CURE Webinar
SUDEP
(Transcript)

Brandon Laughlin:	00:00:06	Welcome everyone to today's webinar. My name is Brandon Laughlin with Citizens United for Research in Epilepsy, or CURE. Thank you for joining us today. Today's webinar, which is being sponsored by our friends at Sunovion will focus on sudden unexpected death in epilepsy or SUDEP and will be presented by Dr. Elizabeth Donner. CURE's mission is to find a cure for epilepsy by funding and promoting cutting-edge research.
Brandon Laughlin:	00:00:55	We've been instrumental in advancing the science in many areas of epilepsy research, including post traumatic epilepsy, infantile spasms, post-traumatic epilepsy devices and technology and epilepsy genetics, and we hosted webinars on all of those topics this past month. Today's focus is on SUDEP, a field that is deeply personal to many members of the CURE community and that has remained a funding priority of CURE's since we funded our first grant in this field of research back in 2004. I'd like to introduce our expert for today's webinar. Dr Elizabeth Donner is the director of the Comprehensive Epilepsy Program at the hospital for sick children in Toronto and an associate professor in the faculty of medicine at The University of Toronto.
Brandon Laughlin:	00:01:52	Dr. Donner is a clinician researcher with peer reviewed funding to examine the risk factors for sudden death in children with epilepsy. Dr. Donner has a long standing commitment to the epilepsy community. She is co-founder of SUDEP Aware, a volunteer run nonprofit organization, which promotes knowledge and understanding of sudden unexplained and unexpected death in epilepsy through education, research and support. She has held leadership positions with the Canadian League Against Epilepsy, Canadian Pediatric Epilepsy Network and Epilepsy Toronto. She was chair of the American Epilepsy Society, SUDEP Task Force and is a member of the steering committee of the epilepsy foundation SUDEP Institute. Before Dr Donner begins, I'd like to encourage everyone to ask questions. You may submit your questions at any time during the presentation by typing them into the questions tab of the GoToWebinar control panel and clicking send. I will go ahead and read those out loud during the Q&A portion of the webinar.
Brandon Laughlin:	00:03:03	We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we do 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 the entire leaders in epilepsy research

webinar series will be recorded and available on the CURE website. Now, I'll go ahead and turn it over to Dr. Donner.

Dr. Elizabeth Donner: 00:03:48 Thank you so much. In fact, before we start, I really would like to recognize the efforts of CURE in the SUDEP arena. CURE has just been a tremendous leader in this field, and really that's been driven by a highly motivated and passionate group, including some tremendous dedicated parents such as Jeanne Donalty and Gardiner Lapham, mothers of children who were lost to SUDEP. And CURE was so early in the field to work on finding answers to this tragedy. They have such a long and successful record of funding research to understand SUDEP that I just really am continued to be grateful for their work in this area. Thank you for that and for this opportunity to present today. Whenever I talk about SUDEP, I always feel like I need to talk about some of the people and families that have been most impacted by this.

Dr. Elizabeth Donner: 00:04:50 Because I'm a child neurologist, a lot of my SUDEP work is focused on children. Just before we start talking more about what is SUDEP, I'd like to share very briefly a story of two children that I've come to know, or at least I've come to know their families through my work. This beautiful boy is Nathan. Nathan was almost five years old when he died. He had Dravet syndrome, which some of you will know is an epilepsy syndrome that's associated with a genetic mutation, most commonly in a gene that encodes for a sodium channel, and we'll talk a little bit more about that later. Kids with Dravet syndrome usually have a lot of seizures that are difficult to control. From what his mother has told me, this was true for Nathan.

Dr. Elizabeth Donner: 00:05:40 However, in the one and a half to two months prior to his death, he had actually been seizure free, or at least seizure-free as best as they knew. They were actually discussing reducing some of the medications he took for his epilepsy with Nathan's doctors. Then, he'd had a good day, they'd been to the park and went to bed without issue. Then, the following morning he was found by his mother in his usual sleeping position. He didn't even look like he'd had a seizure. He was curled up in his usual position. Then of course, tragically, she recognized that he had died. There was some evidence that he'd had a seizure because he had had some like a bite on his tongue and a little bit of vomit on his pillow, but perhaps he'd had that seizure and then resettled himself back into his usual position. No autopsy was performed on Nathan. However, review of all this seems that it's most consistent with sudden unexpected death in epilepsy.

Dr. Elizabeth Donner: 00:06:50 I also want you to tell you about Jordan. This beautiful young woman began having seizures at 14 years of age. I've come to know her well only through the stories that her parents and her brother have told me about her. She was a very high achieving high school student and an athlete. She had very infrequent seizures. Her seizures seemed to come under good control with the second medication that was tried, only because the first gave her some side effects. She was very compliant with her medications. She did not want to have a seizure while she was engaging in athletics or at school, and so she worked hard to take care of her epilepsy. Not dissimilar from the previous story, Jordan had had a normal day and went to bed normally and then in the morning when she did not come up for breakfast as she normally would, her father went down to check on her and found her again in her bed, and she had passed.

Dr. Elizabeth Donner: 00:07:53 There was again, some suggestion that a seizure had occurred because of the way the sheets were ruffled in her body position. Jordan did undergo an autopsy which did not demonstrate any notable cause of death, and so that makes her death as well to be consistent with SUDEP. I know that those are sad stories, but I think it's very important for us to remember the people behind this tragedy as we talk about some of the science and what we've come to learn. We know that people with epilepsy are at an increased risk of premature death compared to the general population. A standardized mortality ratio compares the death rate in a specific population to the general population. The standardized mortality ratio for epilepsy is 2.3, which means that people with epilepsy are two times a little bit more than two times more likely to die than people who don't have epilepsy.

Dr. Elizabeth Donner: 00:08:51 That's for all people with epilepsy. If you look specifically at children, the rates of death are higher. Really, what that reflects is the high death rates among higher death rates among children who have significant neurological impairments. Because a lot of children who have epilepsy have a lot of things associated with their epilepsy, be that motor or cognitive impairments. This high relative mortality rate also reflects, thankfully, the very low overall mortality rate we see in children in general. A very nice study was conducted by Matti Sillanpaa and Shlomo Shinnar, where they looked at 245 people. Found them as children. They were diagnosed with epilepsy in 1964 when they were children, and they followed that group of children forward for 40 years as they became adults and further on.

Dr. Elizabeth Donner: 00:09:52 What they found in that long study confirmed that the mortality rate was about three times that of the general population. About 24% of the cohort that they followed had died within the 40 year followup. The risk factors for premature death in this group, meaning the factors that put people more at risk of having died included active epilepsy and what active epilepsy means is not being seizure-free for five years. So still having seizures within the last five years and also symptomatic epilepsy. What symptomatic epilepsy means is having a known underlying cause for the seizures, be it a brain injury or a metabolic condition or something of that type.

Dr. Elizabeth Donner: 00:10:48 Other studies have shown that when we look at people with epilepsy and try and understand who's most at risk for premature death, other studies have shown that not being compliant with drug treatment, and so that's what's meant by poor antiepileptic drug or AD adherence, and having drug resistant seizures or medically intractable seizures, meaning that seizures aren't well controlled by medication are also risk factors for premature mortality. When a person with epilepsy dies, of course we can consider a variety of causes. For sure, the death could be unrelated to epilepsy at all. The deaths could be related to the cause of the epilepsy. For example, in a neurodegenerative disease that causes both seizures and premature deaths or in the case of a brain tumor, or deaths can be due to epilepsy. When we consider deaths that are actually due to epilepsy, there are really two categories here that I think of.

Dr. Elizabeth Donner: 00:11:48 One is due to the direct consequence of a seizure, that could be prolonged seizures like status epilepticus, although deaths due to that are quite rare. That could be deaths due to the consequences of a seizure and an accident or trauma like a drowning or a car accident related to a seizure having occurred. The other category of deaths due to epilepsy or what we're talking about today, which is sudden unexpected death in epilepsy. Now, I've written unexplained/expected because the term unexplained needs to be used more commonly. We've switched to unexpected, but I do want everybody to know that we're talking about the same condition when those two words are used.

Dr. Elizabeth Donner: 00:12:33 Because I'm a child neurologist, I just want to share a little bit of child information here, child data around what we know about when children with epilepsy die. I think it's really important to recognize that most deaths in children with epilepsy are not epilepsy related. I thank Elaine Wirrell for the next few slides which she shared with me. What this demonstrates is in three very nice large studies where they've looked at groups of children with epilepsy and looked at cause of death in those groups, they found that the vast majority of deaths represented in the yellow bars were not epilepsy related. When you dig deeper into that, on my next slide, you'll see that we can look at the causes of death in those different groups. By far, greatest cause of death, non-epilepsy related cause of death in children who have epilepsy is actually pneumonia, and that's represented in the red bars.

Dr. Elizabeth Donner: 00:13:33 This relates to what I was talking about at the beginning when I explained why children have a higher risk of premature deaths, children with epilepsy, it's because of this higher risk of death related to pneumonia, and it's really related to children who have significant neuro-disability that affects their lung function and their breathing function and their breathing health. When we look at epilepsy related deaths ,again, this is in children and this is data that comes from four separate studies. You can see that even though most deaths in children are not epilepsy related, when you look at the epilepsy related deaths, SUDEP, in all four of these studies, is absolutely the greatest, most frequent cause of death.

Dr. Elizabeth Donner: 00:14:23 SUDEP accounts for most epilepsy related deaths in children. Other causes include things like status, aspiration, which is choking and things like drowning. But SUDEP in the red bars is accounting for most epilepsy related deaths in children. This is true for adults as well. So what is SUDEP? Well, I already told you it stands for sudden unexpected death in epilepsy, and that really explains what it is. SUDEP is the death of a person who had epilepsy. The deaths needs to have been unexpected, so they weren't dying of an underlying disease. The death should have occurred suddenly. It does not matter if the death was witnessed or unwitnessed, and it does not matter if there was a seizure preceeding death, and we'll talk a little bit more about that, but there is not always a seizure proceeding the death in SUDEP.

Dr. Elizabeth Donner: 00:15:17 Then really, the important consideration for SUDEP is that there isn't another cause of death found. So, it's the sudden unexpected death of a person when no other cause of death can be found. To do that, really we do need an autopsy or a postmortem examination. That's the same thing. But sometimes we don't actually have autopsy information on patients. For example, in Nathan's case, no autopsy was done. For the purpose of the research that I do and many of my colleagues do, we have categories of SUDEP that help us to categorize cases of sudden unexpected death in people with epilepsy even when autopsy isn't performed.

Dr. Elizabeth Donner: 00:16:02 The American Academy of Neurology and the American Epilepsy Society recently, in 2017, published practice guidelines with regards to SUDEP. I was part of the group that worked on this report. I'm going to talk a little bit about that because I think this has been a very powerful document for both people living with epilepsy, their families, and also healthcare practitioners, treating people with epilepsy, because it has really given some kind of concrete facts the epilepsy community can use when talking about SUDEP. The AAN, which stands for American Academy of Neurology and AES, American Epilepsy Society. The AAN and AES Guideline asked two questions. First, we looked at the literature to try and determine what is the incidence rate of SUDEP in different epilepsy populations? To really nail down, how big of a problem is this? How common is this?

Dr. Elizabeth Donner: 00:17:06 The second question was, are there specific risk factors for SUDEP? A risk factor, I'll remind you, is something that puts a person at an increased risk of something occurring. For example, a really nice easy example is we know that smoking is a risk factor for lung cancer. We reviewed the literature to try and identify what are the strongest risk factors for SUDEP. Let's start first and talk about incidents. These slides come from the American Academy of Neurology based directly from the guideline that was published earlier this year. What this is showing you here is that the overall incidents in all people with epilepsy, be they adults or children, the overall incidents of SUDEP was deemed to be about 0.6 per 1000 patient years.

Dr. Elizabeth Donner: 00:17:57 What that means is, in one year, if you look at a thousand people who are living with epilepsy, just under one of them will die from SUDEP and then the next year you have to put one back to make up another 1000 people living with epilepsy and another one will die. One of the interesting things about reviewing the literature to look at SUDEP incident rates, and this was pretty well established before the guideline came out as well because there'd been quite a few good quality studies done looking at the incidence of SUDEP in both children and adults. One of the interesting findings was that the incidents of SUDEP in childhood was felt to be quite a bit lower than the incidents in adults. What we tend to say is that in adults the risk is one per 1000 people with epilepsy per year, but in childhood it's actually closer to one in 4,500 children with epilepsy per year.

Dr. Elizabeth Donner: 00:19:00 This is based on a good review of the literature. However, oh and this, just to demonstrate, and I mentioned that ... In fact, this was pretty well established before in this nice paper by Dave Thurman and his colleagues, they summarize the data on incidents as well that was available from lots of studies that had been published. They show that, here you look at the proportion of SUDEP cases that occur across the age range. Sorry, I'm actually using my mouse. I hope that it shows up. I'm looking at those blue bars, and you can see that the blue bars are highest indicating that most SUDEP cases happen in the ages between 20 to 50 years of age.

Dr. Elizabeth Donner: 00:19:46 Likewise, the other graph which shows the red, blue and green lines, if you look at the risk of SUDEP goes up as people get older. The green, blue and red lines represent whether the epilepsy began at one year of age or under one year of age, whether the epilepsy began under 15 years of age or whether the epilepsy began under 30 years of age. So, you can see also that the SUDEP risk is higher in people who have epilepsy of a younger onset. We had been reading the literature and understanding that SUDEP appear to be more rare in children, although for those of us that work in this arena, I became quite acutely aware that it was very difficult to obtain information about SUDEP deaths in children. A lot of the children that I believed were dying of SUDEP had a lot of other disabilities and medical problems and autopsy often was not performed, families had never heard about SUDEP, and perhaps identify to the coroner or to the doctors looking after the child at the time of death.

Dr. Elizabeth Donner: 00:21:17 They didn't ask about whether SUDEP could be a possibility. I really felt strongly that we were missing a lot of cases of SUDEP in children, and that in fact the rates might not be that much lower in children than they were in adults. Actually, on my next slide, I'll tell you about the work that we've done with funding from CURE to try and investigate that problem. But before I tell you about that, I will tell you that it was good for me to see the study that came out earlier this year by Sveinsson, et al, which wasn't incidents study of SUDEP over one year in Sweden. What they found is that SUDEP actually may be more common in children than previously documented and some of us had been previously wondering about. Now they've given us that evidence, which is great. I'm sad to see that, but I think it's important that we recognize the extent of the problem. What Sveinsson and colleagues show here in this table is the blue bars represent males, deaths in males, and the red bars represent deaths in females.

Dr. Elizabeth Donner: 00:22:24 We'll talk about that in a moment, but you can see that under the age of 20, there are still some SUDEP deaths. When you look at the table over to the right, what they found is the incidents in all ages was 1.2 per 1000 people per year, which is exactly what we found from all the other studies and when we reviewed it for the AAN, ASS Guideline, but when they looked at the under 16 population, they actually found that the incidence is essentially the same as it is in adults, so 1.1. Now, those of you that are familiar with statistics will see that the confidence intervals are wider on the pediatric age group. We can debate that, but I do think that this data suggests that previous studies have been missing some SUDEP deaths in children.

Dr. Elizabeth Donner: 00:23:17 Another finding that we can't ignore from this data is that in fact, all the deaths that happened in the pediatric age group in this study, in this Sveinsson study were actually in boys rather than girls. I actually don't have an explanation for that. I'd be happy to ask the authors when I see them next I'm not able to explain that, unfortunately, but I do think it's important to recognize they are now documented in incidents of SUDEP in children to be essentially equal to the incidents in adults. I mentioned that I was lucky enough to receive funding from CURE quite a few years ago now. What that helped me do was set up a pediatric SUDEP registry across Canada. I worked with three groups. I have worked with three groups.

Dr. Elizabeth Donner: 00:24:12 I've worked with the Canadian pediatric Epilepsy network, which is a group of pediatric neurologist, child neurologist treating epilepsy that represents across the country of Canada. I've worked with the Canadian Pediatric Surveillance program, which has allowed me to ask pediatricians about their experience with sudden death in epilepsy. Finally, I've had the opportunity to review the autopsy report reports from the province of Ontario's Forensic Pathology service. What we did because we felt we had quite comprehensive data collection in the province of Ontario because we had both pediatricians, neurologists and autopsy reports, is we decided to look at the incidents of SUDEP in children in the province of Ontario.

Dr. Elizabeth Donner: 00:25:02 Over 24 months of surveillance, we found 17 SUDEP deaths in children under the age of 18 years. You can see from the red and green bars. The red graph represents the deaths that occurred in girls and the green bars represent deaths that occurred in boys, that in fact, we had deaths in both boys and girls, not replicating the male predominant seen in this Sveinsson paper. When we look at 17 deaths, and we consider and do the math, and I am grateful to Ann Keller for working on this project with me. When we do the calculations to consider how many people with epilepsy were living in the province of Ontario during that period of time, we can come up with an incidence of SUDEP over that period. In fact, our incidence of SUDEP in children is essentially the same as what Sveinsson found, 1.1 per 1000 per year, and essentially the same as the overall SUDEP incident rate in adults.

Dr. Elizabeth Donner: 00:26:05

So we now have a couple of lines of evidence to suggest that SUDEP may not be as rare in children as we have previously believed. This data, I haven't put a reference on it yet. It says yet unpublished, but is under consideration at this time for publication. I've told you how common or rare we consider SUDEP to be.

CHARACTERISTICS OF DEATH FROM SUDEP

Let's talk a little bit about the details of these deaths. In fact, when I told you about Nathan and Jordan at the beginning of the presentation, both of those deaths are quite characteristic of what we hear about the circumstances of death in SUDEP. The vast majority of deaths occur in bed, and people are usually found in the prone or face down position. It's pretty uncommon for a SUDEP death to be witnessed. Depending on the study you read, about 10% to 20% of the time deaths are witnessed.

Dr. Elizabeth Donner: 00:27:12

But when deaths are witnessed, from about half to up to 90% of the time, there's evidence that the person who died had a seizure immediately before they died, had a big shaking or convulsive seizure before they died. We know that witnessed SUDEP is more common in children. That's not surprising. For those of you that live with a child with epilepsy, I'm sure you know how carefully children with epilepsy are watched by their parents and the people that care for them, and so it's not surprising that kids with epilepsy are rarely left alone. In our study published in 2001, we reported 27 SUDEP deaths in children, of which actually 10 were witnessed. Of those 10 witnessed deaths, in five of the cases, the people who were present when the child died actually saw the child have a seizure before they died. In the other cases, they didn't see the child have a seizure.

Dr. Elizabeth Donner: 00:28:07

Now, it's possible that there was a seizure that was quite subtle, or sometimes you may know that you can have a seizure in the brain that doesn't come out in the body, so it's possible that that's what was happening. This strong finding that SUDEP deaths frequently occur from sleep or in bed or overnight has made people wonder about whether watching people overnight or using some kind of monitor overnight like an auditory monitor or a baby monitor, whether that can reduce the risk of SUDEP, and we'll talk a little bit more about that going forward, but it does appear that nocturnal supervision may be protective for SUDEP. Sorry, just hoping to advance this slide. Oh, advanced it too much. Okay. Sorry.

Dr. Elizabeth Donner: 00:29:12 I told you that a risk factor is something that makes a person more likely to have an outcome or have a disease. It's been quite important for us to try and identify who among all the people living with epilepsy are more at risk for SUDEP. Especially if we're going to say things like using a baby monitor might help reduce your risk or there are other interventions that may help reduce risk, we really want to get an understanding of who's at the highest risk. There was a very nice study done by Dale Hesdorffer on behalf of the International League Against epilepsy. Dr. Hesdorffer and her colleagues had access to 289 cases of SUDEP and they compared the circumstances to 958 people who were living with epilepsy.

Dr. Elizabeth Donner: 00:29:58 You'll remember before that, I told you that SUDEP is more common in people with younger age of epilepsy onset. What they did is they stratified or divided the groups by epilepsy age of onset, to try and understand what are the other risk factors besides age of epilepsy onset that can put people at increased risk of SUDEP. The strongest risk factor was frequent generalized tonic-clonic seizures. In fact, as is demonstrated in that last bullet point, having more than three or more generalized tonic-clonic seizures per year, actually increases epilepsy risk. Pardon me, increases SUDEP risk sometimes 12 up to 38 times more. I'm going to speak about this a little bit further, but I think it's important when we have a look at this study, and you'll see that I've written here in polytherapy, but then I struck a red line through it.

Dr. Elizabeth Donner: 00:31:01 I just want to point out that in this study it actually appeared that people who were taking multiple medications at once for their epilepsy prescribed by their healthcare team, and we call that polytherapy when you are using more than one anti-convulsant at a time. People who are using polytherapy appear to be at increased risk of seizures. Pardon me, increased risk of SUDEP. However, when they went back and adjusted and looked more carefully and adjusted for the number of generalized tonic-clonic seizures those people were having, remembering of course that if you are taking more medication for your seizures, it's probably because you've been having more seizures and that's why the healthcare team has been suggesting to add extra medications on. When you actually consider how many generalized tonic-clonic seizures the individuals have, there is no increased risk associated with being on a single drug versus being on polytherapy or any specific epilepsy drug.

Dr. Elizabeth Donner: 00:32:01 In fact, a very elegant study done by Philippe Ryvlin and his colleagues, where they looked at the information collected from 112 eligible randomized trials of drugs. This is when an industry wants to obtain approval for a new anti-convulsant and they do a randomized control trial to compare their new medication to existing medications with placebo to see whether a new medication is more effective at controlling seizures. Those industry studies always report their SUDEP rates within their trials. What Dr. Ryvlin did in this study is he looked at the deaths from SUDEP that occurred during randomized controlled trials. What they found is that the rates of SUDEP among people who had received, as part of the trial, who had received a good dose of the new anti-convulsant, new anti-epileptic drug, AED had what we expect, is just the general rate of SUDEP at about one per 1000 per year.

Dr. Elizabeth Donner: 00:33:14 But people who had received placebo who did not get the new add on drug actually had a higher rate of SUDEP. What this suggests is that, in fact, being on polytherapy is not a risk factor for SUDEP. In fact, the opposite. Failing to add new drugs and continue to try and control seizures with new drugs may increase risk. Risk factors was an important focus for the American Academy of Neurology and AES Guideline. This is a table from that guideline which highlights the most concerning risk factors for SUDEP. By and large, the most important risk factor is having generalized tonic-clonic seizures. You can see that the odds ratio for having generalized tonic-clonic seizures rather than not, it's 10, meaning that people with generalized tonic-clonic seizures are 10 times more likely to die of SUDEP than people with epilepsy, but without generalized tonic-clonic seizures.

Dr. Elizabeth Donner: 00:34:18 Similarly, this is a number I like to highlight because I think it's very powerful. The number of generalized tonic-clonic seizures per year is very important. I know for a lot of the families that I work with and people that we treat with epilepsy, that it can be hard to control seizures. In some instances, people don't consider their seizures to be frequent if they have a few generalized tonic-clonic seizures per year. But in fact, having simply more than three generalized tonic-clonic seizures per year actually increases the risk of SUDEP over 15 times. It's really important that we remember when we're trying to control seizures, that reducing the number of generalized tonic-clonic seizures is not just about trying to maintain a driver's license or trying to not have seizures that interfere with our work life or social life. It's actually a life saving measure to try and reduce the frequency of generalized tonic-clonic seizures.

Dr. Elizabeth Donner: 00:35:18 There are important risk factors identified by the AAN, AES guidelines included that idea of active epilepsy that I mentioned at the beginning of the talk or not being seizure-free within the last five years, not adding another drug when seizures are medically refractory, which means not well controlled on medication. Then, there were two things that were found to reduce risk. These were found with less confidence, but the Guideline Committee still felt it was worth noting. And that’s this issue of nocturnal supervision or using a nocturnal listening device. Terminal supervision here is defined as either having frequent checks through the night or sharing a room with another person an adult or an adolescent at least.

Dr. Elizabeth Donner: 00:36:18 Both that and the use of an auditory listening device, really what we're talking about here is like the old-fashioned maybe monitors, both of those interventions appear to reduce SUDEP risk. There is a limited amount of data on this, but the Guideline Committee, after much discussion felt it was important to share that with the greater neurology community. I know that it's called sudden unexpected death in epilepsy and we still have a lot to learn, but I do feel that it's worth highlighting that we are able to identify who is at highest risk of SUDEP. These are people with early onset of epilepsy, refractory, generalized tonic-clonic seizures, not controlled by medication, and probably those without some element of nocturnal supervision.

Dr. Elizabeth Donner: 00:37:13 However, many of us who work with people with epilepsy know lots of adults and children who fit into that category, yet, and thankfully, not all of those people, by far, will be affected by SUDEP. We are still working actively and there are some really exciting research going on to try and identify within that high risk group really, who is at the high, high risk? Is there something we can look for or identify in certain individuals that can even further quantify their risk? The idea of a biomarker is something that we can measure in a person that then helps us to predict something or tell us something about their disease. There has been a lot of work looking for biomarkers for sudden unexpected death in epilepsy. I'm just going to very, very briefly highlight a couple of areas of research because I thought they'd be of interest to the group.

Dr. Elizabeth Donner: 00:38:20 There has been some great work looking at whether there are genetic markers that may increase SUDEP risk. Some of this work was started by Jeff Noebels and Alicia Goldman, and in fact, Dr. Noebels was earlier a speaker on one of these CURE webinars. What this group demonstrated was that there was a potassium channel mutation, which means a gene mutation that encodes for a channel within nerve cells that lets potassium ions go in and out of the nerve cells. They found in mutation that in rodents, if that gene is mutated and that potassium channel is not working properly, that those rodents can have both seizures and also cardiac arrhythmias can result in sudden death. That's a very attractive hypothesis because we know that there are quite a few epilepsy conditions that are caused by mutations in channels that allow ions, like potassium and sodium and calcium, to move in and out of the cells.

Dr. Elizabeth Donner: 00:39:34 We also know that those type of mutations can cause problems with the heart. It's quite an attractive hypothesis that there might be a single mutation that can cause both cardiac arrhythmia and epilepsy and thereby confer risk of sudden death. Dr. Noebel's group very elegantly demonstrated that in their animal models, and since that time there's been really very impressive increase in work in this area, which I don't have time to summarize for you now, but I will just point out that it has very much entered the clinical sphere as we have begun to demonstrate any increased risk of SUDEP in association with some of these genetic epilepsy syndromes such as Dravet syndrome associated with sodium channel mutation in the SCN1A gene, the early infantile epileptic encephalopathy is also associated with two sodium channel mutations listed there and also in the DEPDC5 familial focal epilepsy. Looking for genetic biomarkers for SUDEP is a very active area of inquiry at this time.

Dr. Elizabeth Donner: 00:40:47 Another area that people have been trying to explore is looking at the EEG and trying to see whether the EEG of a person living with epilepsy may demonstrate or give us information about their risk of SUDEP. This study, by Philippe Ryvlin and many colleagues, looked at SUDEP deaths that had occurred in epilepsy monitoring unit. This is when people with epilepsy are admitted to hospital for prolonged video EEG monitoring. They identified 16 SUDEPs or near SUDEPs, meaning where a person died, but was resuscitated by CPR. So they identified 16 cases of SUDEP or near SUDEP that had occurred in these epilepsy monitoring units or EMUs. All of the SUDEP cases, 11 of 11 and five of the six near SUDEPs occurred after a generalized tonic clonic seizure, and they all had a very similar pattern of events where first, there was the seizure followed by to tachypnea, which is fast breathing, followed by a slowing of the heart rate or bradycardia, and then apnea, which was stopping breathing, and then eventually a cardiac arrest.

Dr. Elizabeth Donner: 00:42:12 In all cases, the EEG following the seizure demonstrated a very dramatic flattening of the brainwaves, and this is called postictal generalized EEG suppression. In all cases of SUDEP, a seizure occurred and then the EEG demonstrated that's flattening of the brainwaves, and then the SUDEP occurred. Now, this is likely not representative of all cases of SUDEP because this is a pretty specific situation. These are cases in which people were admitted to the hospital, many times their regular anti-convulsant medications are reduced to encourage them to have seizures. There are a specific group of patients who were admitted, for the most part, to see if they could have surgery for their epilepsy. This does not represent all SUDEP, but it does tell us that in this group of patients that EEG flattening seems to be associated with SUDEP.

Dr. Elizabeth Donner: 00:43:10 What we and others have done, and again, I told you before, I'm a child neurologist, so I tend to study these things in children, but what we and others have done is just how to look at how common is this EEG flattening in children with epilepsy in general. In fact, it seems to be pretty common even though we know all those kids will not, by any means, go on to suffer from SUDEP. Brian Mosely and his group showed that 32% of the children admitted to his hospital to have a video EEG actually had that EEG flattening, which is called PGES or postictal generalized EEG suppression. When we looked in our group and Dr. Okanri's paper, Dr. Okanari's the first author on this work, we looked at 400 video EGS that were done at our institution, sick kids, and of all the kids that had generalized convulsive seizures akin to generalized tonic clonic seizures, actually almost 50% of them had that PGES following the seizure.

Dr. Elizabeth Donner: 00:44:12 We did try to look for predictors of PGES so that we could say, well, what kind of seizure is it that produces PGES? We found that, as expected, PGES always followed a generalized tonic-clonic seizure that when PGES occurred, it followed a seizure that had symmetric tonic extensor posturing, which means that all the limbs, the arms and legs were stretched out during the beginning part of the seizure and also those seizures had a shorter shaking phase or a shorter clonic phase. Frequently, there was a certain EEG pattern called burst-suppression. What this work is telling us is, first we were wondering, so is PGES associated with SUDEP? Well, it seems that PGES is associated with SUDEP, but at the same time, PGES is also very common. Here's an example of something that could potentially be a biomarker, but needs really more honing down for us to really better understand, again, which patients who have PGES will actually be effected by SUDEP.

Dr. Elizabeth Donner: 00:45:24 I've already shown you this slide, but I just wanted to remind you and re-center us that we still are able to identify who's at the highest risk, that it's people with early onset epilepsy, refractory generalized tonic-clonic seizures and probably a lack of nocturnal supervision. The search is on for potential biomarkers, genetic biomarkers, EEG biomarkers and a host of other interesting studies, including neuroimaging that I'm aware of. But using what we know and what we've learned so far, there is a good plan for SUDEP risk reduction. Really what that is, is active epilepsy management. Now, I talk to groups of healthcare providers all the time about SUDEP. It's actually something I enjoy doing. Frequently, I will hear or see that people think, well, yeah, but we already do this. But what's important to realize is when we're working with our patients or when families are working with their loved one to try and reduce the number of seizures they're having, particularly the number of generalized tonic-clonic seizures are having, we're really working to reduce SUDEP risk, along with all the other benefits that could entail.

Dr. Elizabeth Donner: 00:46:45 I think it's very important that people understand that. Active epilepsy management means reducing seizure frequency, particularly generalized tonic-clonic seizures. It means treatment adherence using the medications and other treatments as prescribed by the healthcare provider. Number three is identifying and avoiding triggers for seizures when possible. Consider using a nocturnal listening device when that's feasible. I clearly recognize that that's not a possibility for everybody living with epilepsy. Finally, and really important, we haven't talked about this so far, but when medications are not sufficient to control seizures, we really need to encourage people to seek out other epilepsy treatments. That could be a dietary treatment for epilepsy such as the ketogenic diet, and it should definitely be surgical evaluation to see whether the person's epilepsy can be treated with surgery.

Dr. Elizabeth Donner: 00:47:40 It's great for me to tell you that, but unless people know about SUDEP and unless they're talking about it, I don't think we're going to move forward. This has actually been…. There's been a history of reluctance within the medical community to actually talk about SUDEP with people living with epilepsy and their families. In answer to this, in 2008, we wrote a report for the American Epilepsy Society. We clearly included in that report that the increased risk of death associated with epilepsy should be discussed with people as part of all the epilepsy education they get. This was followed up in 2012 in an Institute of medicine report that clearly stated that the discussion of SUDEP may actually help to manage fears and prevent unnecessary

		anxiety, and that people with epilepsy in their families need complete and accurate information about all the comorbidities and mortality risks associated with epilepsy, including SUDEP.
Dr. Elizabeth Donner:	00:48:50	The AAN, AES Guideline also recommends that healthcare practitioners should be discussing SUDEP with people with epilepsy and their caregivers. That includes, and these are their very specific recommendations, informing parents that there is a rare risk of SUDEP in children with epilepsy, informing adults with epilepsy that there's a small risk of SUDEP, and informing people with epilepsy that seizure freedom, particularly freedom from generalized tonic-clonic seizures is strongly associated with a decreased risk of SUDEP. You see the part in parentheses there, that medication adherence is one important way of trying to achieve seizure freedom.
Dr. Elizabeth Donner:	00:49:39	Professional bodies are telling us that we should be talking about SUDEP with our patients and we actually know that people with epilepsy and their caregivers want to know more about their risk. In one study, up to 62% of adults with epilepsy and up to 94% of caregivers are people with epilepsy were actually worried about the risk of deaths related to epilepsy. In a kind of neat study, they looked at the number of Google searches for the term SUDEP and found that between 2004 and 2013, there were 21,000 Google searches for the term SUDEP. Between those years from 2004 to 2013, there was a 5,000% increase in how often the search term epilepsy SUDEP was used. So people are Googling this. In a nice a survey of parents in the UK, parents of children with epilepsy, 34% already knew about SUDEP anyways and 91% wanted to know more.
Dr. Elizabeth Donner:	00:50:41	I frequently make this argument, and I'll use this platform to make it again, I think we really need to encourage open discussion about SUDEP. It is time to talk about SUDEP. I do feel that education is the most accessible tool we actually have to reduce the burden of mortality and epilepsy. By talking to people about their risk and how to reduce their risk, I think we will see positive change. To help with that, there are lots of resources available online. There's a few websites you can check out, including CURE's website, which has some valuable information, and the other websites listed there. With that, I will stop and take questions.
Brandon Laughlin:	00:51:54	All right. I'm in the few minutes that we have, I'll try to get through as many questions as I can. Dr. Donner, you were mentioning there at the end about talking or education being something that we need in regards to in SUDEP. What are some

of the barriers that healthcare professionals have when talking about SUDEP?

Dr. Elizabeth Donner: 00:52:12 Thanks Brandon. That's a good question and it's one that I get a fair bit, and I actually have slides about that too, but I can't show everything in one short talk. One of the big issues has been the fear of healthcare providers that learning about SUDEP, that if they're patients or parents of kids with epilepsy, learning about SUDEP, that they will actually be causing more harm than good, that the anxiety produced by learning about SUDEP will surpass any potential benefit. But there's actually been some nice studies about this. There's really no evidence that learning about SUDEP causes any undue anxiety or ha There has been some qualitative research done by my colleague Rajesh Ramachandran Nair at McMaster University where he's talked to parents of children with epilepsy and people living with epilepsy about their interest in SUDEP information. They clearly have expressed a need for more information about SUDEP.

Dr. Elizabeth Donner: 00:53:15 There has been a study out of Susan Duncan's group in the UK that showed that, upon learning about SUDEP, there was no significant change in anxiety or worry related to their risk. That's probably been the biggest barrier.

Brandon Laughlin: 00:53:34 Thank you. Actually, this question is from a couple people, but talking about face down position, does this indicate suffocation? If so, are there things that can be done to prevent that?

Dr. Elizabeth Donner: 00:53:53 The suffocation question is a really good question and it's kind of complicated, but I want people to think about the fact that when a person is sleeping and they're in otherwise good health, if they roll over and their face goes into the pillow, and this probably happens to us a few times a night, what happens is, we're not breathing well. Actually, our brain wakes us up and we roll over. You don't suffocate while you're sleeping because your brain has a mechanism to know when you're not breathing well when you're sleeping, and you wake up. What might be happening in some SUDEP cases is that, after people have a seizure, and many of you will know that often in the immediate period of time after a seizure, people can be, what we call a postictal state. Quite sedated, unresponsive like they're in a very, very deep sleep.

Dr. Elizabeth Donner: 00:54:56 It's quite possible that the brain in that state is unable to respond to the cues that allow us to roll over when we're breathing into our pillow. We don't exactly call it suffocation because what's happening is the effect of the seizure has made it such that the brain doesn't wake up because the person is face down in their pillow. I hope that answers the question, and I recognize it's a bit of a complicated explanation. With regards to the more practical side of the question around, well, does that mean that people would be safer if they just slept on their back all the time? There is some newer research coming out that shows that actually some SUDEP deaths people are found on their side or on their back position as well. Even if that was the case, it wouldn't completely fix the problem, but there's two important considerations.

Dr. Elizabeth Donner: 00:55:51 One is that when we look at people who are having seizures, and we have the opportunity through our video EEG monitoring to review lots of people having seizures on videotape, we can see that most of the time in a generalized tonic-clonic seizures, the movements of the body causes the person to roll over onto their stomach. Even if you could convince the body to always stay sleeping on the back, it's quite possible that during a seizure, a person flips over onto their stomach. The other is we move around while we're sleeping. There are some tricks, different things you can wear and stuff that make it uncomfortable to sleep on your stomach, but even if we were to do that, it's quite likely that the body flips over during a seizure. Unfortunately, I don't think that's been very well developed as a prevention technique.

Brandon Laughlin: 00:56:45 Great. Thank you. Then, I'm going to ask one last question since we had a few questions regarding technology and devices. Are there any wearable devices that could monitor epilepsy and that risk for SUDEP?

Dr. Elizabeth Donner: 00:57:00 Another really great question. Something that gets a lot of attention, for sure, is the advent of all these new epilepsy monitoring devices. There are quite a few devices available to the general public that monitor for seizures. There really is no evidence that these devices actually reduce SUDEP risk. Now, of course, it's difficult prove that because, practically speaking, you would need to give devices to so many people and then wait to see whether it reduces the risk of SUDEP. What we know about some of these epilepsy devices is that they can alert a caregiver when a seizure occurs. Then, what we need to then extrapolate from that is whether going to a person when they have a seizure, so the person who had the seizure, whether they benefit from the attention of a caregiver in the immediate post seizure period and whether that will reduce SUDEP risk.

Dr. Elizabeth Donner: 00:58:05 I think it's going to be almost impossible to prove that the devices can reduce SUDEP risk, but I definitely think that the devices have a place in alerting caregivers that a person has had a seizure, and that those can, at times, give peace of mind to caregivers. But we need to be cautious because devices can have both false positive and false negative alarms. Meaning sometimes the devices don't pick up all the seizures and sometimes the devices pick up all sorts of movements that aren't seizures and alarming all the time. Also, I'll remind you that 10 of the 27 pediatric cases that I reported back in 2001, there was someone present with the child when they died. Just because there was someone there, they still are not able to save that life even if we're alerted to seizures, it doesn't mean we're going to be able to save every life, unfortunately.

Brandon Laughlin: 00:59:04 This concludes our webinar today about SUDEP. Thank you to Dr. Donner for a wonderful presentation. And to Sunovion for sponsoring today’s webinar. Also, I'd like to thank our audience for being very engaged and asking great questions. If you have any further questions on this topic, please visit our new website at www.CUREepilepsy.org, or you can email us at info@cureepilepsy.org. Thank you.