of high quality studies that they could believe.

And they said that with this, that there was potential effects in hurting yourself, reducing anger, reducing hyperactivity, reducing irritability, along with sleep, anxiety, restlessness. But again, the conclusion of this paper was, we need more.
data, we need more studies. And that there's some real suggestions that cannabidiol or medical marijuana products, could be helpful for these symptoms. More information is needed.

Now, there was one study which did a placebo controlled study, a small study out of Israel, that also looked at behaviors in kids with autism. And what they found was, there was some improvement in self-injury and rage attacks, in hyperactivity symptoms, in sleep symptoms and anxiety. But again, this was a small study, so more information to suggest that there's something there, but we need more data to really prove this. And the same with sleep. So as you can see, there's a lot of people who publish little bits of cases here.

So this is another meta review using a different type of medical analysis called the PRISMA analysis, where they looked at 4300 studies to start, and when they weaned them down, they got to really, kind of 12 studies that had reasonable data. And these 12 studies are shown here on right. And they then said, which of these studies were good studies? So the ones in red, they said, ah, they had some issues, they were high risk to use the data. And the ones in green were better, more well-designed studies that you could trust the data. And from these low risk data, they were able to conclude, again, that there was a suggestion that cannabidiol might be useful for improvement in sleep. But their overall conclusion was that, more information is needed to study this.

So for those people who are interested in obtaining medical marijuana for some of the symptoms that are associated with epilepsy, what you should know is that, there is anecdotes and a little bit of data out there, but be careful and don't presume it's going to work, because we don't really know it's going to work very well for a lot of these things. So be very objective when you're treating yourself, or your loved one, with these types of products, to make sure that it's really having an effect, the same type of an effect you would expect or want from something your doctor prescribed to you.

So this next slide gets to the issue that Laura raised in the introduction, is that, what is the quality if you get it from a dispensary? What is the quality of the product that you're getting? So this was published back in 2017, where a group went to a variety of different dispensaries, both online and in person, obtained their product, and then tested the product to see what was in it. And what they found that, only 45% of oils were accurately labeled, only 25% of alcohol-based tinctures, and only 12% of vaporization liquids, were accurately labeled. So they actually said what was in it was actually in it. The number of them, 36% under-counted what was in it, and 22% over counted.

And that's a problem, because if you don't think there's any THC in there, and there's actually a decent amount of THC in there, you could be giving your child something that's getting them high, that could be altering them, that you don't want to do. So really what this tells us is that, these dispensaries are not supervised as well as they should be, to be ensuring that they're producing the product that they're saying they're producing.
So when we talk about dispensaries, the important thing to know is, what is the state law? Because in the United States, the federal law is still that marijuana is a controlled substance. It is illegal to buy or sell marijuana nationally. The federal government has allowed states to kind of move forward on their own, and allow state dependent rules. And you see, based upon this map, that the legality is variable from state to state. Where in black, are states where it's completely legalized, both for medical and recreational use. In dark green are states where medical is allowed, and they've decriminalized recreational use, meaning that you can't get arrested for it, but it's still not allowed. And then there are states where you're only allowed CBD in certain states. And then, the orange states are the states where it's still fully illegal, both for medicinal use as well as recreational use. So knowing where you live, and what the rules are in the state, is something you should think about. So you don't want to get yourself in trouble by accident. So it's good to be informed of what the rules are where you live.

So with that, we're going to conclude by saying, cannabis contains a number of compounds with various therapeutic potentials, and there's still an awful lot to learn about what the therapeutic potential is. That there are long-term health related issues of smoking marijuana. So the view that it's perfectly safe and healthy to smoke is actually not true. CBD is effective, or purified CBD is effective and safe for pediatric epilepsies. There's less good quality information for medical marijuana more broadly. Sorry, that's a strange typo I had there. There's less data on behavioral and sleep issues, and that using dispensaries has limitations, so you really want to be careful with what you’re using.

And with that, I will end, and we’ll hopefully have some questions to answer. Thank you very much.

Dr. Laura Lubbers: Great. Thank you so much, Dr. Marsh. It's really helpful to review all of this. So we'll start the Q&A now. I know that some questions have already been submitted, but just a reminder for others, if you have any questions, please submit them in the Q&A tab on the Zoom panel, and click send, and we'll get right to it. So just a comment or correction that came in is that, Missouri is now an adult use state, as of February 2023. So we'll have to update the graphic there. Thank you.

Dr. Eric Marsh: Yes, thank you.

Dr. Laura Lubbers: Yes. Rapid changes in the country for sure on this topic. So a medically oriented question, has CBD been found to affect the metabolism of benzos other than Onfi?

Dr. Eric Marsh: So yes it does. Onfi is a unique benzodiazepine, in that its structure is different. So most benzodiazepines, the side chains off the benzo ring, which is why it's called a benzodiazepine, are on the first and sixth carbon. Onfi, it's the first and fifth carbon, so it's a unique benzodiazepine. That's the name Onfi, one five. It's
off of the first and fifth carbon, so it's a unique benzodiazepine. But all benzodiazepine are affected, though Onfi more so than the rest.

Dr. Laura Lubbers: Okay. Okay, thank you. So here's a bit of a complex situation, and it's a rare disorder, and you would be positioned to know more than most on these. And I may get the name of this wrong, but for patients who have megalencephalic leukoencephalopathy, or MLC, with subcortical cysts, would CBD or Epidiolex be considered treatment for epilepsy or autism in this disorder?

Dr. Eric Marsh: So there's kind of two ways to answer that. So our expanded access program included a lot of different rare genetic disorders, and the effect was the same across the board. I think everyone now believes that Epidiolex, or purified CBD, is a good broad spectrum anti-seizure medication, and that, for any different cause of epilepsy, it should potentially have some effect. As the data showed, it's not a cure for most, it just reduces seizures. And you would expect the same for whether MLC is the cause of the person's epilepsy or anything else.

The second way to answer is that too, for the FDA approved Epidiolex, there are indications that are required, including Lennox-Gastaut syndrome, Dravet, and TSC. So for MLC, the question would be, does the child have the electrical clinical pattern consistent with LGS, in which case, they could have LGS due to their MLC, in which case they'd actually be allowed to be prescribed the FDA approved Epidiolex. If they don't, then your doctor would have to prescribe it off label, and that's a discussion to have with your doctor.

And then same thing with the behavior, as I said, there might be positive responses in behavior. I think you just have to be very critical if you try to treat an individual with this. If you don't see anything, then like any drug, stop it. Don't continue it just because you want it to work, but really be critical of whether you think it's working or not.

Dr. Laura Lubbers: Great. Thank you. It's very interesting how the diagnosis of LGS can certainly help patients gain access.

Dr. Eric Marsh: Yes, absolutely.

Dr. Laura Lubbers: Yeah. So can oils from dispensaries be tested, to understand what they correct amounts are from using a third party tester?

Dr. Eric Marsh: Yeah, so absolutely. There are labs around the country that will test. I don't know what the cost is, so I don't know if it's prohibitive to have something tested. Which also brings up the other issue with dispensaries, which I didn't mention, because that study didn't go over it, is batch to batch variability. So if you test it at one time, you might say, oh look, it actually is exactly what it says, but the next time they produce that batch, will they have the same accuracy of what they say is in the product is now in the product?
So you could get to a third party tester to test, but that will just give you reassurance for that batch of the product you have. For the next batch, you'd have to do it again. So I think, to some degree, when you go to a dispensary, you have to have a conversation with them, get as much reassurance from them that they're doing it in a rigorous way, the way they grow, and the way they extract, and the way they produce. And then, just know that if you see a difference from time to time that it could happen. And if seizures are in good control, and seizures stop being under good control, it could be because the product has changed.

Dr. Laura Lubbers: Okay. Here's a question. Is there a shelf life for these products in oil? How long can you keep them?

Dr. Eric Marsh: Yeah, so there is. Cannabinoids are actually light sensitive compounds. So that's why the bottle that it comes in, like Epidiolex comes in, is a brown bottle, in order to filter out light getting into it. And you should store any dispensary or FDA approved cannabidiol in a cabinet out of the light, because light will make the product degrade rapidly. In the dark, in a cool environment, its shelf life is fairly stable. I don't want to give you numbers, because I don't actually, don't quote me on a number, but it is fairly stable if it's kept in the dark and cool. But I'm not going to give a number, because I don't remember offhand what the stability is.

Dr. Laura Lubbers: But great awareness to have for these products in general. Don't leave it out on your windowsill.

Dr. Eric Marsh: Right. Exactly.

Dr. Laura Lubbers: Right. Right. Do you know offhand the dosage of CBD in Epidiolex?

Dr. Eric Marsh: Epidiolex is 100 milligrams of CBD per ml. And the FDA recommended starting dose is five milligrams per kilogram per day, divided in two doses. And there actually is no max dose. So it's based by weight. There's no max dose in reality. The FDA label might have one, so I don't remember if the FDA label has a max dose of like 1000 milligrams a day. Most of my patients are little kids, so we don't get to that, they're all small, so that's not an issue. It's all weight based dose for me.

Dr. Laura Lubbers: Okay, thank you. So is cannabidiol only used as a treatment for tonic, clonic, and atonic seizures? Are there other seizure types that might be, it might be useful for?

Dr. Eric Marsh: So for the studies, motor seizures, whether tonic, clonic, or atonic, were the primary endpoint, and that's where we saw the greatest effect. In my own personal practice, I've had families who have LGS with multiple different seizure types, see response to a variety of the different seizure types, including
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myoclonic seizures, absence seizures, and focal seizures. Though it seems to be greatest for the kind of generalized tonic, clonic, bigger seizures.

Dr. Laura Lubbers: Thank you. So here's a bit of a switch for you. Would using THC recreationally affect the effectiveness of clobazam or lamotrigine in generalized epilepsy?

Dr. Eric Marsh: So yeah, THC also alters the metabolism of some of the CYP enzymes, and I don't remember the direction to which it does, but it does. So medical marijuana, taking a whole product recreationally, is going to potentially alter the metabolism of some of your medications, particularly in that case, clobazam. Less so lamotrigine, but I'd have to look up what the metabolism of lamotrigine is, to say for sure.

Dr. Laura Lubbers: Okay. Right. We're getting a number of questions along those lines, so perhaps we can reach back out to you in the days to come, to see if we can get a summary of where there might be interactions there. I think that might be helpful for our audience here.

Have the individual terpenes been studied for their potential therapeutic effects on epilepsy?

Dr. Eric Marsh: Not that I'm aware of. So I know that GW/Jazz is really interested in exploring other aspects of the cannabinoids and terpenes for their role. But I'm not aware of any information that they've published to this end. And there are mouse basic science studies looking at some terpenes and other cannabinoids, but nothing human that I'm aware of.

Dr. Laura Lubbers: Okay. Are there substantial side effects, such as liver or kidney damage, with use of CBD?

Dr. Eric Marsh: So far, the answer is no. That it is, in all the studies, there was no effect on kidney function. The liver questions a good question. So what was found in the studies, was that there was a increase in liver enzymes in a group of the patients. None of the patients got to the point where there was any issue of liver damage, but there was suggestion that the liver was being irritated. Because an elevation of the ALT and AST, the enzymes we used to measure kind of liver function, and they all went back to normal when you stopped the cannabidiol. So we don't think there's any long-term effect, but again, the medication's only been approved now for six, seven years. So I think, long-term we'll learn more about that, as people follow patients who are on cannabidiol for longer and longer periods of time.

Dr. Laura Lubbers: Sure. Okay. Thank you. Another thing that we might learn more about as we go. This person says that their son is on Epidiolex, and it causes high anxiety. Is there anything else that might explain this, or might not cause the high anxiety? Is there anything that could be done?
Dr. Eric Marsh: Yeah. That's a good question, and I would need a lot more information to really answer that question. As the Epidiolex could be interacting with other drugs, it's possible by the alteration of the metabolism of another drug is bringing out his anxiety. So it could be related, but indirectly related. And in my experience, I've had families report that when they started Epidiolex, that it improved anxiety. But I also have some families who've reported that they think their kid's more anxious, or their behavior has gotten worse on Epidiolex. So I think there's a lot of variability there.

And one of the things I didn't mention is that, these cannabinoids are actually, they don't get absorbed very well via the gut, and so, they're the metabolism and the individual's ability to absorb and process these are going to be very variable. So some of the differences we might see in this might be due not to how the drug works in their brain, but also, how the drug even gets into the body. So differences you see, something like that, could potentially be what we call pharmacokinetic, or pharmacodynamic properties, and not actual brain-derived properties. But that said, we do, there's a lot more we need to learn about these things.

Dr. Laura Lubbers: Right. Right. Right. It strikes me, as I remember the graph that you showed, where the majority of people showed a reduction in seizure activity, but some actually saw an increase in seizure activity. I'm wondering if you can comment on that, and the variability there?

Dr. Eric Marsh: Yeah. So there's two aspects of that. So one is that, we know that individuals who have epilepsy, and particularly epilepsy that has not responded to many medications, their seizures often fluctuate, and that they go up and down. And there's some really nice data from people who've had RNSs implanted in them, where they've been able to follow count, people's seizure counts for months on end, that we see these oscillations in people's seizures. So one possibility for that increase, is that they started the trial at the low point, and they, as the trial went on, they just were in their normal up oscillation, and the medication had no effect, neither good nor bad, but it just looks like it went up, because they happened to be on an up oscillation.

The other potential possibility is that, yeah, for whether it's a metabolism issue or a brain issue, that it actually altered the brain dynamics in such a way that it made someone's seizures worse. So again, there's still a lot we need to learn about that group who did really well. Who are they? Why are they? And can we figure those people out? So we know, hey, you're their best people to put on Epidiolex. That would be something that would be great to be able to do. And unfortunately, we don't have that type of data.

Dr. Laura Lubbers: Right. Right. We need better biomarkers.

Dr. Eric Marsh: Yes, we do.
Dr. Laura Lubbers: For sure. For sure. We'll take one more question. Can you take Epidiolex at the same time as Depakote or other seizure drugs, or should you be separating them in time?

Dr. Eric Marsh: Yeah. So you can take them at the same time. What's important for Epidiolex is, because of the absorption issues that I just mentioned, is that you try to do it always at the same time, or approximately the same time, particularly around meals. So you don't want to give it one time with food, and the next time without it, because it's going to be absorbed differently. So always give it with food, or always give it without food, so that you're just consistent. So that's the best advice for when you give it, is trying to give it as consistently as possible, so that you know its effect, and that you're not getting variable amounts based upon how it's being absorbed.

Dr. Laura Lubbers: Great. Great guidance. Thank you so much. And thank you again for a terrific talk. It was great to see the data again. It is a topic that we need to continue to educate on in our community for sure. So thank you very much for taking the time to do that.

And thank you to our audience, for asking always great questions. Appreciate that so much, and your participation in these events.

I'd also like to thank today's sponsor, Jazz Pharmaceuticals, for bringing this topic to our attention.

So if you'd like to ask additional questions, or want to learn more about our epilepsy, Cure Epilepsy research programs, please visit our website, or you can email us at research@cureepilepsy.org.

Finally, please join us on April 20th, for a special online forum, that will provide a general understanding of the prescription medicine supply chain, and how it impacts access to your medications. A really important topic when you run into challenges in getting medications. This forum will also provide some current resources that are available to the epilepsy community, and attendees will also have the opportunity to ask questions about this complex topic. Registration for the event will be open in the next few days, so please stay tuned for more information on that.

And again, thank you everyone for your attendance, and be well.