CURE Webinar
Post Traumatic Epilepsy
(Transcript)

Brandon Laughlin:	00:00	Welcome everyone to today's webinar. My name is Brandon Laughlin from 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 post-traumatic epilepsy and will be presented by Dr. Ramon Diaz-Arrastia.
Brandon Laughlin:	00:21	For those of you who may not be familiar with CURE, our mission is to find a cure for epilepsy by promoting and funding patient focused research. CURE has been the pioneer in many areas of epilepsy research, including SUDEP, where we have invested over four million into research.
Brandon Laughlin:	00:38	CURE has also worked to accelerate the understanding of infantile spasms using a multicenter, multi investigator research approach. CURE is supporting development of new technology that may be able to help detect seizures and alert caregivers. CURE also realizes that anyone is at risk for developing epilepsy because it can be acquired over time and as a result of brain injury.
Brandon Laughlin:	01:03	We have a grant from the US Department of Defense that supports a team approach to understanding post-traumatic epilepsy. Dr. Diaz-Arrastia is Professor of Neurology at the University of Pennsylvania Perelman School of Medicine. At Penn, he serves as Director of Clinical Traumatic Brain Injury Research and Associate Director of the Penn Center for Brain Injury and Repair.
Brandon Laughlin:	01:25	Dr. Diaz-Arrastia's research interests have been focused on understanding the molecular, cellular, and tissue level mechanisms of trauma induced, neuro regeneration, and injury related synaptic plasticity with the goal of developing effective therapies. Dr. Diaz-Arrastia received his MD and PhD degrees at the Baylor College of Medicine in 1988. After an internship with Beth Israel Hospital and the Harvard Medical School, he trained in neurology at Columbia Presbyterian Medical Center.
Brandon Laughlin:	01:59	Dr. Diaz-Arrastia has published over 170 primary research papers as well as over 40 invited reviews and book chapters. He has also served in several national committees related to TBI and post-traumatic epilepsy convened by the Institute of Medicine, the National Institute of Neurological Disorders and Stroke, the National Institute of Aging, the Department of Defense, and the Veterans Administration.

Brandon Laughlin:	02:24	Before Dr. Diaz-Arrastia begins, I would like to encourage everyone to ask questions. You may submit your questions anytime during the presentation, by typing them into the questions tab of the GoTo webinar control panel and clicking Send. At the conclusion of Dr. Diaz-Arrastia's presentation, I will read them aloud during the Q&A portion of the webinar.
Brandon Laughlin:	02:45	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 is available on the CURE website.
Dr. Ramon Diaz-Arrastia:	03:08	Well, thank you very much for that very, very nice introduction. And thanks for putting together this terrific series of presentations. So, let me start by letting everyone know... Let me see here, if we can get to the first slide. In a historical note, and I want to make the point here that traumatic brain injury is probably among the oldest maladies that has affected humankind.
Dr. Ramon Diaz-Arrastia:	03:36	In fact, before we were humans, we were already bashing each other in the head. There is evidence of a South African australopithecine skeleton, a three million year old skull that this particular individual appears to have been killed as a result of an assault by another australopithecine that hit him over the head with an antelope humerus.
Dr. Ramon Diaz-Arrastia:	03:59	In fact, The Edwin Smith Surgical Papyrus, which is the oldest medical text, provides a very clear description of a traumatic brain injury sustained during war time with contralateral paralysis and coma. There's been some scientific word trying to quantify this prevalence of traumatic brain injury during prehistoric times.
Dr. Ramon Diaz-Arrastia:	04:30	In physical anthropologists who have studied ancient burial sites, find that anywhere from 15 to as much as 40% of all skulls found in these ancient burial sites have evidence of skull fractures. In many cases, healed skull fractures that people survived, and in many cases survived for many years. So, it's very clear that traumatic brain injury was an important factor, an important selective factor, in human evolution. Any genes that would have predisposed to promoting resilience, some brain injury or promoting repair and regeneration after a brain injury were probably genes that were selected for by evolution.

Dr. Ramon Diaz-Arrastia: 05:16 In some ways, the way to think of post-traumatic epilepsy is that this is the price we have to pay in a sense in order to allow for repair and recovery after traumatic brain injury. Obviously in the modern era, we are not constantly going over to the tribe in the next valley and attacking them and trying to bash them over the head, but traumatic brain injury remains a big problem in modern societies.

Dr. Ramon Diaz-Arrastia: 05:45 In the United States, there are approximately three million emergency room visits per year as a consequence of traumatic brain injury. The vast majority of those are classified as mild traumatic brain injury, although that in itself is a misnomer because some of those injuries have pretty significant consequences. They're called mild because the patient is not in a coma, usually does not require admission to the hospital.

Dr. Ramon Diaz-Arrastia: 06:11 Approximately 20% though of these three million emergency room visits do require admission to the hospital, and a fraction of those folks are in coma and require very aggressive and very expensive care in a Neurological Intensive Care Unit. There are approximately 50,000 fatalities due to traumatic brain injury a year in the United States.

Dr. Ramon Diaz-Arrastia: 06:34 And because traumatic brain injury is primarily a disease of young people, and if they survive the acute injury, they can live for many years and in fact many decades, the prevalence of disability resulting from traumatic brain injury is very, very high. The estimates are that somewhere around 2% of the U.S. population is living with disabilities resulting from a TBI. And of those, post-traumatic epilepsy is one of the common disabilities.

Dr. Ramon Diaz-Arrastia: 07:02 This is in fact the single most common cause of death and disability in young people. Meaning young people under 45. Obviously cancer, heart disease are rare in young people under the age of 45, but in that most important stage of life, this is the stage of life when we are completing our education, when we are finding a mate, starting a family, starting our careers. During this most important stage of life, traumatic brain injury and post-traumatic epilepsy is a significant cause of disability.

Dr. Ramon Diaz-Arrastia: 07:34 The costs to society are obviously very, very high. Looking at the epidemiology, looking at it from the other end of the telescope, in terms of how many people who have epilepsy, how frequently is that due to traumatic brain injury. Studies over the years and this is one of the earlier studies, but this has been confirmed over and over, indicates that if you take all comers with epilepsy, about two thirds of the time, we are unable to

determine what the cause is. These are the so called idiopathic or cryptogenic cases. Obviously, anything that can result in an insult to the brain can result in epilepsy down the line.

Dr. Ramon Diaz-Arrastia: 08:16 Traumatic brain injury accounts for about 4 to 5% of all cases of epilepsy affecting our society. So, it's not the most important cost, but it's not insignificant either. The other thing that's important to notice is that there is a relationship to age. Early in life, developmental disorders and infections are the primary cause of epilepsy and late in life, strokes and tumors are the most common cause of new onset epilepsy.

Dr. Ramon Diaz-Arrastia: 08:49 On the other hand, in young adolescents, in adolescents and young adults, traumatic brain injury is in fact the most common cause of new onset symptomatic epilepsy. That reflects the epidemiology of TBI as a condition. The risk of post-traumatic epilepsy is directly related to the severity of the injury. This is an important old study. It's still. I want to show it because it's one of the most important studies out there. This is from the Rochester, Minnesota, the Olmsted County Epidemiology Project, and individuals who have a severe traumatic brain injury in this top line here.

Dr. Ramon Diaz-Arrastia: 09:36 Severe traumatic brain injury is defined as anyone who was in a coma for longer than 24 hours, or who required a neurosurgical intervention to treat their traumatic brain injury. Individuals who've had a traumatic brain injury are approximately at about a 20 fold increased risk of developing epilepsy compared to the general population. The cumulative probability of developing post-traumatic epilepsy approaches 15 to 20%.

Dr. Ramon Diaz-Arrastia: 10:05 Individuals who have suffered a moderate brain injury, which is this middle line here, well, their risk of post-traumatic epilepsy is lower, but it's still significantly higher than in the general population. It's a partially a three to four fold increased risk over the general population. Then finally, the group of people who have suffered a mild traumatic brain injury, well, they are probably at a somewhat slightly increased risk as well.

Dr. Ramon Diaz-Arrastia: 10:32 Looking at the actual numbers from that study, as you can see here, about a 17 fold increased risk for severe TBI, about a threefold increased risk for moderate TBI. For mild traumatic brain injury, the point estimate for the incidence ratio is only 1.5.

Dr. Ramon Diaz-Arrastia: 10:55 Now, this was not quite statistically significant, the confidence interval approach one. However, a more recent study using epidemiologic data from the Veterans Administration, and this

is looking at administrative databases, largely confirmed the results of that earlier civilian study in Olmsted County. But because it's a much larger study, it does in fact show with statistical confidence that mild traumatic brain injury does in fact increase the risk of post-traumatic epilepsy although only modestly, only somewhere in the range of 1.6 to two fold or so. So, this gives us an idea of the problem we're dealing with.

Dr. Ramon Diaz-Arrastia: 11:41 Now, because mild traumatic brain injury is so much more common than moderate to severe traumatic brain injury, it actually accounts for a dispropotionate fraction of the population attributable risk. This is extrapolating from numbers from the VA Epidemiology Study knowing what the fraction of all TBI falls into each severity band, as well as the odd's ratio for each severity.

Dr. Ramon Diaz-Arrastia: 12:14 The estimates are that almost 60% of all post-traumatic epilepsy is due to mild traumatic brain injury, whereas obviously smaller numbers for both moderate and severe TBI. So, this is a really important number to realize, and this is an understudied population, right? What is the mechanism of post-traumatic epilepsy in these folks with mild traumatic brain injury.

Dr. Ramon Diaz-Arrastia: 12:42 Now, because the precipitating event is usually very obvious, most of us know exactly when someone's involved in a car accident or in a fall or an assault. So, the precipitating event that ends up causing the epilepsy is usually very easily recognized and very clear. Post-traumatic epilepsy represents perhaps the ideal model in which to study the mechanisms of epileptogenesis and also to develop therapies to try to prevent epilepsy. Yeah, the therapies that are truly anti epileptogenic. That has been an effort that has gone back really many decades.

Dr. Ramon Diaz-Arrastia: 13:31 Really going back to the 1980s, there were efforts trying to determine if prophylactic use of antiepileptic drugs were effective in preventing the development of epilepsy or were effective as anti-epileptogenic drugs. The answer unfortunately is no, right? Those studies showed and I'll show you some of the data is that while prophylactic use of antiepileptic drugs prevent the early seizures after a brain injury, they are not effective in preventing late post-traumatic seizures or defending late post-traumatic epilepsy.

Dr. Ramon Diaz-Arrastia: 14:09 So, this is a figure from a very important study published by Dr. Nancy Temkin and colleagues from the University of Washington. Again, many decades old, but still a very important study. It shows very clearly, and this is a randomized control trial, that individuals randomized to phenytoin therapy had a

much lower number of seizures within the first seven days compared to placebo.

Dr. Ramon Diaz-Arrastia: 14:37 Based on this study, it is standard practice in most neurological ICUs and most trauma centers to use prophylactic antiepileptic drugs. Phenytoin was used for many, many years. Now, the more commonly used drug is Levetiracetam. On the other hand, the study by Temkin et al, and the way this study was designed, the patients were randomized to either placebo or phenytoin for six months. Then at six months, if they had had no seizures, the antiepileptic drugs were weaned off and they were followed for a total of 24 months.

Dr. Ramon Diaz-Arrastia: 15:14 What you can see from the slide is that, although there is a clear benefit within the first seven days, that benefit wears off and certainly by 24 months, there was no difference between the phenytoin and the placebo group in terms of the likelihood of developing late post-traumatic seizures. That appears to be the case also with other drugs that have been tested, including valproic acid and phenobarbital. So, the answer is that we do not have an anti-epileptogenic therapy and clearly would very much like to develop one. And post-traumatic epilepsy is one of the potentially good models to study that.

Dr. Ramon Diaz-Arrastia: 15:55 So, how are we going to ever get to that point of developing anti-epileptogenic therapies, something that we could give to someone after a traumatic brain injury, or potentially after a febrile seizure, or after an episode of viral encephalitis or bacterial meningitis with the goal of preventing the development of epilepsy down the line? So, in order to do that, we're going to have to understand the mechanisms by which the injury affects synaptic plasticity and recovery. Trauma is a good way by which you try to understand those mechanisms.

Dr. Ramon Diaz-Arrastia: 16:34 In general, brain injury results in both focal and diffuse injury to the central nervous system. Really, either can result in epileptogenesis. Focal injury results in a contusion, hemorrhage, infarction, necrosis, and resulting in a cortical scar. This is an example from a patient we took care of years ago, who as you can see had suffered a traumatic brain injury has this scar and this area of encephalomalacia in the right frontal lobe. He had seizures coming from this area. We know that because this patient underwent an operation and removing this epileptogenic zone was able to make him seizure free, right? So, that is clearly one mechanism by which post-traumatic epilepsy can kind of establish itself.

Dr. Ramon Diaz-Arrastia: 17:26 On the other hand, in addition to focal insults, traumatic brain injury also has diffuse mechanisms as a result of axonal shear injury, microvascular injury release of inflammatory mediators, and release of free radicals. These produce not a focal scar, but rather damage to vulnerable neuronal structures and vulnerable white matter tracks.

Dr. Ramon Diaz-Arrastia: 17:54 This is, again, an example of another patient we took care of several years ago. As you can see this, this young man had a severe traumatic brain injury. He was in a coma for approximately a week, and then he developed epilepsy approximately one year later. His MRI, the only key abnormality, was that there was atrophy and sclerosis in the right hippocampus, as you can see here. Again, we know that that's where his seizures are coming from because he underwent surgery. He underwent an interior temporal lobectomy, and he became seizure free after that.

Dr. Ramon Diaz-Arrastia: 18:32 So, those are observations. A couple of years ago, we published a paper summarizing the experience from our center. This is the University of Texas Southwestern in Dallas, which we looked at approximately 10 years worth of experience from a single epilepsy center. Approximately 4% of the patients that were evaluated in our EMU at the time, met the inclusion criteria for post-traumatic epilepsy. That is roughly comparable to the data from the Rochester Epidemiology projects. So, we think that's a reasonable number.

Dr. Ramon Diaz-Arrastia: 19:12 The average age at injury was 20 years. That's again, reflecting the epidemiology of TBI. It's primarily a disease of young people. But in fact, primarily a disease of young men. The average age at evaluation though was almost 20 years later. The latency, the time that it took from injury to developing epilepsy, the median was one year, but it was a highly skewed distribution. So, the average is really 3.5 years. So, these folks had epilepsy for an average of 20 years before they were referred for EEG monitoring and an inpatient EMU evaluation.

Dr. Ramon Diaz-Arrastia: 19:49 The duration of monitoring was just short of the week, and we were able to make the diagnosis in the vast majority of cases. We found several patterns, right? Some patients had epilepsy resulting from a lesional frontal lobe injury. We also had mesial temporal sclerosis. We also had lesional temporal lobe injuries. Looking overall, approximately a quarter or actually approximately a quarter of the patients had mesial temporal sclerosis as the etiology, or as soon as the mechanism of their traumatic brain injury that was considered at the time, this was

initially published. This was considered controversial, but this has since been confirmed by other groups.

Dr. Ramon Diaz-Arrastia: 20:42 Almost half of them, just under half of them, had neocortical lesions, but approximately the quarter were non-lesional. These are cases in whom the MRI, at least the MRI that was being done at the time did not reveal any focal or even any diffused lesions, but nonetheless the patients developed epilepsy. These are probably due to some of those diffuse mechanisms. We also had a few cases, not a large number where the epilepsy syndrome that was noted after trauma was that of a generalized epilepsy, either idiopathic or symptomatic and not totally sure what to make of this as the numbers were low, but it is likely that trauma may unmask a genetic predisposition to having epilepsy. This is something that needs obviously further study.

Dr. Ramon Diaz-Arrastia: 21:34 But the vast majority of cases clearly were focal epilepsies. Again, I mentioned that our initial observation of the high frequency, relatively high frequency, about 25% of hippocampus sclerosis occurring as a consequence of trauma that was initially controversial, but in a sense, be confirmed by other groups, including our colleagues at University of California at Los Angeles, where they looked at their surgical series of approximately 200 consecutive temporal lobectomies. They found 21 cases of post-traumatic epilepsy and they found 50% of those had hippocampal sclerosis.

Dr. Ramon Diaz-Arrastia: 22:17 So, I think it is pretty well accepted now that in at least some cases of post-traumatic epilepsy, the mechanism of the epilepsy is hippocampal sclerosis. Another concept that has become clear over the last several years is that properly chosen cases of post-traumatic epilepsy can be treated successfully with surgical therapy. In our center, we found that the cases of post-traumatic epilepsy that were found to be appropriate surgical candidates and underwent surgery, the outcomes were roughly comparable to all the other surgical cases that we were doing at the time.

Dr. Ramon Diaz-Arrastia: 23:13 Approximately 60% ended up being engel class one and other 20% or so ended up being engel class two. So, roughly 80% had a favorable outcome resulting from epilepsy surgery. Likewise, that was totally dependent on the epilepsy syndrome that they had, right? Those that had mesial temporal sclerosis as the epilepsy syndrome had approximately 92% class one and two outcome.

Dr. Ramon Diaz-Arrastia: 23:45 Obviously, the lesional cases were somewhat less favorable. The frontals less than the temporals. Unfortunately, the non-lesional cases, we only had two of those, the outcome was less favorable. So, I think the message is that even if the mechanism of epilepsy is brain trauma, one should still consider a surgical option because some fraction of the time these folks will be found to be appropriate surgical candidates and surgical therapy is certainly going to be useful and effective therapy for some of those patients.

Dr. Ramon Diaz-Arrastia: 24:23 A similar kind of result was also been reported by our colleagues in the Mayo clinic. However, what we would clearly like is some kind of medical therapy that would prevent the epileptogenic process that would block whatever aberrant synaptic plasticity is occurring, that could result in post-traumatic epilepsy. To do that, we've done some studies looking at early MRI to see if that gives us a clue as to what the mechanism of epilepsy may be.

Dr. Ramon Diaz-Arrastia: 24:59 So, in this particular study, we did diffusion weighted MRI in approximately 70 patients with acute TBI. They were all scanned within one week of injury. What we found is in approximately a quarter of cases, there was hippocampal damage that was noted in these early MRIs. On both flares, you can see here as well as diffusion weighted imaging.

Dr. Ramon Diaz-Arrastia: 25:25 Our colleagues at UCLA, and this is a paper published by Paul Vespa several years ago, had found a very similar thing. In their series, they had one patient that they had the opportunity to obtain a PET scan while they were in coma in the ICU. In fact, they found that this area of flare and diffusion weighted abnormality corresponded with a hotspot in the PET scanner, indicating that this patient likely was experiencing a subclinical seizure at the time of the PET scan and that corresponding to this diffusion weighted abnormality.

Dr. Ramon Diaz-Arrastia: 26:04 In that same paper, Dr. Vespa showed that in those patients that had seizures during their ICU stay in the first several days after injury, there was atrophy of the hippocampus ipsilateral to the seizure. That could be a mechanism by which a subset of these people went on to develop late post-traumatic epilepsy. Now, what is the mechanism for that? Again, in our studies using a technique called diffusion tensor imaging, which allows very high resolution analysis of the white matter tracks in the brain, we felt that the white matter tracks that are afferent and efferent into the hippocampus are particularly sensitive to the sharing and stretching forces that occur after TBI.

Dr. Ramon Diaz-Arrastia:	26:58	As you can see here, this is a study showing lesions in the peripheral path in this case, in the left peripheral path in this patient, and that's an afferent structure into the hippocampus. This is one patient that we had the opportunity to study. As you can see here, there's tractography of the perforant path. This particular patient had, as you can see, dropout of the axonal integrity in the left perforant path that was associated with the development of left hippocampal atrophy and left hippocampal epilepsy in this particular individual.
Dr. Ramon Diaz-Arrastia:	27:37	So, the conclusion of this kind of work is that at least in some cases, the mechanism of epileptogenesis or trauma is resulting from a deafferentation in a sense of a disconnection of the hippocampus from the longer term synaptic connections. And that that is responsible for the epileptogenesis that develops over time. Another possible mechanism, and this is just something that we've started studying more recently is that trauma results in breakdown of the blood brain barrier that can be subtle, but can also persist for many months or many years.
Dr. Ramon Diaz-Arrastia:	28:18	That breakdown of the blood brain barrier may result in local inflammation release of inflammatory mediators into the brain, and that can result in epileptogenesis down the line. So, in conclusion, I want to make a case, I hope I've shown you that post-traumatic epilepsy is phenotypically heterogeneous in humans, and that we have to understand that phenotypic heterogeneity in order to have a chance of developing anti-epileptogenic drugs. Both focal and diffuse mechanisms can result in post-traumatic epilepsy of somewhere between 25 and 30% of intractable epilepsy after TBI is associated with mesial temporal sclerosis.
Dr. Ramon Diaz-Arrastia:	29:02	Surgical therapy is a viable option in appropriately selected cases, and that these kinds of studies and our future goal is to understand the mechanisms of epileptogenesis after TBI, which will help us identify and develop and validate effective therapeutic strategies that will prevent not only post-traumatic epilepsy, but potentially have a role in preventing future cases of other symptomatic epilepsies. So, that was my last slide. I hope that I have not gone over too much over time, and I'd be happy to entertain some questions.
Brandon Laughlin:	29:39	Thank you, Dr. Diaz-Arrastia. We will now begin the Q&A session. Again, if you have any questions, please submit them in the questions tab of the GoTo webinar control panel and click Send, and I will read them out loud. Our first question, Dr. Diaz-Arrastia, what strategies may be developed to help prevent post-traumatic epilepsy?

Dr. Ramon Diaz-Arrastia:	30:02	Well, through our work on understanding the mechanisms, I did point to some strategies that may be very attractive. So, I do think we now know that anti-epileptic drugs are not epileptogenic necessarily, and we rather need drugs that are going to promote the integrity of the axonal connections into the hippocampus. We may also need drugs that promote the repair of the blood brain barrier and perhaps block some of the long acting or long duration inflammation that occurs in the brain.
Dr. Ramon Diaz-Arrastia:	30:40	So, the goal of developing or the mechanism of developing anti-epileptogenic drugs is really going to be tied in to these strategies to promote the integrity of resilience and recovery of these particular neural structures.
Brandon Laughlin:	31:00	Great. Thank you. Next question is, if you have decades of seizures and epilepsy and you've had multiple brain surgeries, would you say that you have a brain injury? Would that be an accurate statement? Obviously, it's not a TBI, but would you call it an ABI?
Dr. Ramon Diaz-Arrastia:	31:21	Well, of course, I mean, I think obviously epilepsy can occur from many different consequences, but certainly anything that injures the brain, be it a traumatic insult to the head, or be it an ischemic insult or an inflammatory insult or an infectious insult can result in epilepsy. Now, many cases of epilepsy, such an insult is not recognized, which is not to say that it wasn't there, right? It may have been a subclinical or a subtle insult, but nonetheless resulted in an injury.
Dr. Ramon Diaz-Arrastia:	32:02	So, now, I do think the answer to the question is right, that in most cases epilepsy does result from some kind of injury and that discovering how that happens is potentially a value in preventing the development of epilepsy and also potentially treating the seizures after it already develops.
Brandon Laughlin:	32:30	Next question. Are there specific symptoms that indicate if epilepsy is due to a brain injury as compared to other epilepsy causes?
Dr. Ramon Diaz-Arrastia:	32:40	Well, most patients who develop epilepsy after brain injury develop a focal epilepsy syndrome although it can be anywhere in the brain, right? It turns out that temporal lobe epilepsies appear to be the most common. There is something about the temporal lobes, particularly the mesial temporal structures that make it uniquely pro epileptogenic, but we certainly can have frontal lobe epilepsy, parietal lobe epilepsy, occipital lobe epilepsy. It can start from anywhere where there is an injury

and the manifestations of the seizure obviously depends on where in the brain the seizure is starting.

Dr. Ramon Diaz-Arrastia: 33:20 So, the manifestations of the frontal lobe seizure are going to be different from a temporal lobe seizure, or an occipital loop seizure. So, it's the kind of stuff that requires careful evaluation, and in most cases require admission to an epilepsy monitoring unit for video EEG monitoring. But yes, one can determine what kinds of epilepsy develops from what.

Brandon Laughlin: 33:52 Thank you. Next question, we have a question about veterans and the prevalence post-traumatic epilepsy in the veteran population to other types of populations with head trauma.

Dr. Ramon Diaz-Arrastia: 34:05 Well, veterans are at a particularly high risk of suffering traumatic brain injury, and this is a consequence of their military service, but it's not only... And veterans or military personnel are at high risk of traumatic brain injury, obviously in combat settings but even during practice or during training and just living in a harsh environment is risky and there's a high incidence of brain injury from that.

Dr. Ramon Diaz-Arrastia: 34:40 Brain injuries are very common in a general population, but individuals who have served in the armed forces are at approximately a three to four fold increased risk of having a brain injury and a correspondingly increased risk of developing post-traumatic epilepsy. So, this is a major problem to the Department of Defense, Military Health System, as well as for the Veterans Administration Health System. A lot of the research in this area historically has been funded by the DoD and the VA.

Brandon Laughlin: 35:19 Great. Thank you. Do you happen to know the percentage or approximate percentage of post-traumatic epilepsy patients that are candidates for brain surgery?

Dr. Ramon Diaz-Arrastia: 35:28 Well, unfortunately, that's a very hard number to know. It's certainly not the majority, but it could be as much as 10, 20%. I think everyone who has epilepsy that is refractory to medications, which means that they have been on good doses of at least two anti-epileptic medicines and they continue to have frequent disabling seizures. That is someone who regardless of the etiology of their epilepsy, regardless of the cause of their epilepsy, should be referred for Epilepsy Monitoring Unit Admission and Video EEG Monitoring to determine if they are surgical candidates. I think surgery remains an underutilized therapy option in post-traumatic epilepsy, as well as in many other causes of focal epilepsy.

Brandon Laughlin:	36:26	Thank you. Next question. What are your thoughts about the predisposition to Alzheimer's after one has had a closed head traumatic brain injury?
Dr. Ramon Diaz-Arrastia:	36:35	Well, again, this is another area my laboratory is very busy in investigating. So, it appears that individuals who sustain a moderate to severe traumatic brain injury are at greater risk of developing late life dementia. That risk is somewhere in the order of about three to four fold for severe traumatic brain injury. But then even mild traumatic brain injury increases risk of late life dementia modestly, but probably by around 30 to 50%.
Dr. Ramon Diaz-Arrastia:	37:11	Now, that doesn't sound like much. On the other hand, given that late life dementia is so common, even a modest increase in relative risk does translate into a large number of cases. Now, whether that dementia is Alzheimer's disease or whether it is some other kind of late life dementia, that remains to be proven, right? Again, that's one of the things that we very much need to investigate is if we can identify what is the mechanism of that risk of late life dementia after a TBI, what can be done to prevent it? Do we have any strategies that could help in promoting the resilience or promoting the recovery of the brain after a brain injury? And we just don't know yet, but it's an area of very active research.
Brandon Laughlin:	38:05	Great. Thank you. The next few questions have to do with therapeutics and drug therapies. Do you feel that there is an ideal anti-epileptogenic drug profile?
Dr. Ramon Diaz-Arrastia:	38:17	Well, the ideal anti-epileptogenic drug profile is one that controls the seizures 100%. It doesn't produce significant side effects, right? Now, that ideal drug is going to be different for every patient, right? But many patients are able to find a drug or drug combinations that is ideal for them, meaning that it controls the seizures and allows them to continue their life without significant side effects.
Dr. Ramon Diaz-Arrastia:	38:47	Unfortunately, that only happens about 60% of the time. So, that is a significant number of people and many of the drugs that we have are good drugs, but that remains that about 40% of patients with epilepsy and that includes post-traumatic epilepsy as well as other causes are unable to find an ideal drug or drug combination that works for them. That remains a big problem, which certainly stimulates our work in the area trying to develop preventative therapies and also trying to develop better symptomatic therapies.

Brandon Laughlin:	39:31	What about starting a ketogenic diet post TBI as a possible seizure prevention protocol?
Dr. Ramon Diaz-Arrastia:	39:36	Well, I mean, I think that's a potentially good strategy, right? There are some work primarily so far in animal models that a ketogenic diet appears to be neuroprotective, appears to prevent the death of neurons in some of the aberrant synaptic plasticity. Research in this area is very, very early, I must say. It's so far mainly in animal models, but it certainly looks promising. Not an unreasonable approach to try.
Brandon Laughlin:	40:12	What about researching the space dealing with devices such as brain cooling?
Dr. Ramon Diaz-Arrastia:	40:19	Well, so likewise in animal models, there is very good evidence that cooling the brain soon after the injury prevents the development of post-traumatic epilepsy. In fact, helps in preserving neural structures and preventing neuro degeneration. So, I think that is likewise an attractive strategy. So far, it's really only been tried in preclinical models. It appears that focal brain cooling is what's important. There have been several studies in patients with TBI doing whole body cooling, and that does not appear to work as well. It's mainly because cooling can have deleterious effects on pulmonary function and cardiac function and renal function. But focal brain cooling is certainly a promising strategy.
Brandon Laughlin:	41:21	Now, do you feel that preventing hippocampal neurogenesis after TBI is a viable therapeutic direction for preventing mesial temporal lobe epilepsy?
Dr. Ramon Diaz-Arrastia:	41:31	Well, gosh, that's a very loaded question. So, there is neurogenesis in the hippocampus after TBI. In most cases, that is a good thing because that allows the recovery of memory function and attention and things that the hippocampus does. So I think one would have to be very, very careful about a strategy where one tries to prevent the normal healing pathway.
Dr. Ramon Diaz-Arrastia:	42:04	On the other hand, it is likely that as I mentioned earlier in my talk that post-traumatic epilepsy may result from those attempts of the tissue to rewire and repair itself, that some of those repairative processes may not be totally perfect and result in a circuit that is epileptogenic. So, I would say that one has to be very careful and one has to be very precise on strategy, such as this, and obviously develop strategies that target the aberrant neurogenesis and the aberrant

synaptogenesis while leaving the neurogenesis and synaptogenesis that are important for more recovery in place.

Brandon Laughlin: 42:54 Great. Thank you. Another therapeutic question, are sodium channel blockers therapeutic in post-traumatic epilepsy?

Dr. Ramon Diaz-Arrastia: 43:02 Well, I mean, so Dilantin for examples is one of channel blocker and it does not appear to be effective, although it blocks the early seizures, does not appear to be effective as an anti-epileptogenic agent. I would say that although not every sort of general blocker has been tested, more likely we are going to need alternate strategies to come up with a truly anti-epileptogenic compound. Those alternate strategies are going to have to rely on things like blocking inflammation or promoting repair of the blood brain barrier, or perhaps promoting integrity of the external pathways that become disconnected.

Dr. Ramon Diaz-Arrastia: 43:46 I'm personally not that hopeful that just because a drug is anti-epileptic, that it will be anti-epileptogenic. I think the data we have so far seems to indicate that it's not the case.

Brandon Laughlin: 44:05 Thank you. Next question. Are there any specific group of neurons implicated in post-traumatic epilepsy?

Dr. Ramon Diaz-Arrastia: 44:12 Well, I think that there's not any one specific group. I think that depends a lot on the location. I think what tends to happen is that when you have a brain injury, many neurons are lost and are damaged, and then the neurons that remain attempt to rewire in order to repair the function of the circuit. But that rewiring is sometimes not perfect and that's how an epileptic circuit presents itself. So, it appears to be mostly the neurons that are relatively resilient to injury that may be responsible.

Dr. Ramon Diaz-Arrastia: 44:59 Again, I think it's a two-edge sword. You would not want to prevent epileptogenesis with a strategy that also prevents the repair and recovery. We would have to be a lot more precise and a lot more clever to come up with strategies that prevent the aberrant synaptic plasticity while allowing the functional or the positive synaptic plasticity to persist.

Brandon Laughlin: 45:29 Great. Thank you. Can seizure type after a traumatic brain injury be a basis for predicting the risk of recurrence?

Dr. Ramon Diaz-Arrastia: 45:40 Well, I don't think we know the answer to that yet, right? I think what very frequently happens that it often takes a while for the diagnosis of post-traumatic epilepsy to be made. When we talk

to patients who have developed epilepsy after a brain injury in reality, they often have subtle behavioral problems or subtle memory problems that proceed the development of clinically apparent seizures.

Dr. Ramon Diaz-Arrastia: 46:13 In retrospect, those were probably very small, very focal seizures that were occurring before the clinically apparent seizures presented themselves. So, I think the answer is that we're going to need strategies that allow the diagnosis of post-traumatic seizures very early on in many cases before it's very clinically apparent in order to develop effective therapies.

Brandon Laughlin: 46:47 Great. Thank you. We've come to the end of our audience questions. So, I'm going to go ahead and turn it back over to Kate.

Kate: 46:53 Thank you to our audience. I want to say you've been really tremendously engaged with great questions. Dr. Diaz-Arrastia, I have a question for you. You just spoke about the need for early diagnosis so that we can get to effective treatments. May I ask, are you hopeful about the near term future for patients with TBI?

Dr. Ramon Diaz-Arrastia: 47:21 Well, gosh, boy, that's a good question. I've been working in this field for about 25 years and we have had great progress. On the other hand, when I started working on it, I certainly would have hoped that we would have been further ahead by now. So, I have long accepted and I've told my wife and children this that optimism is one of my personality flaws. So, I do believe that we will develop some effective anti-epileptogenic therapies before I retire, right? Obviously, that's only a belief in terms of having very solid therapies.

Dr. Ramon Diaz-Arrastia: 48:05 I do know that the amount of research in this field has skyrocketed over the last several years. This is mainly through the support of the Department of Defense, but also through the CURE Foundation and many others. We now have much better animal models. We have much better understanding of what's going on at a cellular molecular level. We have much better biomarkers, be the imaging biomarkers or molecular biomarkers.

Dr. Ramon Diaz-Arrastia: 48:36 So, I do think we have the tools in place, and we certainly have some strategies that appear to be successful in animal models. Obviously, translating those into humans is not necessarily an easy or even a linear proposition. But I am an optimist, and I think the answer is that we will have something in the next 10 to 15 years or so.

Brandon Laughlin:	48:59	This concludes our webinar about post-traumatic epilepsy. I would like to thank everyone for joining us today and give a special thank you to Dr. Diaz-Arrastia for sharing your knowledge of post-traumatic epilepsy. Also, I'd like to thank the team at Sunovion for sponsoring today's webinar.
Brandon Laughlin:	49:15	If you happen to have any questions about this topic or any of CURE's research programs, please visit our new website at www.cureepilepsy.org. Or, email us at info@cureepilepsy.org.