Breathing and SUDEP Webinar
Transcript

Dr. Laura Lubbers: 00:00 Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer of CURE Epilepsy. I want to thank you all for joining us today, which happens to be SUDEP Action Day, a day devoted to raising awareness about sudden unexpected death in epilepsy, encouraging people with epilepsy to learn about SUDEP and their risk and honoring the lives of those we have lost. Today's webinar is entitled Breathing and SUDEP: Research and the Impact of Seizures on the Respiratory System, and it will introduce basic concepts and terminology for how the respiratory system functions.

Dr. Laura Lubbers: 00:38 The webinar will also review the data for breathing dysfunction as a potential cause as well as a warning sign for SUDEP, and as a possible means to intervene and prevent SUDEP. You may have noticed that we have updated our organizational name and logo, which is a recognition and reinforcement of who we are and who we have been for the past 20 or more years, an organization that is single-mindedly focused on finding a cure for epilepsy by promoting and funding patient-focused research. This webinar is part of CURE Epilepsy's 2020 Leaders in Research webinar series, where we highlight some of the critical research that's being done on epilepsy.

Dr. Laura Lubbers: 01:24 Today's webinar is being sponsored by our friends at the BAND Foundation. I also want to mention that today's webinar as well as all previous and future webinars will be recorded and are available on the CURE Epilepsy website. The topic of today's webinar, The Role of the Respiratory System on Seizures, and more specifically SUDEP is of particular importance to the epilepsy community now due to the current global pandemic. Research suggests that breathing dysfunction following generalized convulsive seizures can lead to SUDEP. Interruptions in breathing can occur during and after seizures leading to an imbalance of carbon dioxide and oxygen in the body. The ability to restore normal breathing patterns and remove excess carbon dioxide may be weakened in some people with epilepsy, potentially increasing the risk of SUDEP.

Dr. Laura Lubbers: 02:20 Today's webinar is being presented by Dr. Rup Sainju, who is an assistant professor of neurology and medical director of the EEG laboratory at the University of Iowa Health Care. Dr. Sainju is a 2016 CURE Epilepsy Award grantee whose research found that respiratory response to high carbon dioxide levels in the blood may be weakened in some people with drug-resistant epilepsy. This could put them at a risk... or increased risk of severe breathing abnormalities and SUDEP following a generalized

convulsive seizure. Before Dr. Sainju begins, I would like to encourage everyone to ask questions. You may submit your questions anytime during the presentation by typing them into the Q and A tab located at the bottom of your Zoom panel, and then click send.

Dr. Laura Lubbers: 03:12 I want to thank those who have already submitted questions, I know we have a number in queue already. We will do our best to get through as many questions as we can. And we do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy or your own epilepsy. So with that, I'd like to turn it over to Dr. Sainju.

Dr. Rup Sainju: 03:41 Good afternoon everyone. Thank you for joining today. And I would like to thank for this opportunity to talk today in this webinar. And I'd also like to thank CURE specifically for the excellent work that it has been doing over the past several years promoting epilepsy awareness as well as SUDEP awareness, along with also putting a huge effort in support in research, both in clinical, translational, as well as basic science with a goal of understanding nature of epilepsy, mechanism of disease, as well as best way of treating and preventing the conditions, which is very, very important for patients with epilepsy, as well as families who take care of patients with epilepsy.

Dr. Rup Sainju: 04:39 As a physician that has been working in field of epilepsy, this is very important and personal to me as well. So today, in next 40 minutes or so we will be discussing about breathing and epilepsy and we'll also relate how that could be a cause or a potential mechanism for SUDEP. So let's begins. Yeah. So we'll start with learning very basic concept about breathing apparatus as well as control of breathing, then we'll review some data suggesting of breathing dysfunction related to seizure, and we will also review how breathing dysfunctions and serotonin is related to SUDEP risk, and potential interventions to reduce this risk.

Dr. Rup Sainju: 05:46 So it turns out, we know oxygen is one of the essential element for us to sustain life in earth. And we need oxygen to burn our food, to get energy, and in byproduct we get carbon dioxide, which is a gas, which is mildly acidic. So if you are a single cell as a living organism, life is very simple. You get your oxygen from air by process of diffusion and then you get rid of carbon dioxide again by the way of diffusion back into the air. But because we are very sophisticated organism, our system to handle oxygen and carbon dioxide is also very sophisticated,

which is primarily a complex interaction between our heart, cardiovascular system and our breathing system.

Dr. Rup Sainju: 06:57 Okay. So, in the next few minutes, we'll discuss a little bit about breathing apparatus and control of breathing. I will be discussing very basic concepts. And I would like to apologize for those who already know this information, but because there is a likely very wide understanding of these concepts in the audience today, I think learning very basic concepts would be very beneficial for many. Okay. So we've been equipped with organs to breathe. And mainly the apparatus for breathing consist of airways and lungs. Airways can be further divided into upper airways, that starts from the nasal cavity that goes back of the mouth into throat and ends in your vocal cord, and lower airways that starts at the end of the vocal cord with trachea and continues inside the lung further branching off. And they end with a structure called alveoli, which is like a bunch of grapes with air-filled cavities and which are densely covered by a network of very fine hair-like blood vessels called capillaries.

Dr. Rup Sainju: 08:31 Then we have muscles to help us breathe as well as to keep our airways open. So there are muscles that is built around the upper airways and these muscle contract constantly to make sure that airway is patent. And then we have muscles that actually helps move in and air out of our lungs. And one of the muscle that is very important is diaphragm, which is one of the largest muscle, and this muscle right here which separates our thoracic cavity to the abdominal cavity. And then there are different sets of muscle in between the ribs called intercostal muscle. These muscles also help us move air in and out of our lungs.

Dr. Rup Sainju: 09:21 So very important action that happens in lungs is gaseous exchange. So here's a basic figure of how cardiovascular and the lungs are very closely working for gaseous exchange. If you start with the left side of the heart where you have blood containing higher amount of oxygen is pumped into different areas of the body, and this whole system is called systemic circulation. So oxygen from the blood is extracted by tissues and then carbon dioxide that is produced because of the metabolism is released back to the blood, which is then carried to the right side of the heart from where it is pumped into the lungs where the gaseous exchange occurs in the alveoli and where you breathe out carbon dioxide and breathe in oxygen.

Dr. Rup Sainju: 10:35 Hence, the blood in raising oxygen is then pushed back into the left side of the heart to complete the cycle. So you could measure this oxygen content either by invasive, by puncturing

your artery... And the normal arterial oxygen content is between 80 to 100 mmHg. You can also measure by noninvasively using a pulse oximeter using a probe in your finger, and it gives you a number which just generally tells you how much of the hemoglobin is saturated with oxygen. And if you look at the relationship between the percent of oxygen saturation and the amount of oxygen actually in blood, this is not linear, this is rather a curve, this is a sigmoid curve, S-shaped curve. And an important data is... of this curve is as you can notice, even when oxygen saturation drops from 100% to 95%, or close 90% rather, now you have already lost about 20% to 40% of oxygen content of your blood.

Dr. Rup Sainju: 11:54 And it furthers go down very fast as oxygen saturation goes down. So this is a great non-invasive tool but this again may not be a very accurate tool to measure oxygen content of blood. However, on the other hand, our handling of carbon dioxide is very neatly related to how much you breathe every minute. As this graph shows, as we have carbon dioxide level, which is tightly controlled between 35 to 45 mmHg in our blood, if the carbon dioxide rises in compensation, body tries to breathe out carbon dioxide to get rid of excess carbon dioxide. So that's why you're going to be breathing faster. And if the carbon dioxide is pretty low, your breathing rate or alveolar ventilation would also goes down. So turns out this is very handy mechanism also to maintain our body pH, which is usually controlled between 7.35 to 7.45, a very small range where our body has to function or function optimally. Any deviation from these level could cause dysfunction and severe abnormalities actually could also lead to death.

Dr. Rup Sainju: 13:28 Well, let's talk a little bit about control of breathing. So it turns out whether you are aware or not, we breathe more than 20,000 times per day. And we have great ability of control of breathing for different activities for example singing, talking, eating, exercise, so forth and so on. And the question arises, how do we do it? So to understand that, I think I'm going to introduce to very basic concept of the breathing control here. So we have important breathing areas in back of our brain or brainstem, which is the main area where a breathing rhythm generates. And higher centers, as we have just discussed talking, singing, eating, sometimes emotion, fear, anger, these can directly affect how the breathing areas work. It also gets input from different sensors. One of the very important sensor includes chemical sensors and of those that contributes mostly is carbon dioxide, pH and oxygen.

Dr. Rup Sainju:	14:51	And these sensors are present in big arteries as well as brainstem. Along with chemical sensors, there are also mechanical sensors that are present in lungs, muscles, joints, which also senses, send signal to the breathing areas in the brainstem to modulate how fast or how slow this breathing should occur. And what different areas in brainstem does is it acts via... It provides information through nerves and it takes the information from nerves to muscles, as well as lungs to make it happen, to make it breathe in and out, faster or slower, however way the situation demands. So in nutshell, we have to summarize. So we have higher centers that's provide cortical drive, which is the drive that you have when you are awake. So when you're asleep or comatose, you don't have this drive for breathing. And then we have chemical drive, which is mainly derived by CO2 and pH in usual normal situation. And this drive becomes the primary drive when you are asleep or comatose.
Dr. Rup Sainju:	16:23	Here's a section of brain, the vertical section of brain showing right and left side of the brain. And this through the brainstem here this part is pons, medulla, and spinal cord. And I just wanted to show you different respiratory nuclei or areas that resides in brainstem. So majority of the nuclei are in medulla. There are a couple few nuclei in pons. In terms of medullary respiratory nuclei, there are a dorsal group of respiratory nuclei as well as the ventral group of respiratory nuclei. And one of the areas in the ventral group is called pre-Bötzinger complex which is like a pacemaker of breathing. It's a breathing rhythm generator area, if you will. And there are Raphe nuclei which is kind of in the midline, which a majority are serotonin neurons. And these neurons are responsible for the sensing a change in carbon dioxide level as well as pH in blood, which is the chemical drive for breathing.
Dr. Rup Sainju:	17:42	And these nuclei interact with each other as well as they also get information again from higher centers, as well as serotonin neurons for chemical drive, and then they send their output through nerves, through spinal cord to muscles that helps to keep our upper airway patent as well as muscles that helps us move air in and out from our lungs.
Dr. Rup Sainju:	18:14	So let's talk a little bit about evidence behind breathing dysfunction during seizures. Even before I think moving into that topic, we should talk a little bit about how do we actually monitor breathing during studies? We can do as an outpatient, but in inpatient with epilepsy, mostly we're talking about video EEG study in patient while they're also getting information for breathing as well. So you can have a lots of different sensors around your body. So A is showing the EEG electrodes, all these

three, B is... This is a nasal cannula that measures airflow and pressure through the nose as you breathe in, breathe out. Then you have this belt here around the chest, which is C, to measure the chest effort or movement of breathing. Similarly, D is the abdominal effort belt which again tells us the breathing movement during effort of breathing. And then E is the pulse oximetry which again gives us information about oxygen saturation and pulse.

Dr. Rup Sainju: 19:31 Let's review some important terminologies that I would be using during the remaining of the talk. So first thing first is apnea. Apnea just means there is no breathing. And it could be one of these three types, obstructive, central or mixed. So if you want to focus on this graph here, we have tracing showing airflow and thoracic movement and indication of upper airway occlusion or attempts to breathe. So what happens in obstructive apnea if you're reporting is because there is obstruction in upper airway, there is limitation of airflow. So you don't see airflow here, which is kind of flat. But because the breathing is still happening or the effort is still going on, you could see the movement or the [inaudible 00:20:28] the chest, the thoracic movement on this tracing.

Dr. Rup Sainju: 20:33 In central, there is no movement and there is no airflow. Meaning even though there is no obstruction, there's no airflow, there is no attempt to breathe. So the problem usually is in the brainstem or the breathing center. In the mixed apnea, there is a mixture of both these phenomenon where there's partly obstruction of airflow, and at times there is no effort at all. Okay. So then there are a few other things I would like to understand. Ictal means during a seizure. Postictal means after a seizure. Interictal means just in-between seizures. So it turns out breathing abnormalities during seizure is not a new thing. It was actually described by J.H. Jackson dating 1899.

Dr. Rup Sainju: 21:40 And he is considered to be father of modern epileptology. So he described patients as well as monkeys turning blue during seizures. But until not recently we're focusing now or being more aware of breathing abnormalities during seizure. So even with a focal seizure, breathing abnormalities can happen. And ictal central apnea with oxygen saturation less than 90% can be seen in almost one-third of the seizure when they are monitored in epilepsy monitoring unit. And in one intense seizure could have mixed or obstructive sleep... Excuse me. Obstructive apnea due to seizures.

Dr. Rup Sainju: 22:27 Ictal central apnea longer than 60 seconds is less common and in about one in 16 patients, but when that happen it's often

associated with even severe de-saturation of oxygen with less than 75%. And it's known now apnea occurs more commonly with temporal lobe seizures than seizures from other areas of the brain. Carbon dioxide is often elevated when there is less than 85% of oxygen saturation during focal seizures, and almost invariably after generalized convulsive seizures or GCS. And some patients have severe and prolonged elevation of CO2 level after GCS with no proportionate increase in breathing effort.

Dr. Rup Sainju: 23:17

So this lack of increased breathing despite elevated CO2 level which should provide a chemical drive to breathe suggests there is a defect in chemical drive. So let's talk about possible mechanisms how seizure can affect breathing. One of the study I often quote is this study where our neurosurgeon Dr. Dlouhy here in University of Iowa noticed very interesting findings in one of the patients that had intracranial EEG monitoring for surgical evaluation. So this patient has a lots of electrodes mostly on the right side of the brain in their frontal, temporal, as well as in the inner side of the temporal including amygdala. What you're seeing this on the top graph is all EEG and the bottom is the breathing tracing. So he noticed that when seizure started, this seizure was on the right frontal area, breathing was occurring normally up until the point where the seizure spread... where you can see this time here, when the seizure spread to the left amygdala, then breathings changes started and after a little bit, there was a period of apnea.

Dr. Rup Sainju: 24:55

And he did a further testing on this gentleman. He actually stimulated his left amygdala for 47 seconds. And during the whole time he stopped breathing, but he was not aware and he did not feel short of breath. And this stimulation was done when he was not having seizure. So this tells us that amygdala or seizure spread to amygdala could be one of the way how seizure can modulate or even stop breathing.

Dr. Rup Sainju: 25:36

Well, let's talk in next few minutes about breathing dysfunction, serotonin, and its role or their role in SUDEP. We'll begin with SUDEP definition, which I'm sure many of you already know SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus in which the postmortem examination does not reveal a toxicologic or anatomic cause of death. SUDEP is very important and leading cause of death in patients with epilepsy. Known risk factors include drug-resistant epilepsy and particularly if you have frequent generalized tonic-clonic seizures. Some of the possible

risk factors include having nocturnal generalized convulsive seizures and lack of supervision or living alone.

Dr. Rup Sainju: 26:46 So with that, let's review some of the information regarding breathing dysfunction as potential cause for SUDEP. Although we don't understand exact mechanism of SUDEP, I think it's a mixed bag of different things, but more and more studies suggest breathing dysfunction is likely a primary cause for SUDEP in many SUDEPs. So there are animal models of SUDEP or seizure-induced sudden death. These models, DBA/1, DBA/2, Lmx1bf/f/p mice they all have defect in serotonin neurons or serotonin transmission, and they all exhibit breathing arrest after induction of seizure, and they all die. And when they look at the tracing of breathing, EEG and EKG or ECG, they found breathing stops before heart prior to death in all these animals. And deaths were prevented if they were ventilated or artificially ventilated immediately after a seizure or they were pre-treated by medicine that increase serotonin transmission. Hence serotonin seems like it has important role both in breathing and potentially in preventing death at least in these seizure-induced death models of SUDEP.

Dr. Rup Sainju: 28:31 Let's talk about human studies. One of the study, one of them... The only study I would say that looked at 160 epilepsy monitoring units across the globe and collected all the people that died of SUDEP and evaluated their breathing and heart and other things happened during the death or prior to death, they found very interesting fundamental. So they'd had 16 SUDEP, 14 actually died at night and nine of those people had tracing where you could look at breathing as well as ECG. So each block here... So the first block is breathing, second block is ECG on each patient here. And you can see that on each patient, the blue bar is terminal apnea or terminal stopping of breathing and the red bar is terminal asystole or heart-stop. So in all these cases, breathing stopped before heart prior to death.

Dr. Rup Sainju: 29:57 In a different study where in investigator study, patients admitted to epilepsy monitoring unit and look for central apnea that happens after the convulsion's over. So they found that some people have post-convulsive central apnea, and that could be of varying length and severity. And in two patients though, they occur concurrently with loss of heartbeat or asystole, so likely near SUDEP, but it's they were near SUDEP because they were able to recover back. So they didn't die. However, one patient died of SUDEP during the followup at home. So these data suggest severe breathing problem following generalized convulsive seizure is likely a biomarker for SUDEP.

Dr. Rup Sainju: 30:53 Let's review evidence behind the role of serotonin in seizures in human studies. We do not, unfortunately have lots of data for this. There are a couple small studies. One is actually a multicenter study. Both are retrospective study, so going back into the chart and looking at the data and trying to find information about them. So they found seizures in patients taking serotonergic medicine had lower occurrence of ICA or ictal central apnea and have little bit smaller seizure-related drop in oxygen saturation. There is a study actually measuring serotonin level in blood before and after convulsion. And they found that people who had higher amount of serotonin level in the postictal period, following a convulsion, compared to their baseline or before the seizure, they tend to have no post-convulsive central apnea compared to those who had less amount of serotonin elevation after convulsion. Again, suggesting serotonin may be protective against apnea during seizure.

Dr. Rup Sainju: 32:24 And very interesting thought that comes to our mind is, okay. We know now at least seizure in some way can affect breathing, but what happens with chronic epilepsy? Does it actually affect on breathing? It's reasonable to believe or hypothesize that repeated severe hypoxia or low oxygen level related to seizure may cause some structural or functional problem with control of breathing in the long run, but we have very limited data on it. And data comes from studies looking at brain imaging and post-mortem findings in [inaudible 00:33:09] people who died of SUDEP as researchers have found that midbrain and upper portion of medulla were relatively smaller in size in patients who died of SUDEP. Again, in nutshell, it's unclear at this point if and how chronic epilepsy affects breathing or breathing center in the brainstem in the long run.

Dr. Rup Sainju: 33:35 Well, let's review our summary so far here. So we've discussed drives for breathing which are cortical drive and chemical drive, which is mainly through carbon dioxide mediated by serotonin neurons in the brainstem. We've reviewed now breathing abnormality is relatively common with seizure, but severe breathing abnormality is less common. Breathing stops prior to heart in all documented SUDEPs in the study I showed you as well as in animal models of SUDEP. And there is potential role of serotonin as a protection against breathing abnormalities or apnea. Severe breathing problem following generalized convulsive seizure is likely a biomarker for SUDEP risk. However, it can only be assessed in epilepsy monitoring unit. And some patients have prolonged rise of CO2 level without increase in breathing during postictal phase suggesting a defect in a chemical drive for breathing.

Dr. Rup Sainju: 34:49 So from here onward, I will be talking about some of the research that I have been involved in looking at the... or looking at the chemical drive of breathing, because it appears that there is a problem in some people. So this was not measured previously, and we could measure or quantify the chemical drive of breathing by measuring breathing that happens during re-breathing of CO2. So we actually had a protocol that was designed to test this, and we have a respiratory therapist that works with us very closely. And we have two re-breathing bags filled with 50% oxygen, 6% carbon dioxide and balance nitrogen, and what we ask people to do is to breathe through this closed system for a few minutes. As they breathe in and out through this bag prefilled with 6% carbon dioxide, they're body carbon dioxide level gradually rises. And we also monitor constantly about how their breathing changes, how their carbon dioxide level changes gradually over time and look at the relationship between those two.

Dr. Rup Sainju: 36:25 And we call this CO2 re-breathing test or hypercapnic ventilatory response or HCVR. And [inaudible 00:36:34] thing about this is it can be performed either at the bedside in the EMU or in outpatient setting. And we studied 68 patients and published the findings in a epilepsy journal in 2019. So what we basically found was people have varying response on this test. Here's a person who has sort of a most average response where this axis is carbon dioxide, this axis is breathing that happens every minute or per minute. And as you see, as the CO2 rises in the body, gradually breathing increases, and this is sort of pretty good.

Dr. Rup Sainju: 37:27 Second person is the one where the response was very robust, where a little bit of change in carbon dioxide lead to really high change in the breathing. And the third person is a person who actually died of SUDEP Plus during followup at home that had very attenuated or very low response. Despite increase in CO2 in the body, the breathing actually doesn't change. And we could actually measure this slope of each of the line, and we call them HCVR slope.

Dr. Rup Sainju: 38:05 So some people with epilepsy have really low response. And these tests were done during interictal or in between seizures. And here's the distribution of all the people we studied. So this is the slope that I was mentioning, so on the X axis and Y axis is number of subjects, number of people. Black arrow is the person who has the most average response. Red arrow is the person who actually died of SUDEP Plus during the follow-up. It almost follows a bell's shape or the normal curve where some people are really highly responsive and some people are very

not responsive. We also have some people testing before convulsion and after convulsion and found that their response actually further goes down in postictal state, so which suggest the HCVR slopes again further attenuates after a convulsion, which brings to an interesting point of what that means with breathing.

Dr. Rup Sainju: 39:18 So we also measured their breathing effort, carbon dioxide level, oxygen level throughout the study, throughout the video EEG study during and before and after seizures. And we correlated their breathing response during interictal period, these interictal period, to the amount of breathing difficulties they had during the postictal period. And we found that an attenuated interictal HCVR highly correlated with severity of breathing problem following generalized convulsion. And HCVR significantly attenuated again following GCS compared to their interictal measurement. Hence, an attenuated HCVR is a likely surrogate for severe breathing dysfunction and a potential biomarker for SUDEP. And good thing is, again, HCVR can be measured in clinic and outpatient setup.

Dr. Rup Sainju: 40:25 So in next couple minutes, we will be talking about potential intervention to reduce SUDEP risk. So unfortunately we don't have targeted therapy at this time that is proven to prevent SUDEP. The best thing we can do right now is still try to optimize seizure control using anti-seizure medicine, as well as other potential therapies including brain surgery so we can control the seizure better. That would ultimately reduce the risk of SUDEP. However, there are potential therapies that should be tested in more research as coming days. This include use of serotonergic medications. As we have reviewed already, there is potential benefit from serotonergic medicine in a smaller studies or retrospective studies, but there isn't a randomized controlled trial to suggest that actually this helps in preventing apnea or lowering seizure-related oxygen level or improving the chemical drive of breathing for these patients.

Dr. Rup Sainju: 41:53 And from a study funded by CURE we actually did a pilot study looking at the feasibility of studying patients with epilepsy to see if we're even able to do the study of such kind. And we actually enrolled and completed the study demonstrating it's feasible to do the study. At this point we still need to work on further to do a more definitive study to prove if this helps or not. Second thing that is potentially helpful could be supplemental oxygen. There is limited study from human, the human studies showing if you are giving supplemental oxygen after a convulsive seizure the amount of oxygen de-saturation during seizure is not as low or it doesn't go down and the

recovery is faster of the oxygen saturation. But we don't have strong enough evidence to say that is the practice to be... or accepted practice at this time, and we again don't have evidence to say this actually helps to prevent SUDEP.

Dr. Rup Sainju: 43:27 And then I would like to again focus on how lack of supervision or living alone was or still is a major risk factor... a potential risk factor for SUDEP. So having some sort of supervision, whether direct supervision or by using seizure detection or alarm, I think could be a reasonable thing or things to test if that can actually translate into preventing SUDEP. But for now the best weapon we have is try to optimize seizure control using seizure medicine as well as other therapies. If surgery is something potentially helpful, should consider surgery. Okay. With that I would like to thank my research team, particularly Dr. George Richerson and Brian Gehlbach who are my mentors, as well as collaborator Mark Granner and Patrick Ten Eyck as well as Harold who's our respiratory therapist and doing all the studies and Deidre Dragon who's our study coordinator who is on top of things that we need to do to make sure the study runs smoothly. Well, thank you everyone. With that, I think we should open up for the questions.

Dr. Laura Lubbers: 44:46 Yes. Thank you Dr. Sainju. That was terrific. Again, if you have questions, I know a number have come in already, but if you have questions, please submit them in the Q and A tab located at the bottom of the Zoom panel and click send, and we'll do the best that we can to get through them all. I know there were a number of questions that came in in advance. And so I'd like to address those. The first one is can individuals with severe intractable LGS with multiple seizures die because of SUDEP during sleep, even with no presence of clinical seizures?

Dr. Rup Sainju: 45:21 This is very interesting questions. Again, if you review the risk factor, the number one risk factor for SUDEP is drug-resistant epilepsy. However, having tonic clonic or convulsive seizures seems to be in terms of types of seizure. Amongst types of seizure tonic-clonic seizure seems to be the highest in potential for causing SUDEP. But the question here is whether if the patient is having nonclinical seizure, can there be increased risk of SUDEP? I don't think we know the answer fully but it sounds unlikely. However, we're still learning a lot about SUDEP and SUDEP mechanism. So we still don't know the full answer at this time. However, it sounds unlikely given the evidence so far.

Dr. Laura Lubbers: 46:18 Okay. Thank you. Here are a couple of questions related to mask use, which I know is of great attention in our country right

now and across the world. So what is the best type of oxygen mask to use after a seizure and are they postictal?

Dr. Rup Sainju: 46:37 Number one, again, we don't know for sure if... We don't have strong enough evidence to suggest that we should be using oxygen as a therapy after convulsive seizure. We just have some evidence showing that it may reduce the amount of oxygen or the lowest drop in oxygen. It may prevent drop in oxygen and may recover the oxygen level a little bit faster. But that does not tells us how it changes SUDEP risk. So again, we don't know that yet. We still need more studies addressing these questions.

Dr. Laura Lubbers: 47:21 Okay. Here's another question again related to daytime use of masks. What would be the risk for someone with a genetic seizure disorder to wear a mask for a work shift six to eight hours a day for three days a week? Is there any mask that would be considered safe for such long-term use? Are there any challenges with using the masks that we're wearing today?

Dr. Rup Sainju: 47:50 Yeah. So I don't think I have a good answer for this question as well. Given COVID pandemic that's going on, wearing mask is something we should all consider. One thing is for sure is it does not prevent you getting sick, it also prevents spread of disease if you are asymptomatic and still has infection. So, I don't know that there is a good mask or what type of mask that we should be using. If you are taking care of patients, you should probably use medical grade mask, but if not, then at least using some sort of mask is still good. In relation to epilepsy, we don't have good information to suggest what's the best kind of mask for you if you have epilepsy.

Dr. Laura Lubbers: 48:44 Okay. Thank you. So here's another question. When does SUDEP occur the most when the patient is sleeping in a safe position under monitoring, and what can parents do to lessen the chance of its occurrence?

Dr. Rup Sainju: 48:58 So most witnessed death from SUDEPs reportedly happen after a convulsive seizure. So it's not during, it's rather after convulsive seizure. And there is good suggestion that there is something to do with sleep and if you are alone then you actually are on a really high risk of dying with SUDEP. So if you are monitored by some mechanism... Direct mechanism probably is good for a lot of people who don't mind their privacy, but this is a very personal situation for a lot of our patient with epilepsy. So having some sort of indirect monitoring may help, but again, we don't know for sure which monitor, whether it's seizure detector or a video monitor or a seizure alarm like a bracelet or... There is actually FDA approved

device, a watch, Empatica, that is approved to detect, an alert system after a convulsion has happened.

Dr. Rup Sainju: 50:29 So we don't know, again, to the extent how much these intervention are helpful, but I want to highlight that's why we need more research trying to get more information so we can have more intervention that is available for patients and families. What I tell my patient and their family is I would consider based on the situation, individual situation and preference, having some sort of monitoring or surveillance is reasonable thing to try. It may not have to be the video surveillance. You may just sleep next door or maybe on the same floor. So some studies suggest that when people intervene during or after convulsive seizures, sooner you go and talk to them or try to intervene in some way, recovery seems to be a little bit faster. Their oxygen recovery, as well as their arousal seems to be a little bit faster. So it's reasonable based on the situation, but there is no single thing that is proven that we can recommend at this time.

Dr. Laura Lubbers: 51:55 Okay. Yes. Absolutely. More research is needed. So here's another question. Do you suggest that people with epilepsy have a sleep study done to monitor breathing during sleep? Is that possible?

Dr. Rup Sainju: 52:11 Best thing for people with epilepsy is to take your medicine, talk to your doctor how best you can control your seizure. Because again, we don't have a medicine to prevent SUDEP at this point given all the potential we discussed. Best approach still is try to control your seizure best. Having said that there is a good proportion of people who have epilepsy that may have obstructive sleep apnea. So if you have some of the simple symptoms of potential obstructive sleep apnea, for example, feeling fatigue, lack of energy, headaches, or people actually witnessed you snore during sleep or stop breathing during sleep, I think that would be very reasonable time to evaluate for a sleep study and get it treated because poorly controlled sleep apnea or untreated sleep apnea can worsen seizure and epilepsy control.

Dr. Laura Lubbers: 53:23 That's very important information and actually addresses another question that was asked in the Q and A. Here's another question for you. Does a co-morbidity of autonomic dysfunction increase SUDEP risk in epilepsy patients?

Dr. Rup Sainju: 53:39 We don't have much information about this yet and what we have is during or after convulsive seizure, some people can have really irregular heart rate or problem with blood pressure. How

that translates into SUDEP risk is not clear. How common that is is also not clear at this time.

Dr. Laura Lubbers: 54:14 Okay. Will the pulse-ox be a helpful alarm for people while they're sleeping?

Dr. Rup Sainju: 54:27 So again, it depends on the type of epilepsy as well as type of seizure that we're dealing with. And if you're talking about monitoring a child, that may be a problem putting the probe in to begin with. But if pulse oximetry is good enough to detect seizure-related drop in oxygen and alarm you, it sounds reasonable to think about it, but we don't have a study showing that is what is very helpful. But again, I'll circle back to the same thing. Some sort of supervision is reasonable, including pulse oximetry, but you have to think about it has a lots of false alarm that is associated. And false alarm could be because the probe is displaced while during movement or during sleep versus there are... So many different things can go wrong and give you a wrong pulse oximetry read.

Dr. Laura Lubbers: 55:41 Okay. It sounds like some monitoring is always a useful thing if you can, knowing that certainly more work needs to be done.

Dr. Rup Sainju: 55:52 Absolutely.

Dr. Laura Lubbers: 55:54 A couple more questions before we wrap up. A couple of people asked about examples of serotonin medications. What are those?

Dr. Rup Sainju: 56:04 Yeah. So a very commonly prescribed group of medicine includes SSRI or selective serotonin reuptake inhibitors. These are a group of anti-depressant. Or most medicines that is often used by psychiatrists. And the studies I alluded in this talk that were included in human, part of the human studies were people taking either SSRI or similar medicine. There are a group of... Another group called SNRI is non-selective serotonin reuptake medicines. These are also antidepressant medicines. And there are some... or supplement rather that can convert into serotonin in body like tryptophan or 5-hydroxytryptophan. So these would be considered as serotonergic medicine in general, if that's what we're getting at.

Dr. Laura Lubbers: 57:11 Yeah. Okay. Great. Some common names. Some common [crosstalk 00:57:17]-

Dr. Rup Sainju:	57:17	Yeah. So in terms of common names, Prozac would be a common name people might recognize. Celexa or citalopram, escitalopram would be some other names.
Dr. Laura Lubbers:	57:32	Okay. Great. I think that will be helpful. So I know there are a number of questions still in the queue. I do think we should wrap up now just to be respectful of people's times, but we will try to get these questions addressed and sent back to you. So I do want to thank you Dr. Sainju for this really helpful webinar, we've got a lot of very positive comments about the importance of the information and how valued it is. So I want to thank you. I also want to thank the BAND Foundation for supporting today's webinar, and of course our audience. I always appreciate your attendance and your great questions that make us think and inspire us. If you have additional questions about this topic or wish to learn about any of CURE Epilepsy's research programs or future webinars please visit our website @www.cureepilepsy.org.
Dr. Laura Lubbers:	58:29	Also, please be sure to register for our next CURE Epilepsy webinar that will examine the research surrounding disparities in epilepsy care and outcomes as we strive to create awareness and knowledge of the social factors that influence epilepsy and its care in hopes of improving outcomes for all. This webinar will be presented during Epilepsy Awareness Month on November 16th at noon Central Time. Thank you all and have a wonderful day.