CURE Webinar
Promising Anti-Epileptic Drugs in Development
(Transcript)

Dr. Laura Lubbers:	00:06	Welcome everyone to today's webinar. My name is Laura Lubbers and I am the Chief Scientific Officer for Citizens United for Research in Epilepsy or CURE. I want to thank you all for joining us today. CURE is pleased to continue our Leaders in Epilepsy Research Webinar Series in 2018, this series started and just last year. This year's series will consist of multiple webinars throughout the year that highlights some of the key research that's being done in epilepsy. Today's webinar, which is being sponsored by our friends at Sunovion, will focus on the latest research in epilepsy drug development and will be presented by Dr. Jacqueline French. CURE's mission is to identify and fund cutting edge research in search of a cure for epilepsy. In fact, we are celebrating 20 years of impact in the field of epilepsy research this year. CURE has been instrumental in advancing the science of epilepsy research in many areas including post-traumatic epilepsy, infantile spasms, devices in technology, sudden unexpected death in epilepsy or SUDEP, and epilepsy genetics, just to name a few areas.
Dr. Laura Lubbers:	01:21	Today's webinar is entitled Promising Anti-Epileptic Drugs in Development and we'll outline new therapies that are currently in development for epilepsy, including a number of promising therapies for patients with treatment-resistant epilepsy, children with severe epilepsy and drugs that actually may not only treat seizures, but improve the underlying disease. It is my deep pleasure to introduce Dr. Jacqueline French, who is a professor of neurology in the comprehensive epilepsy center at NYU Langone School of Medicine. She's also the founder and director of the Epilepsy Study Consortium, an academic group that has performed a number of early phase clinical trials in epilepsy and has developed new methodologies for epilepsy clinical trials. Over the past 20 years, Dr French has served as the principal investigator on a number of trials for new epilepsy drugs and is responsible for the creation of new clinical trial designs that have been accepted by regulatory authorities for new drug approval.
Dr. Laura Lubbers:	02:28	Dr. French has been active in creating guidelines for the American Academy of Neurology and the International League Against Epilepsy. She chaired a joint committee that produced two widely quoted guidelines on the use of new anti-epileptics drugs. Dr. French also serves as the Chief Scientific Officer of the Epilepsy Foundation. She is the past president of the American Epilepsy Society and past secretary of the American Society for Experimental NeuroTherapeutics. She's receieved numerous awards for her service to the epileptic community. She's

authored over 200 articles and book chapters and is the editor of three books. She also lectures internationally on clinical trials and the use of anti-epileptic drugs and quite a long successful contribution to the epileptic community.

Dr. Laura Lubbers: 03:21 Before Dr. French 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 GoToWebinar control panels 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 as 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 previous and future webinars will be recorded and available on the CURE website. With that I'd like to turn it over to Dr. French.

Dr. Jacqueline French: 04:09 It's my pleasure to be here. Thank you very much for inviting me to talk about my favorite topic, which is, what's new and what's coming in the epilepsy pipeline. I want to start out by just a giving my disclosures. I'm president, as you heard, of the Epilepsy Study Consortium, and if you look at the names of all of the different companies that are on this slide, it actually makes me very happy because that means that all of these companies in one form or another have an interest in developing new therapies for epilepsy and we work with all of them and any funding that comes from that goes back to the Epilepsy Study Consortium.

Dr. Jacqueline French: 04:54 I'm going to start out by talking a little bit about anti-epileptic drug development. As you can see from this slide, with a somewhat slower start over the last 20 years or so, we have seen a skyrocketing of new therapies for epilepsy. Of course, that doesn't mean that we do not have an unmet need. In fact, recent studies have suggested that despite all of the drugs in red that have been developed and approved over the last 20 years, we still have one third of people full with epilepsy whose seizures are not controlled by conventional medication. I just want to call out that we have had a recent approval, which is for the drug, Brivaracetam or Briviact, which was just approved within the last 12 months.

Dr. Jacqueline French: 05:46 There are some very important trends for the next decade of antiepileptic drug development that I want to talk about. One is the concept of, from blockbuster to mini-buster, and I'll explain what I mean by that. The second one is the issue of targeting and focusing on treatment-resistant epilepsies. Then finally, the

very exciting concept of moving from anti-seizure drugs to anti-epilepsy drugs. Let me start with the concept of, from blockbuster to mini-buster. To date, all of the drugs that I showed you on that impressive first slide have been developed primarily for the common epilepsies and those are the focal epilepsies, which are seizures that start at one or two focal areas in the brain and cause focal seizures, focal aware, focal impaired awareness or focal to bilateral convulsive seizures. Those are almost all the trials in fact that have been done.

Dr. Jacqueline French: 06:52

Then, the second group that has been subjected to trials is people with what we call idiopathic or genetic generalized epilepsy who have generalized tonic clonic convulsions as a consequence of that. Together, these two syndromes alone account for about three quarters of all people who have epilepsy, whether they be children or adults, but all of the development in those two areas has definitely left a large portion, that other quarter of people behind. Those are the people, particularly children who suffer from the rarer epilepsies and sometimes we call them the orphan epilepsies.

Dr. Jacqueline French: 07:36

Now, instead of going for the larger groups, there are a lot of companies that are focusing on these rare or orphan epilepsies where there are no good treatments. That's a good thing because these orphan epilepsies actually have a much higher likelihood of being treatment-resistant and rather severe. The majority now of development is for the rare epilepsies rather than for the common ones. We used to have one big target, which was the focal epilepsies and now we have many targets. Dravet, Tuberous Sclerosis, Glut-1 deficiency, CDKL-5, Rett Syndrome, Lennox-Gastaut are among the rare epilepsies that are now the targets for drugs therapy.

Dr. Jacqueline French: 08:26

Why has this occurred? Why are people so interested in rare epilepsies. Well, for one thing, as we understand more and more about these rare epilepsies, we find that there often as a genetic underpinning or some understanding of why these epilepsies occur. There's more chance for a unifying, underlying cause for these epilepsies than for the focal epilepsies, which are basically caused by anything that can injure the brain whether it'd be a stroke or a tumor or a cortical dysplasia. There are many, many causes. The second thing is, as we said, there are a lot of drugs that have been approved in the focal epilepsy space. The marketplace for these rare epilepsies is not as crowded, although I will say it's getting more and more crowded by the day.

Dr. Jacqueline French: 09:20 The third thing is that, often, patient and parent groups are available and motivated to speed development in these areas. That is extremely important if these groups and smaller organizations can quickly identify patients, can get excitement in the community. Sometimes that helps with the development of the drug and the recruitment for trials and even for finding funding for these smaller companies. Another very important issue is that the rare or orphan diseases get special benefits from regulators including the food and drug administration that are intended appropriately to motivate drug development in areas that, otherwise, there may not be any drugs. They don't have to do as many trials in some circumstances and they get longer exclusivity for their drug once it's on the market.

Dr. Jacqueline French: 10:17 Finally, unfortunately, perhaps one of the downsides is that once developed, when there is this only a small number of patients that are going to receive the drug, the drug can command a premium price in the marketplace and insurers that would definitely bulk at paying a premium price for a very large number of people, will say, "Well, it's okay if we're only paying for a small number of people." Sometimes these therapies, depending on the size of the marketplace, can command $100,000 or more price tags. These are the things that we also have to keep an eye on.

Dr. Jacqueline French: 10:59 I have a rather busy slide here that shows you how many different drugs are being developed for orphan syndromes. I'm not going to have time to talk about every single one of them, but I am going to focus on a couple of them that I thought you might be interested in. Specifically, I'm going to be talking about Epidiolex or Cannabidiol, which is in development for Dravet, Lennox-Gastaut and seizures associated with tuberous sclerosis. I'm going to talk a little bit about Fenfluoramine, which is in development for Dravet syndrome and Lennox-Gastaut. To get back to the more common epilepsies, I am going to talk about inhaled Alprazolam, which is a drug that is in development for anybody who has seizures in clusters, no matter whether it's focal or generalized or in an orphan syndrome. It's more for the general population of people with epilepsy.

Dr. Jacqueline French: 11:59 I'm going to start talking about CBD cannabidiol or Epidiolex and obviously there's a great deal of interest in our community around Epidiolex. In fact, the food and drug administration very soon is going to be having an advisory panel to discuss whether this drug will be approved by the FDA for the treatment of Dravet Syndrome. I'm showing you here some of the data from the Dravet syndrome study. I actually saw a press report today saying that the FDA has stated that they feel that the company

has been provided reasonable data to support an approval of this drug, which is of course good news for everybody in the community who's waiting for the drug to be approved. Once the drug is approved and there is a medical use for it, a CBD will no longer be schedule 1, which makes it very, very difficult for people to get ahold of.

Dr. Jacqueline French: 13:01 Once there is a medical use, hopefully, at least it will be downgraded to a schedule 2 drug, again, that will make it much easier for doctors to prescribe it. Okay. Here you see the results in convulsive seizures. What this is, is a graph that shows you the approximate percent reduction on average that each of these children experienced who was in the trial. The green bar is the children who here or is the children who we're on placebo or a sugar pill. You can see that they did have a reduction also, which is always interesting. Why do people who have a sugar pill added, have a reduction in their seizures? Some of it could be just that, people who have an increase in seizures are more likely to enroll in trials and seizures have a tendency to ebb and flow.

Dr. Jacqueline French: 14:00 They may just have gone up right before the trial started that made people more motivated to go into the trial and then just naturally they go back down again. Also it may be that people have such high hopes when they go into a trial that they actually get better just from the expectations that they will get better. If you see the blue line, is the people who were actually getting the active drug and this was a blinded study, which means that neither the doctors who were recruiting people into the trial nor the patients themselves knew which group they were in, the treated group or the placebo or sugar pill group. You can see that the people who got the drug had about a 40% overall reduction in convulsive seizures.

Dr. Jacqueline French: 14:59 This is for Dravet, which is a very severe childhood onset epilepsy associated with a genetic abnormality. Again, this is an indication that this drug is in fact effective for people with seizures and you can see on the other side of this slide is an indication of the reduction in total seizures. Now, that's slightly less than the reduction in convulsive seizures, but still much, much greater than the reduction that's seen in the people who had the sugar pill. Again, this is a very good evidence that's going to go before the Food and Drug Administration that says, "Yes, this drug does have an impact on epilepsy and it reduces seizures." Now, there are people who say, "Well, I want cannabidiol or CBD because it's a natural compound and it's unlike a drug and I want something that's more natural and doesn't have side effects." I am here to tell you that a CBD or

cannabidiol is indeed a drug and it does indeed have side effects.

Dr. Jacqueline French: 16:13 This slide is here to demonstrate that point. You can see that all caused side effects in the people who had CBD added to their regimen, the children, as opposed to having placebo added to their regimen, had more side effects of any cause. Interestingly enough, even those who went on the sugar pill had additional side effects. If you look at the side effects that the doctors thought were related to treatment, then you start to see quite a big difference where you can see that, 70% of the children who were on the active drug had side effects related to the treatment whereas only 27% of those on the sugar pill had side effects related to the treatment. In fact, about 15% of the children who were on the active drug had to come off of treatment because of those side effects as opposed to only 1.7% of those with the sugar pill.

Dr. Jacqueline French: 17:18 When you look at people who had serious of what they consider to be serious side effects, again, you see about three times as many, had serious side effects when they were on the active drug as compared to the placebo. This is not uncommon for new therapies and it's certainly not worse than any of the other new therapies that we have, but this drug does have side effects like other new therapies. You can see that at the top of the list was sleepiness, and diarrhea, and decreased appetite and fatigue.

Dr. Jacqueline French: 17:53 Some of these were actually related to interactions with other drugs that the children were taking. That has to be kept in mind and that is why this drug is best used in conjunction with medical supervision. Some of the side effects included abnormal liver functions and that happened particularly when CBD was combined with valproic acid or Depakote. The sleepiness was much more significant when the drug was combined with Clobazam or Onfi because CBD does cause an increase in the amount of the CBD or Onfi that is in the bloodstream due to an interaction. That's why it's important that, there be a doctor who's sort of supervising all of this when CBD is added.

Dr. Jacqueline French: 18:51 I also wanted to show you the results in another Dravet study. Perhaps people are not as familiar with this drug and they should be. This is Fenfluramine from a company called Zogenix. They also did a study in children with this severe epilepsy called Dravet Syndrome. Here you can see that they're actually at the higher dose compared to 7.5% of the children who had a 50% reduction in seizures with the sugar pill. 70% of these children had a 50% reduction in seizures with fenfluramine. When you

look at the number of children who had a 75% reduction, that was even less common in the children who had the sugar pill, but 45% of the higher dose of fenfluramine had a 75% reduction in seizures. This was significant enough that the FDA is considering this as a breakthrough therapy and that is a big deal.

Dr. Jacqueline French: 19:55

What does that mean? That means that the Food and Drug Administration is saying, "We think that your drug has sufficient data that it is going to substantially benefit people with epilepsy or people depending on the indication. that it is our responsibility as the government to help you get this on the market as quickly as possible so that people can benefit from it as quickly as possible." There has not been been a drug designated as a breakthrough therapy in the epilepsy space, so this is a real indicator from the FDA that they are excited about this data and we should be too.

Dr. Jacqueline French: 20:38

Again, no drug is without risks and side effects as well as it's benefits. Fenfluramine actually used to be part of a combination therapy called Fen-phen that some of you may remember, depending on how old you are, that was given as a treatment for obesity to make people lose weight. It was pulled off the market because people were noted to have heart valve thickening as well as some pulmonary fibrosis. That occurred only in the combination of fenfluramine and phentermine and this is only fenfluramine that's being given now and also the doses that were used were much higher. We are hoping very much that as the lower doses that are being used and with fenfluramine alone, that this is not a risk, but obviously we have to keep a very, very close eye on the children who are being treated with this drug to make sure that they are not having heart valvular thickening or pulmonary fibrosis.

Dr. Jacqueline French: 21:43

Fortunately, you can look at this relatively easily with a non invasive test and if there is any indication that something is happening, one could remove the therapy before any serious damage happens now that we know to look for this. We are keeping a close eye on that. In addition, you can see that there were treatment emergent side effects just as there were in this study of a CBD where 95%, approximately, of children on the active drug had side effects compared to only 65% on the sugar pill or placebo. When you look at the number of children who had serious treatment emergent adverse events, there actually was not a substantial difference between those on the sugar pill and those on the active drug and that obviously is very good news.

Dr. Jacqueline French: 22:46

I'm going to move on to talk about inhaled alprazolam. We use a lot of drugs in the class called benzodiazepines, and you may have heard of Valium, which is diazepam and ativan, which is lorazepam. A lot of people use these as what we call rescue therapies to make their seizure clusters stop. Unfortunately, and they can use it as a pill, they can use it these days, it is possible to get it to be used in the nose, sometimes to be used as a buccal administration. Even when it's used in the nose and the buccal administration, it takes about 10 to 15 minutes before it works. I shouldn't, by the way, forget to say that some people still use it rectally as Diastat. Any of these ways that people use it, it still takes 10 to 15 to work.

Dr. Jacqueline French: 23:46

That is not helpful when you are, for example, having an aura for a seizure and you know that a minute from now you might be having a generalized convulsion or you're having a cluster of myoclonic jerks. It's going to go on for 15 to 20 minutes. You want something that works as fast as possible to stop the seizure activity. The lung, fortunately, has a lot of area to absorb drug and a rescue inhaler is a concept that people use for other conditions. Obviously, they use it for migraine, they use it for asthma.

Dr. Jacqueline French: 24:26

The idea behind inhaled alprazolam is really to have a rescue inhaler for epilepsy that at the first sign of trouble, if you have an aura or you start to have any type of seizure activity, if the individual is able to breathe in, then at that point then they can breathe in through this device and they can rapidly perhaps within even seconds to minutes, to a minute or two, they can cause that seizure activity to stop. That is the goal. That is the hope. The device exists, the drug exists and it's currently in very early trials and hopefully those trials will be successful and eventually this drug will prove to be of benefit to the community.

Dr. Jacqueline French: 25:18

I'm going to change gears now and talk about treating a drug resistant epilepsies. As we talked about earlier on, two thirds of people with the common epilepsies respond to the drugs that are now available. For the last several decades, all of the drugs that I showed you on the first slide, in the figure that have been approved over the last many decades, have initially been tested in treatment-resistant patients. However, they have not been specifically designed for use in treatment-resistant patients. This what we call a population of convenience.

Dr. Jacqueline French: 26:00

You obviously can't try new drugs in seizure-free patients because there's nothing to test against. You're going to have to use treatment-resistant patients in your studies, but, eventually, the intent is, that that drug, let me take an example of levetiracetam, Keppra or lacosamide, Vimpat that were initially tested and treatment-resistant patients, but eventually were used earlier in the lifespan of an epilepsy and now are often used in patients who just have been diagnosed or recently have been diagnosed. That is different from trying to develop a drug specifically to treat those treatment-resistant patients.

Dr. Jacqueline French: 26:51

The new way of thinking is that, epilepsies that don't respond to drugs are biologically different than epilepsies that do respond to drugs. Maybe we need different drugs to treat those epilepsies than the drugs that we have to treat newly diagnosed or more early epilepsies. How are we going to find those drugs to treat the treatment-resistant? Well, we need new animal models for one thing, that are reflecting the patients who are treatment-resistant rather than the population as whole, with the goal of creating a drug to work specifically for those patients. Fortunately we do have some drugs that are under development. CBD gel is one of them, Cenobamate, a drug called Padsevonil and another drug that also is in the Cannabinoid line called Cannabidavarin. I am going to focus because it's closest to the clinic on a drug called Cenobamate.

Dr. Jacqueline French: 28:02

This drug actually has gone through the majority of the testing that it needs to go through in order to be approved by the FDA. We're hoping that perhaps even within a year, it will be submitted to the FDA for approval. You can see this is a very early trial that was done where, again, patients with treatment-resistant epilepsy were randomized in the trial. This was a relatively short study. It was only eight weeks in duration as opposed to to the typical study that's 12 weeks. Nonetheless, you can see that the individuals who were were randomized to take the drug as opposed to take the placebo sugar pill, the ones that were randomized to the drug had actually, 32% of them had a 90% reduction in seizures over that short period of time granted, versus only 8% of those who were randomized to the sugar pill.

Dr. Jacqueline French: 29:09

When you look at the ones who had no seizures over the course of the trial, more than a quarter of them, and these are treatment-resistant patients who had failed many, many other drugs before that, a quarter of them did not have any seizures over the course of the trial as opposed to the patients who were randomized to the placebo. This is a drug that we believe does have the possibility of taking people who have not responded to

other drugs and making them seizure-free. Many of those patients were then continued in a long-term extension of the trial and were found to remain seizure-free during the long-term extension of the trial. This is an exciting drug.

Dr. Jacqueline French: 29:57 Again, it's not without its side effects. When you go higher on the dosage, it does make people fatigued than it does make people have a dizziness at higher doses and there is a risk of a rash, which is also a common risk with other anti-epileptic medications that people are put on, so it's not one that we don't understand or haven't dealt with before. Nonetheless, it's important to know, but this does represent a really promising new approach for people who have not responded to other medications in the past.

Dr. Jacqueline French: 30:41 Now I want to switch gears and talk about the idea of anti-epilepsy drugs versus anti-seizure drugs. All of the drugs available currently to treat epilepsy are actually anti-seizure drugs. That means that they don't act to stop the cause of seizures. They just block the excitation or increase inhibition in the brain or prevent repetitive firing in the brain to block the seizures. The analogy that I often use with my patients when I'm talking about this is, imagine that your seizures are a big, nasty, ugly spider that just crawled out from someplace and is sitting in front of you ready to bite you. If I were to take a cup and put it right over the spider, then I would neutralize the spider. It couldn't bite you, it couldn't hurt you and everything would be fine. However, I have not in any way, shape or form done anything to the spider.

Dr. Jacqueline French: 31:44 Eventually, if medications are withdrawn or I lift that cup in my analogy, then the spider might still be there and it might still be just as virulent as when the cup went over it. Perhaps the spider passed away from old age while it's under the cup or whatever and so sometimes when we take the medications away, no more seizures happen. With the cup over the spider, we have no idea whether that spider is alive or dead and that is the same thing that's true when we give anti-seizure medications. We've just neutralized the seizures, but we have done nothing to actually change the disease.

Dr. Jacqueline French: 32:29 As we gain better understanding of what causes seizures, and unfortunately in many people we still don't know what causes their seizures, but as we gain a better understanding, we hope that we can change from anti-seizure drugs to anti-epilepsy drugs. In my example, this would be some poison that would actually neutralize the spider. If we did have such a treatment, it could actually lead to what we call disease modification, which

means that over time perhaps you could eliminate the risk of seizures, eliminate the excitability in the brain and no longer need medication. We would be getting closer to what we might call and this is obviously relevant here, a cure because that's what this organization is all about is cure.

Dr. Jacqueline French: 33:20

I am very happy to say that just last week a drug that is our first real approach to an anti-epilepsy drug was approved by the FDA for a very specific type of epilepsy. This is a drug that works on something called the M-Tor pathway. It's rather complicated scientifically, but M-Tor stands for the Mammalian Target of Rapamycin. It's a signaling pathway that regulates how brain cells grow, differentiate and multiply. In some people, they have a gene defect that causes this particular pathway just to go wild. Brain cells are growing and multiplying in a way that's just erratic. It leads to several things, but it leads to poor connections that can cause excitability in the brain. The people who have this genetic defect have a disease called Tuberous Sclerosis Complex. We think that this M-Tor pathway going awry may also lead to another type of epilepsy called cortical dysplasia, although the evidence is not quite as clear.

Dr. Jacqueline French: 34:44

With tuberous sclerosis Complex, we know for a fact that there is a defect in the gene that regulates the M-Tor pathway and that is why they have this disease, Tuberous Sclerosis. We know also that in animal models, if you can find a drug that inhibits or tamps down this M-Tor pathway, you can prevent or reverse epilepsy caused by these illnesses. We now have a drug and it's actually been available for quite a while as a chemotherapeutic agent called Everolimus. Everolimus is known to be an inhibitor of the M-Tor pathway. Because it is a used as a chemotherapeutic agent against tumors, it was tried in children with tuberous sclerosis who developed these tumors in their brain called giant cell astrocytomas. As you can see on this MRI that I'm showing you here in this child, a big tumor was shrunk down in this child by being on Everolimus.

Dr. Jacqueline French: 35:54

As these children with Tuberous Sclerosis who also happen to have epilepsy, were getting treated for their tumors, it was noticed that their seizures were also getting better. Somebody said, "Well, maybe this not only will help with the tumors, but can also help with the disruption that causes seizures." Sure enough, they did a randomized-controlled trial and they showed that there was a substantial reduction in seizures even in children who didn't have these tumors in their brain, if they were given Everolimus. On April 10th, Everolimus was approved for the add-on treatment of adults and pediatric patients aged two years and older with tuberous sclerosis-associated partial

onset seizures. This really is the first drug that is working on what we know to be wrong in the brain that cause these children and adults to have seizures. We hope that this is just one of many such treatments that we will be finding and testing over the next decade.

Dr. Jacqueline French: 37:07 In conclusion, we have a very robust pipeline. I wasn't able to show you everything, but I hope I showed you a few things that are exciting. Many new anti-epileptic drugs are being evaluated in the clinic and many more are about to emerge and many of them are very promising. Every new drug will need to undergo clinical trials and clinical testing similar to what I showed you here and we absolutely need the support of the community to enroll in these trials.

Dr. Jacqueline French: 37:38 A lot of the people who did stand up and enrolled in these trials are now experiencing a benefit of the drugs that they used in the trials. The nice thing about these trials is that, yes, you can be randomized to a sugar pill during the trial, but the drugs that you're already taking are not taken away, so you're still on the medications that you've been given initially. Also, after the duration of the placebo controlled part of the trial, everybody in almost every circumstance is given the opportunity to try the experimental drug to see whether it's going to work for them. With that I will stop and I will ask for questions.

Dr. Laura Lubbers: 38:28 Thank you so very much Dr. French. That was wonderful. We will now begin our Q&A session. Again, If you have questions, please submit them in the questions tab to the GoToWebinar control panel and click send and Brandon can go ahead and read them aloud. Brandon-

Brandon Laughlin: 38:47 I'll tell you in advance, we did receive a lot of questions, so I'll try and get through as many as I can given the time available. More of a clarification question to start out, Dr French. You mentioned schedule 1 and schedule 2. Can you explain these different stages a little bit further?

Dr. Jacqueline French: 39:14 There are drugs that are considered to be controlled substances, which means that people can become dependent or get addicted to them. The more likelihood that there is that people will get addicted to them, the higher the level of control that the government puts on the distribution of those drugs. We all think of drugs like heroin and morphine. Heroin, in fact, is the most controlled of drugs because it is so addictive and also because it has no medicinal use. The drugs that are in the schedule 1 are considered to be highly addictive and have no medicinal use whatsoever. People are surprised to know

cocaine, for example, is not schedule 1 because there is a use of cocaine for some eye diseases, so it's actually scheduled 2.

Dr. Jacqueline French: 40:14 It's extremely difficult to even do research on schedule 1 compounds because they are so highly regulated by the government and very difficult, obviously, you can't prescribe them because they have no medicinal use. Once a drug is known to have a medicinal use and it becomes schedule 2, then it is much more easier to move that product around to have it in pharmacies without like 10,000 lock on every door where this substance is being held and it just makes things much, much easier. Then you go down the line. For example, many of our epilepsy drugs are on the schedule of potentially addictive drugs.

Dr. Jacqueline French: 41:04 You'd be surprised, drugs that perhaps people who take them would say, "I can't imagine anybody would use these if they didn't have to." There is some evidence that in fact people do try and get them for recreational use and not for medicinal use and that includes drugs such as Pregabalin or Lyrica drugs such as a Vimpat or Lacosamide. Yes, those are restricted to some degree, but they're only scheduled 4, so they're lightly restricted. As you go up to schedule 3, schedule 2 and schedule 1, you get more and more and more restriction.

Brandon Laughlin: 41:49 Great. Thank you. Next question, I've actually received a few questions actually on this topic, but a drug such as Epidiolex and Fenfluramine and drugs that are being developed for Dravet Syndrome for instance, will they be available to others with similar seizures, but may not have the Dravet or that clinical diagnosis?

Dr. Jacqueline French: 42:11 It's a very good question. In the United States specifically, the FDA doesn't put restrictions on doctors to say, "You can only prescribe a drug for what it has been FDA approved for and is on the FDA label." The studies that are done and the diseases that are studied in the trials, will lead to a label that says, "This has been shown to be safe and effective in condition A, B, or C." I could prescribed that drug for condition, D, E and F, but there are a couple of issues that I would have to have in mind as a physician.

Dr. Jacqueline French: 42:53 Number one is that, there is a certain amount of liability because I am going what's called off-label. My patient that I'm treating might say, "I came to some harm from what you did and really you weren't doing the proper thing because the FDA didn't say it was approved for this particular indication." You

were taking on some risk when you prescribed off-label, although many, many, many people do it. It's done all the time.

Dr. Jacqueline French: 43:24 The second thing is that, your insurance company might say, "Hey, this is a reasonably expensive drug and nobody has said that for your condition it's effective, so why are we going to pay for it?" One or two things can happen. It may be that your doctor can then appeal to the insurance company and provide extra information and the insurance company can eventually agree to pay for it or they may just completely not agree under any circumstances. We have had that issue arise with one of our other drugs that is only approved for what we call an orphan condition and that is a Clobazam or Onfi. It's a reasonably expensive drug and it's only approved for Lennox-Gastaut Syndrome and sometimes I can get it for my patients and sometimes the insurance company will just completely stonewall and say, "No, you can't have it."

Brandon Laughlin: 44:27 Great, thank you. The next question actually deals the Cenobamate trial that you referenced earlier and a few actually asked if we know what the mechanism of action in that study was.

Dr. Jacqueline French: 44:43 There's some very smart people out there asking questions. Cenobamate, we do not specifically know the mechanism of action. However, it is in the class of drugs called carbamate. There was one other drug that was approved for epilepsy that's in that class and that is Felbamate. We do not know its mechanism. We know that it is somewhat related. It's a second cousin or a third cousin of Felbamate. Felbamate was a very effective drug for many people with epilepsy, but as a many of the audience may know, it is used very rarely now because it caused serious liver problems and a plastic anemia which has not been seen with this drug. If it was as efficacious as Felbamate, that would be a good thing and perhaps in some conditions it's more and the rest remains to be seen.

Brandon Laughlin: 45:46 Well, that was a great answer because you actually answered my next two questions with that answer, so that was great. The next question, we'll go back to the Epidiolex study. Will Epidiolex have to be de-scheduled by the DDA after FDA approval?

Dr. Jacqueline French: 46:02 I am really not entirely familiar with that process. I think that there, there's not an instantaneous change. I'm going to ask a Dr Lubbers whether she has any idea about the answer to that.

Dr. Laura Lubbers: 46:17 That is a great question and we can certainly look into it.

Dr. Jacqueline French: 46:21 Okay.

Brandon Laughlin: 46:25 Great. Thank you. The next question actually deals with targeted treatments for the genetic epilepsies outside of Dravet. Do we know whether there are targeted treatments for those epilepsies in development?

Dr. Jacqueline French: 46:45 The first answer is yes. On the slide that I showed, there were a couple of genetic conditions that there are targeted treatments. Excuse me. Glut-1 deficiency is a great example where these are children who have a genetic defect that prevents their brains from turning glucose into energy. They have an energy defect in the brain and over time, that leads to seizures as well as an increase in cognitive dysfunction. There is a targeted therapy of a drug that can be used by the brain to produce energy that's not glucose and therefore could reverse the specific problem in these children. That is one example of a treatment that is specifically targeting one genetic condition.

Dr. Jacqueline French: 47:53 There is a drug called Ganaxolone that is being tried specifically in children with CDKL-5, which is another specific genetic defect. It doesn't reverse the specific issue in CDKL-5, but there are reasons to believe it might be effective in CDKL-5. There are a number of drugs that are specifically targeting genetic defects. I think that what you may also be asking is, are we trying to reverse the genetic defect that caused the epilepsy to begin with, as was the case with the tuberous sclerosis and Everolimus? There are some attempts at that. They're a little bit further away probably from the clinic, but, for example, there's a drug called Endololin being tested in children with genetic code problems where there's a certain part of the gene that's supposed to create a protein that is very important for the development or the running of the brain. When that gene is being read, it comes upon a mutation and that whole mechanisms stops. It's called the stop codon and that protein can't be created.

Dr. Jacqueline French: 49:21 This drug actually allows the information in the gene to be read even when that mutation is in the middle of it and that protein to be created. That would be really amazing if that works and it might actually be able to prevent the disease if it was given early enough to a child who had that genetic defect. These are the almost science fiction things that are turning into reality in clinical trials.

Brandon Laughlin: 49:59 Thank you. In reference to a slide earlier, when you said the period of follow up is eight weeks or 12 weeks, are they on drug

during those eight to 12 weeks or do they stop taking drugs and see what happens in the next eight to 12 weeks?

Dr. Jacqueline French: 50:15 It's also a good question. The way trials work is, usually, they start with what's called the baseline period, which is just a period where we can figure out what the frequency, the typical frequency of seizures is. Let's say an individual has four seizures a month or five seizures a month or 10 seizures a month, whatever that number is, it's determined during an eight-week baseline. Then at the end of that baseline, they get randomized and they continue on there. During the baseline and during the study, they're continuing to take whatever medication their physician has given them, a combination of medications that is the best control that they can get.

Dr. Jacqueline French: 51:04 At that point they're randomized to either adding the new drug or adding a sugar pill. Then for eight to 12 weeks they carry on and they see whether the seizure frequency that was determined during the baseline, is actually going to go down or go up or whatever happens. That goes on for eight to 12 weeks. Then at the end of that the randomized portion of the trial is over and they go into what's called the open-label extension. During that time, everybody can be on the medication. The doctor knows the dosage, they know that the medication is being administered, they can manipulate it, they can change the background medications or whatever is considered to be optimal for that individual. During the double-blind they may or may not be taking the study medication, but once they get to the open-label extension, everybody is given the study medication on top of the medication that they're already taking.

Brandon Laughlin: 52:08 Great, thank you. Actually you've answered a few more questions in there as well, so this is phenomenal. One of the questions that I received even prior to the webinar and one that came up actually in a few other questions that I received during the webinar, are these drugs safe to take while a woman is pregnant?

Dr. Jacqueline French: 52:30 Pregnancy, we always advise that drugs that are in clinical trials, women should not go into clinical trials if they are planning pregnancy and in fact we have significant safeguards in place. People have to sign a consent that says that during the trial, they will use appropriate birth control, so that they will not get pregnant and we make sure that they or receiving a birth control that's likely to be effective, so that they will not get pregnant because this is not the time when you want to be experimenting to see whether this medication will adversely affect the fetus. Because, first, you want to make sure that the

drug actually works, is safe and effective. Once the drug is safe and effective and is approved and is then available to the public, then over time some women will take it and will become pregnant. Only then, can we really know entirely whether the drug is safe during pregnancy.

Dr. Jacqueline French: 53:32 We have many pregnancy registries that accumulate data on the drugs once they are in the clinic, but it is unfortunately a very slow process. It may take decades before there are enough women in the registries that we have really good information about whether the drug is safe in pregnancy or not. Even some of the drugs that have been around for a really long time and Lacosamide is one good example, we don't have enough information really to say for an absolute assuredness that it is safe in pregnancy. We do have information as immediately when the drug is approved, as to whether it's caused birth defects in animals. The label that's put on the drug by the FDA, will say either the drug has been shown to be safe in animals, but we don't know about humans or the drug has been shown not to be safe in animals, but we don't know about humans or the drug has been shown to be harmful in animals and harmful in humans, so that it gives them an A, B, C or D rating.

Dr. Jacqueline French: 54:45 The higher the letter, the worse it is. A class D drug would be one where it's been shown and this is, Valproic Acid or Depakote is in this class that is both harmful in animals and also has been shown to be harmful in people during pregnancy. The A designation is almost never given where we say, "Oh we absolutely know it's as safe as houses and anybody can take it and it's perfectly fine. Most seizure medications are either B or C.

Brandon Laughlin: 55:26 Wonderful, thank you. I think probably we're coming near the end of questions, so I think the appropriate last question of the day might be, where do we get more information on clinical trials?

Dr. Jacqueline French: 55:41 Good question. The Epilepsy Foundation actually has a lot of information on epilepsy.com. If people want to know whether there is a trial that they could sign up for then that is an excellent place to look, there is a section of epilepsy.com where the trials that are underway describe a little bit of information about what we know about the drug and what the trial would be like if you were to enroll in it. That's one good thing that's on epilepsy.com and there's also a part of epilepsy.com where there is a pipeline. You can see all of the drugs that are currently in development and what stage of development

they're in, whether they're in early development or they're close to the clinic.

Brandon Laughlin: 56:32 Thank you so much Dr. French. I'm going to go ahead and turn it back over to Laura for some final words.

Dr. Laura Lubbers: 56:39 Thank you so very much, Dr. French. That was a really helpful presentation. You reviewed a lot of really exciting things that are coming forward for our community. I also want to thank our sponsors Sunovion for hosting today's webinar. I'd like to thank our audience for being so engaged and asking some great questions that we'll have to follow up on, at least for once. If you do have questions about this topic or any of CURE's other research programs, please do visit our website at www.cureepilepsy.org or you can email us at info@cureepilepsy.org. With that, I want to thank you all once again, and please do stay tuned for our next webinars that will be announced very soon. Take care.