

***Aging and Epilepsy
Consequences and Comorbidities to Consider in Older Individuals
(Transcript)***

- Dr. Laura Lubbers: 00:00 Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer for CURE Epilepsy and I want to thank you all for joining us today. Today's webinar is entitled Aging and Epilepsy: Consequences and Comorbidities to Consider in Older Individuals. This topic is of particular importance as epilepsy is the third most common neurological disorder in people ages 65 and older after stroke and dementia, conditions which themselves increase seizure risk.
- Dr. Laura Lubbers: 00:30 This webinar is part of CURE Epilepsy's 2021 Leaders in Research webinar series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website. You can also download transcripts of all of our webinars for reading.
- Dr. Laura Lubbers: 00:50 For over 20 years, CURE Epilepsy has raised millions of dollars to fund epilepsy research that supports our mission which is to find a cure for epilepsy by promoting and funding patient-focused research. CURE Epilepsy provides grants that support novel research projects and then advance the research for cures and more effective treatments. In 2020, we launched our CURE Epilepsy Catalyst Award to help accelerate the basic research we've traditionally funded into the next stage of development and prepare potential new treatments for clinical trials.
- Dr. Laura Lubbers: 01:23 Today's webinar will discuss the relationship between epilepsy, dementia, and stroke, and whether people with epilepsy have an increased chance of developing dementia as they age. You'll also learn about strategies that people with epilepsy can implement to reduce their risk for these conditions.
- Dr. Laura Lubbers: 01:41 This webinar is presented by Dr. Alice Lam. Dr. Lam is an Assistant Professor of Neurology at Harvard Medical School and the Massachusetts General Hospital. As a physician, Dr. Lam takes care of patients in both the subspecialty Epilepsy Clinic, as well as the Memory Disorders Unit. Her clinical and translational research program explores the interface between epilepsy, the neurodegenerative diseases and cognition, using a combination of neurophysiology, neuroimaging, artificial intelligence approaches, and cognitive outcomes.
- Dr. Laura Lubbers: 02:14 Before Dr. Lam begins I'd like to encourage everyone to ask questions. You may submit your questions anytime during the presentation by typing them into the Q&A tab located on your Zoom panel and then click send. I also want to thank those who

submitted questions in advance of today's webinar. We'll do our best to get through as many questions as we can. We do want this webinar to be as interactive and informative as possible, however, to respect everyone's privacy we ask that you make your questions general. With that, I'll turn it over to Dr. Lam.

- Dr. Alice Lam: 02:47 Great. It's a real pleasure to be here today and to be talking with you all about aging and epilepsy. This is a topic that I think is incredibly important and one that I care really deeply about, and I want to thank Dr. Lubbers and CURE Epilepsy for inviting me to give this webinar today.
- Dr. Alice Lam: 03:10 Our population is aging. The number of Americans over age 65 is going to double in the next 30 to 40 years. And as we're getting older and watching people around us get older I think it's totally natural to wonder how are we going to live our best lives when we're older adults? We all want to have a sense of independence, we want to have the ability to do things for ourselves, to make decisions for ourselves. We all want to preserve our memory, our ability to think clearly, to interact meaningfully with the world around us and to have ourselves represented.
- Dr. Alice Lam: 03:47 Today I want to talk about aging but in the context of epilepsy. Maybe you're someone or you know somebody who developed epilepsy a long time ago when they were a child or a younger adult then is now getting older, or maybe you're someone or somebody who developed epilepsy for the first time at an older age. How will having epilepsy affect your brain as you get older? That's what we'll be talking about today.
- Dr. Alice Lam: 04:18 Let's start with a pop quiz. The first question is what age group has the highest proportion of people who are currently living with epilepsy? That's regardless of when they're actually diagnosed with epilepsy. Is it children, young to middle-aged adults, or older adults? I'll give you the second question, which is, what age group has the highest chance of developing epilepsy, meaning being newly diagnosed with epilepsy? I'll let you think about what you might answer there.
- Dr. Alice Lam: 04:54 The answer turns out for both questions is the same, it's older adults. People over age 65 are most likely to either have a diagnosis of epilepsy already, meaning they developed epilepsy as kids or as adults and have now grown old with epilepsy, or to develop epilepsy for the first time. And in the United States alone, over 100,000 older adults each year are newly diagnosed as having epilepsy. Older adults are the fastest growing demographic in the U.S. as well. I told you earlier that the

number of older adults is estimated to double in the next 30 to 40 years, so now I hope you can see why aging and epilepsy is such an important topic, this is a public health issue. It affects a lot of people currently and it's going to affect a lot more people in the next few decades.

- Dr. Alice Lam: 05:47 All right, here's an outline of what I'll be talking about today. And before I start talking about aging and epilepsy I first want to talk about normal brain aging. What are changes in our thinking and memory that happened normally as we age and how does that differ from dementia? And also I want to tell you about an important concept called cognitive reserve, and we're going to come back to this concept of cognitive reserve again and again over the remainder of the talk.
- Dr. Alice Lam: 06:14 Once we've talked about normal brain aging and cognitive reserve, I think that'll give us a good starting point to start to address some of the most frequent questions I get from many of my patients with epilepsy. Does having epilepsy increase my chances of developing dementia? Does having epilepsy increase my chances of having a stroke, and what are the things I can be doing to keep my brain as healthy as possible as I get older? If you take anything away from this talk I want you to know that, yes, having epilepsy does increase your risk of dementia, and it does increase your risk of stroke. But the good news is that you can substantially reduce your risk of both dementia and stroke with some very simple changes in your day-to-day life. I'll tell you more about this in a little bit, so let's get started.
- Dr. Alice Lam: 07:10 With normal brain aging we know that our brains undergo some normal structural changes. This is a graph that shows you how the total size or the total volume of the human brain changes with age in healthy people. You can see the average trajectory for men and women and in blue and red respectively. And what you see is that in healthy adults it's normal for the brain to shrink a little as we get older. We lose brain cells, we lose connections between brain cells. Some brain cells shrink in size and the wiring between brain cells also shrinks. And related to these structural changes, our cognitive abilities also change.
- Dr. Alice Lam: 07:54 We know that as people get older even if they're healthy we start to have slower processing speed. Our working memory gets a little worse, our autobiographical memory, meaning our recollection of events that happened to us earlier in life, these details start to get a little bit fuzzier, and our ability to solve problems, come up with new ways of doing things also declines. But it's important to note that these normal changes even though they exist they're pretty subtle so many people might

not even realize or might not be aware that these changes are happening. And these changes are generally not significant enough to interfere with a person's ability to perform their daily activities.

- Dr. Alice Lam: 08:37 How is normal brain aging? How's that different from dementia? We know that there are some cognitive declines that happen in normal aging, but when people start to have a decline in their cognition that is more than we'd expect for normal aging, then we start to worry about whether or not they might have dementia. And so the precursor to dementia is called mild cognitive impairment. People with mild cognitive impairment have a decline in their thinking that's significant often, so they notice it themselves or their friends or their families notice it. But despite this decline they're actually still functioning pretty well. They can still work, they can drive, they can take care of their finances, they can cook meals, they can do all the things that they would normally do in their daily life.
- Dr. Alice Lam: 09:24 But when someone's cognitive impairments become severe enough that they start to have problems with their activities of daily living, then we say that that person's developed dementia. This might mean that they're no longer able to figure out how to pay their bills or they're no longer able to work a job that they've worked for the past 10 or 20 years, or they're no longer able to figure out how to cook meals. So there's different stages of dementia depending on how cognitively and how often functionally impaired someone is.
- Dr. Alice Lam: 09:57 I want to point out that the way I've defined mild cognitive impairment and the way I've defined dementia here, those definitions depend on how someone's functioning cognitively and how they're functioning in their day-to-day life. I haven't said anything about what actually caused these changes in function. The point I want to make is that dementia is actually a symptom, it's not a disease, it's a set of symptoms, a syndrome, but it's not a disease. There are actually different diseases that can cause dementia. The most common one is Alzheimer's disease, that one everyone has heard about. But there are other diseases such as vascular dementia, dementia with Lewy bodies, frontotemporal dementia. They can also result in this symptom or the set of symptoms that we call dementia.
- Dr. Alice Lam: 10:47 All right. I want to talk about this concept of cognitive reserve. It turns out that what someone's brain looks like, for example, on an MRI scan or if you could look at it under a microscope at autopsy. What someone's brain looks like doesn't always match up with how that person's brain functions. For example, you

might have an older adult who passes away and at autopsy we might find severe abnormalities in their brain, the kinds of abnormalities that you will typically see in someone who has end stages of Alzheimer's disease. And yet it turns out that this person right up until they passed away could have actually been functioning completely normally. They were living independently, they were cooking their own meals, they were driving, they had no signs of memory problems.

Dr. Alice Lam: 11:34 How do we explain this mismatch that you we can have someone with severe brain pathology whose mind is still able to function at a very high level? Well, one of the ways to explain this is a concept that's called cognitive reserve. You can think of cognitive reserve as your brain's ability to function well even the setting of having brain disease or having an injury to your brain. Cognitive reserve is how well your brain is able to compensate for disease or for injury. It's your brain's ability to find other ways of getting a job done if the usual way of getting things done suddenly becomes unavailable. I think about cognitive reserve in terms of brain networks, how different parts of the brain communicate and work together. And high cognitive reserve means that you've developed brain networks that are efficient and that are flexible.

Dr. Alice Lam: 12:25 And I want to give you a simple example of this. All right. Here's a crayon drawing about as simple as you can get, I think. Let's say you live in this town and you want to go from your house to the pool, that's pretty easy. There is a road that connects those things directly. All right. Think of brain networks as a system of roads in the brain that connects different parts of the brain that need to work together. What happens if there's damage to a brain network, for example, from a stroke or even from a disease like Alzheimer's disease? What happens if the damage affects this brain network that goes from your house to the pool and you can't use it anymore? Now, how are you going to get from the house to the pool?

Dr. Alice Lam: 13:09 Well, if you had developed other roads, other brain networks, even if this one road was blocked you might still be able to figure out how to get from your house to the pool. So you could take this path or you can take this path. These paths may not be as efficient, they might not work as well as the original road you are using but you've used these other networks to compensate for the fact that that main network is no longer working. That's what cognitive reserve allows you to do.

Dr. Alice Lam: 13:39 And I think that one of the best things about cognitive reserve is that it's closely related to your life experiences and to your

lifestyle. And that means that cognitive reserve is something that we can actually modify and improve over the course of our lives. We know that things like education and activities that are intellectually or socially stimulating, these things can greatly build cognitive reserve, and these factors actually it turns out can reduce your risk of dementia by 30 to 40%. While a lot of what I'll say in this talk may sound like doom and gloom and no one wants to hear that they have an increased risk of dementia, what I want you to know now is that you can actually do something to reduce this risk, you can build cognitive reserve.

Dr. Alice Lam: 14:28 How does having more cognitive reserve actually allow you to reduce your risk of dementia? Let's imagine someone who has early stages of Alzheimer's disease. And Alzheimer's disease, it's a slowly progressive disease where your cognitive function gradually worsens over several years. And so what I'm showing you is this decline in cognitive function that you might expect in someone with Alzheimer's disease, is this black curve here. Now, when this person's cognitive function declines enough that it starts to interfere with this person's daily activities, they've crossed the threshold and we can say that this person has developed dementia.

Dr. Alice Lam: 15:07 Now, what would this curve look like if this person had a severe head injury a few years back? Well, if they had a severe head injury there's likely been damage to some of their brain networks and other brain networks are now having to compensate for that injury, so this person will be starting out with less cognitive reserve. And with less cognitive reserve but the same amount of Alzheimer's disease pathology in the brain this person is going to be on a different trajectory shown on this red curve here. And you can see with less cognitive reserve this person will actually develop dementia at an earlier age compared to if they hadn't had this brain injury.

Dr. Alice Lam: 15:47 Now, let's take the opposite example. Okay, let's take someone who has a healthy brain, a high amount of cognitive reserve. And now you can see how the curve shifts outward here. Someone who has high cognitive reserve, even with the same amount of Alzheimer's disease pathology in the brain will actually develop dementia at a later age. And depending on how much later this age it's possible that they might actually pass away from something completely different before they even ever develop memory problems or dementia. And so you can live your whole life without ever developing dementia because you're able to kind of push it far enough down the line.

- Dr. Alice Lam: 16:28 The bottom line that I want to make here is that brain injuries and low cognitive reserve, these things put people at increased risk of developing dementia earlier in life than they normally would. Whereas high cognitive reserve can actually delay the onset of dementia and in some people it might delay the onset of dementia to such an extent that for all practical purposes it's prevented that person from getting dementia. That's why cognitive reserve is really important.
- Dr. Alice Lam: 16:57 Okay. Now that you understand the difference between normal aging and dementia and you understand this concept of cognitive reserve, let's see how this might apply to people with epilepsy. I'll actually address these next two questions together because they turn out to be somewhat related. All right, let's start with the bad news. The bad news is that people with epilepsy are two to three times more likely to develop dementia compared to people without epilepsy. Let's say there's a large amount of person to person variability in calculating this risk and there's many factors that determine a given individual's risk of developing dementia.
- Dr. Alice Lam: 17:40 And some of these things they might include things like when did you first develop epilepsy? What's the cause of your epilepsy? How frequently do you seizures? How many and which seizure medications do you take? How long have you been taking seizure medications? And do you have depression or anxiety? Now, it can be tricky to try to figure out the individual contribution of each of these things because many of these factors are pretty closely intertwined. If you have frequent seizures you're probably going to be on more seizure medications, and if you developed epilepsy early in life you're probably going to have been taking seizure medications for a longer period of time. So it's a little complicated to tease apart.
- Dr. Alice Lam: 18:26 But what I want to do next is I want to consider three different groups of people with epilepsy based on when they first develop epilepsy. So whether they developed epilepsy in childhood, in early to mid adulthood or even as an older adult. And I want to explain how I think about the risks of developing dementia for people in each of these groups as they get older.
- Dr. Alice Lam: 18:49 All right, let's start with individuals who develop epilepsy early in life, and so I'm talking about anyone who developed epilepsy from when they were an infant all the way through adolescence. I think the unique feature to this group in terms of cognitive function is that their epilepsy coincides with a period in which the brain is still developed. and epilepsy and being on seizure medications during that time can affect brain

development. This is a schematic, it's a timeline of the different stages in normal brain development and there's a lot of detail here. You don't need to know the detail, the main point is that most of these changes are taking place in the first 20 years of life. And so having epilepsy being exposed to seizure medications during this period could have adverse effects on this brain development process. I want to show you an example of that.

Dr. Alice Lam: 19:46 This is a graph from a study where they looked at learning and memory performance and it was about 1000 people with temporal lobe epilepsy and about 1000 people without epilepsy at different ages across their lifespan. And the blue curve shows you on average what normal development of learning looks like in people who don't have epilepsy. And you can see that learning performance increases early in life and it actually reaches a peak and the peak is around age 24. And after age 24 you basically have this slow but steady decline. That's a little scary but that's basically how learning development works.

Dr. Alice Lam: 20:31 Now, compare that to this green curve. This is what the learning curve looks like in people with temporal lobe epilepsy especially if they developed epilepsy earlier in life. And what you can see is that on average people who have temporal lobe epilepsy early in life, they don't reach as high of a peak performance as people without epilepsy. And not only that but they reach their peak earlier in life compared to people without epilepsy. And so they actually start their decline in memory performance about seven years earlier than they normally would if they didn't have temporal lobe epilepsy. What this means is that people with epilepsy in early life they may end up with this reduced cognitive reserve because of these kind of effects on brain development where they may not develop as well as they could otherwise, or their development may peak earlier and their decline actually starts earlier.

Dr. Alice Lam: 21:29 All right, let's consider the next group. What about people who develop epilepsy in early to mid adulthood? So here we're largely past the age where epilepsy and seizure medications would affect brain development, but this is early enough in life that this group is going to be chronically exposed to a number of different risk factors for dementia. And I'll actually include people who developed epilepsy earlier in life or in childhood as well here because these people if they continue to have epilepsy would have similar chronic lifelong exposures.

Dr. Alice Lam: 22:03 What kind of risks am I talking about? I'm talking about things like recurrent seizures. Prolonged seizures can damage the

brain and recurrent seizures also put people at risk for repeated head injuries if you're having convulsions and falling and hitting your head during a seizure. We know that head injuries aren't great for your brain health. Chronic exposure to seizure medications or some seizure medications that can do things like increase your cholesterol levels or cause you to gain weight, which can be a long risk factor for your brain health. Reduced physical activity, reduced social interactions, these are things that a lot of people with epilepsy deal with because it's harder to get out, it's harder to socialize, it's harder to live more normal life sometimes. These things will affect your brain health down the line. And then people with epilepsy are also predisposed to having sleep disorders and mood disorders and those things can also affect your health.

- Dr. Alice Lam: 23:06 These risks, basically you can think of them in two categories, risks that may reduce your cognitive reserve either because you're not interacting with other people or you're not having those kinds of social interactions that can enrich your brain, as well as vascular risk factors, things that can potentially affect the health of your blood vessels in your brain which as I'll mention later has a big effect on risk for dementia.
- Dr. Alice Lam: 23:32 But bringing these things up my goal isn't to sound like all doom and gloom about these risks and exposures, it's just to let you know that they exist and that they're happening. Because at the end of the day, things like cognitive reserve and vascular risk factors, these are actually things that we have some control over and can change and so just even being informed and knowing that you might be at heightened risk for these things you can be proactive in terms of trying to boost your cognitive reserve and trying to get these vascular risk factors controlled.
- Dr. Alice Lam: 24:06 All right. Finally, let's talk about epilepsy that develops in older adults, in people over age 65, and we refer to this as late-onset epilepsy. It's kind of interesting, how does someone who's never had a seizure her whole life suddenly develop epilepsy at a late age? Well, the most common causes of epilepsy in this group are stroke, having had a prior stroke, traumatic brain injury, and neurodegenerative diseases like Alzheimer's disease. But what's interesting is that it turns out that about 30 to 50% of people with late-onset epilepsy actually have no obvious cause for their epilepsy. If you look at their brain MRI there's really no smoking gun as to why they suddenly developed seizures. And yet we know that in these patients, in about the five or 10 years after they develop epilepsy, they actually have a threefold increased risk of having a stroke and they have a twofold increased risk of developing dementia.

Dr. Alice Lam: 25:09 Sometimes I think about epilepsy that starts in older age as a possible warning sign. We don't yet know how to predict which of these individuals might go on to develop a stroke or which of these individuals might go on to develop dementia. And there are some people who think that development of epilepsy late in life could actually be an early sign of a neurodegenerative disease like Alzheimer's disease. But this is actually still a very active area of active research and there's a lot that we have to learn still in this area is what I'll say.

Dr. Alice Lam: 25:46 I want to just talk about the relationship between epilepsy, dementia, and stroke. And this chart shows you how complex these relationships are. You can see that having late-onset epilepsy increases your risk for developing dementia but that if you have dementia that also increases your risk for having late-onset epilepsy. And similarly, late-onset epilepsy can increase your risk of having a stroke, that stroke we know is a big risk factor for late-onset epilepsy and stroke is also a big risk factor for developing dementia. It's this big triangle.

Dr. Alice Lam: 26:19 What's interesting is that all three of these entities, epilepsy, stroke, dementia, they share in common a number of risk factors which you can see here. And some of these risks have to do with vascular health, things like high blood pressure, diabetes, smoking. Some of these risks are actually genetic risk factors, things like black race, and the gene variants called APOE4. But I really can't stress this point enough, the fact that high blood pressure, diabetes, smoking, are shared risks for all of these diseases, it's kind of a good thing because these are things that we actually have treatments for. We can reduce these risks with changes in lifestyle and with medications. And so that gives me hope that maybe one day we might be able to prevent a substantial number of new cases of epilepsy in older adults and also prevent a substantial number of cases of stroke and dementia as well.

Dr. Alice Lam: 27:18 I've been talking a lot about the risk of developing dementia in someone with epilepsy but what I want to point out here is that most memory problems in people with epilepsy aren't actually related to dementia. I think that this is something that my patients ask me about a lot because I think most people are... Dementia is one of the most worrisome things for a lot of people because right now we don't have cures for diseases like Alzheimer's disease or vascular dementia. But as I said earlier there are a lot of things we can be doing to reduce our risk of developing dementia and the setting of these diseases.

- Dr. Alice Lam: 27:57 But the point I want to make on this slide is that there are potentially a number of other causes of memory problems in older people with epilepsy and even in young people with epilepsy that aren't related to Alzheimer's disease or to other neurodegenerative diseases. Here are the list of things that I think about most often when I'm evaluating someone, an older adult with epilepsy who's coming in with concerns about their memory.
- Dr. Alice Lam: 28:21 Are they having frequent seizures or epileptiform activity on their EEG? Are they on seizure medications that might be causing worsening of their memory or cognition? Are they on other medications that might be affecting their cognition? Do they have depression or anxiety that's poorly controlled and that can also present with changes in memory? Do they have sleep problems? We know that sleep is very important for memory as well. Again, the good news in many of these cases is that these are things that can be fixed and addressed and that can actually improve memory function in someone with epilepsy.
- Dr. Alice Lam: 28:59 All right. Onto the last part, what can we do to keep our brains as healthy as possible as we get older? Up to one in three cases of dementia could be prevented with just simple changes in lifestyle. What I'm going to share with you are recommendations that are largely agreed upon by many major health organizations on how to maintain brain health. And this applies not just to people with epilepsy, actually these are recommendations that are made to adults, essentially people who will be growing older. And these recommendations though I think that they are informative for people with epilepsy again because as I talked about people with epilepsy have a lot of these risk factors as they're accumulating through life.
- Dr. Alice Lam: 29:53 What are the things that we can do to actually maintain our brain health? First, there are things we can do to increase cognitive reserve, and the biggest one there is to keep your mind active. Think of this as exercise for your brain. This could be reading, doing crossword puzzles, playing card games, using the computer, photography, playing a musical instrument, things that keep your mind going. We know that cognitive activity in mid and late life is associated with a 30 to 40% reduced risk of dementia, so really important to keep your mind active throughout life.
- Dr. Alice Lam: 30:31 Second one there, protect your brain from injuries. Now, particularly for people with epilepsy seizures can put you at risk for head injuries and this is not something that you have much

control over, unfortunately, but that means that you need to be extra careful and protect your brain when you can. So simple things like wearing a helmet if you're riding a bike or wearing your seatbelt in a car. And then getting enough sleep, these are all things that will boost your cognitive reserve.

Dr. Alice Lam: 31:00 And then the second set of things as you might guess from the theme of this talk is controlling vascular risk factors, so stay physically active. The recommendation from the U.S. Department of Health and Human Services is that adults get 150 minutes of moderate intensity aerobic activity each week. What's moderate intensity aerobic activity? This is pretty much any activity that gets your heart rate up, it gets your heart beating faster. It could be something like brisk walking, dancing, gardening, biking, water aerobics, things like that, but it's really important to stay physically active.

Dr. Alice Lam: 31:36 And then work with your primary care doctor to make sure that things like high blood pressure, diabetes, and cholesterol are controlled. These will reduce your cardiovascular risk. Quit smoking. I know that many people think about smoking primarily in terms of risk for lung cancer, but smoking it turns out is horrible for your blood vessels and it's pretty horrible for your brain as well, so if you can quit smoking that may be one of the best things that you can actually do for your brain.

Dr. Alice Lam: 32:07 Eat a heart-healthy diet. What I often recommend to my patients is diet that's similar to a Mediterranean diet. That's a diet that has a lot of fresh fruits and vegetables, lean meats like chicken and fish, and try to avoid red meats like beef. And then finally avoid excessive alcohol consumption. There are mixed studies and you'll probably hear on the news, whether small amounts of moderate amounts of alcohol may be good or bad for your brain health, so that's mixed. But I think pretty much everyone agrees that excessive alcohol use which is basically more than one drink a day for women or more than two drinks a day for men that you should avoid that if you want to maintain good brain health.

Dr. Alice Lam: 32:51 There are lots of things that I've listed here and I'm not saying that you have to do all of these things to be able to prevent your risk for dementia, it turns out that... I mean, if you want to do all these things and if you can do all of these things, that's fantastic. But even if you can just choose one or two of these things and work on them I think that your brain will really benefit and you'll appreciate having done that a few years down the line.

Dr. Alice Lam: 33:15 All right, the take home points for today. The bad news, epilepsy is associated with a two to threefold increased risk for dementia and stroke. The good news, staying mentally and physically active and controlling vascular risk factors can substantially reduce your risk for developing epilepsy and stroke. I hope that encourages you to go out, be mentally and physically active, and to try to keep your brains healthy as you grow older. And with that, I think that's all I want to say and I'll be happy to take any questions.

Dr. Laura Lubbers: 33:51 Thank you so much, Dr. Lam. That was excellent, such great advice. Right now we'll start our Q&A portion of the webinar. Just a reminder, those who would like that if you have any questions you can submit them in the Q&A tab on your Zoom panel and click send. And I know that questions are already arriving but we did have some questions that were submitted in advance so I'd like to start with those.

Dr. Alice Lam: 34:16 Sure.

Dr. Laura Lubbers: 34:19 It is well-documented that AED side effects are more pronounced in the elderly because metabolism is slower. How should this be communicated to neurologists? Are they aware, and how often and what age do you recommend that dosages be lowered because of this?

Dr. Alice Lam: 34:34 That's a great question. The answer to that is a little complicated, but you're definitely right that as people get older our metabolism slows. Our liver slows down the metabolism, our kidneys slow down eliminating medications from the bloodstream. But that's also highly variable from individual to individual and as you know people have different body weights and there's a lot of different variability person to person. I think if you're aware of that and you think that this may be something that affects you I think it's important to talk to your doctor about that.

Dr. Alice Lam: 35:13 And one thing that your doctor can check, they can look at the level of seizure medicine that's actually in your blood and that will give for you... That basically tells you how your body is metabolizing the amount of medication your doctor is prescribing for you. And it might turn out that maybe your doctor was unaware or your level was actually a lot higher than they thought it was and you might be able to reduce your dose of seizure. But that's one objective way you can decide whether you're on too much seizure medication as you get older.

- Dr. Laura Lubbers: 35:47 Great, thank you. Here's another. Can Dilantin affect balance over time and do you have any comments on this or suggestions about what to do about it? There's an article published in Future Medicine entitled Antiepileptic Drugs and Their Impact on Balance, and this person hopes that you can comment on that.
- Dr. Alice Lam: 36:06 Yeah. I haven't read that article but I can say that, yeah, Dilantin can definitely affect your balance and it can do that in a few different ways. One, if you're on too high a dose of Dilantin you can actually have this Dilantin toxicity where you're off balance and you're wildly... Some people describe it as this feeling of being drunk without having had anything to drink. And so if your dose is too high you might notice that, and if that were the case you'll probably notice it usually about the hour or two after you take your medicine. That's one way it can affect dizziness.
- Dr. Alice Lam: 36:47 But long-term it can also affect a dizziness in a number of different ways. Sometimes people can develop what we call a neuropathy that's associated with long-term Dilantin use. That means that the nerves that go from your spinal cord down to your feet and help your brain know where your feet are and what they're feeling on the ground below, those nerves can get damaged and you might not be able to feel your feet as well. And we also know that Dilantin over time can affect the cerebellum. That's a structure in your brain that controls balance and coordination, things like that. So, yeah, I think that there is a fair amount of evidence that Dilantin can affect your balance but again it can do that in different ways.
- Dr. Laura Lubbers: 37:31 Is there anything that can be done about that?
- Dr. Alice Lam: 37:34 Well, if you're on too high a dose of Dilantin then obviously reducing the dose or trying to adjust how you take those doses or maybe even changing the medicine if it's not the right medicine for you would be one way to do it. Obviously Dilantin is an older seizure medicine and I tend to avoid using it in older adults for a number of reasons. It tends to be older adults who are on it because if they were diagnosed with epilepsy years ago that's what was available years ago and a lot of people are very comfortable staying on that medicine if it was working for their seizures, and so that's often the case of patients who come to see me who are on Dilantin already.
- Dr. Alice Lam: 38:14 But there's a lot of newer seizure medications that may not have those kinds of adverse effects, for one. Dilantin also, the way it's metabolized is a little interesting and there can be interactions with a lot of other medications, not even just

seizure medications but other common medications that you might take for other conditions. In an older adult if you're running into these problems you might think about switching off of Dilantin for that reason, the medication interactions and these long-term effects that we know can happen with it.

- Dr. Laura Lubbers: 38:48 I think that's an incredibly helpful answer for this person, so thank you so much for that.
- Dr. Alice Lam: 38:54 Sure.
- Dr. Laura Lubbers: 38:56 If a person is over 80 and has had no seizure activity in 15 years, do you think medication dosages could be lowered? When can...
- Dr. Alice Lam: 39:10 I think I know what answer they're looking for. It's something to think about, again, this is something that's very individual and I can't answer that without knowing more details of what happens to you when you're having a seizure or what risk for injury might you incur if you did have a breakthrough seizure because you lowered your dose. But these are tricky questions. Even if I did know more about this person it's not something that I could answer concretely, it's something that really depends on the risk benefit ratio for each person and how willing they are to take a risk like that. I think you have to think about what would happen if you had a breakthrough seizure versus how bad it is to be on the level of medicine that you're on right now. Are you having a lot of side effects from it or not? You just feel you want to be on a lower dose. [crosstalk 00:40:08]. The good thing is to discuss with your neurologist.
- Dr. Laura Lubbers: 40:10 Yeah, and I think about the risk of falls, and as we get older we have greater propensity to break bones and so we want to avoid falls as well for those reasons so it is trickier.
- Dr. Alice Lam: 40:22 Exactly.
- Dr. Laura Lubbers: 40:22 Sure.
- Dr. Alice Lam: 40:23 Exactly.
- Dr. Laura Lubbers: 40:24 Here's a bit of a different question and you sort of answered it I think during your talk but let's just review. So a rupture of an arterial venous malformation maybe has led to development of tonic-clonic seizures and many cognitive issues, including problems with memory. Is there a greater risk of this person acquiring dementia as they age?

Dr. Alice Lam: 40:50 Yeah. I mean, knowing just that, we can think about this in terms of this whole cognitive reserve a thing that I talked about. And so having this brain injury and having these cognitive issues that result you're now at a lower cognitive reserve than you would have been before this AVM ruptured. And so I would say that, yeah, if you were to develop the kind of changes in your brain from Alzheimer's disease you might be more susceptible to having dementia earlier from that than you would have had you not had this brain injury. But it doesn't mean that you shouldn't still try to reduce your risk for that. But, yeah.

Dr. Laura Lubbers: 41:34 Okay, great. And as an older person with epilepsy, the person recognizes that they may be able to based on your talk, develop dementia or stroke depending on their lifestyle. A person wants to know if their seizures increase with age? And at what point, and this I think is really relevant for those independent older people around driving. At what point in time do you start having the discussion about driving or not driving?

Dr. Alice Lam: 42:14 Okay. The first question with the seizures increase with age, again, I'd have to say it depends but it's not something that I typically see or counsel my patients like, "Oh, we better worry that your seizures are going to get worse as you get older." It's not something that... I would say I don't think that there's a lot of evidence that that occurs but again it depends on each individual.

Dr. Alice Lam: 42:42 The second question about driving, that's a great question. And this is a question that I deal with with people with epilepsy and I take care of people with Alzheimer's disease as well so it always comes up then. I think that sometimes people have awareness or insights to know when they feel it's not safe for them to be driving. But it's a really hard thing to actually make this assessment in my clinic, in my office, because I'm seeing somebody, I'm talking with them but I have no idea when they get behind the wheel how they would react to things. I don't know, what would they do? Would they be able to stop in time if a kid ran out in front of the car to run after a ball or something like that? What would they do if a car swerved into their lane all of a sudden, how would you react to that? These kinds of things are really hard to gauge in a clinic.

Dr. Alice Lam: 43:34 One thing I'll often do is sometimes I think it becomes pretty clear that someone shouldn't be driving. They're either getting into accidents or they're getting lost while they're driving, things like that. And those cases are a little bit more straightforward and often families will take away their loved one's keys before even asking me about it. But when it gets a little grayer, when

things aren't quite working as well as you want to in your brain, but a lot of you've been driving your whole life, it's an automatic thing almost, you don't have to think about it so much.

- Dr. Alice Lam: 44:05 What I'll often do is I'll recommend that people undergo a formal driving assessment. And so there are different centers that do this. There's occupational therapists who are trained in assessing people's safety in driving, and often this kind of driving assessment it may involve pen and paper tests first and if you do fine on that then you would do a behind the wheel on the road test where someone will be with you and assessing how you're able to react to different things that happen. And so I often lean fairly heavily on these kinds of assessments to make a good assessment of that. It's again, as I said, it's really hard to know from just talking to someone in my office how they would actually do on the road.
- Dr. Laura Lubbers: 44:54 Right. But I think that's great advice and great to know that those resources can be out there for people to be thinking about as they consider this question for themselves.
- Dr. Alice Lam: 45:03 Sometimes it's actually more helpful for family members who don't want their loved ones to be driving but their loved ones won't listen to them. And so and if they won't listen to me I'll say, "Well, if you want to drive you need to have a formal driving evaluation." And then it's an objective, it's not just someone judging or wanting to take away their independence it's an objective. You either passed or you didn't pass the test.
- Dr. Laura Lubbers: 45:26 Right, absolutely. Here's a question. Are some epilepsy medications worse for dementia?
- Dr. Alice Lam: 45:36 Let me answer that a different way, or let me pose the question differently. Ways. Maybe one way to ask it would be, are some epilepsy medications worse for cognition, not necessarily dementia? But I guess if they're worse for cognition then they're not going to help if you have dementia either. So if I ask my question, are some medicines worse for cognition? There are some medicines that we know have a worst cognitive profile compared to others.
- Dr. Alice Lam: 46:08 Now, again my patients can respond very differently to seizure medicines. Again, there's a lot of inter-individual variation, but generally there are some medicines that are thought to be relatively neutral or relatively... That they don't really affect cognition too much. And those medicines that people often use in that case are levetiracetam or Keppra and lamotrigine or

Lamictal. Those are thought to have relatively benign cognitive effects.

- Dr. Alice Lam: 46:39 But then there are medicines that we know can definitely worsen cognition. These tend to be some of the older ones, so phenobarbital has been shown to have poor effects on cognition. Dilantin even can do that as well and carbamazepine. Some of these older medicines may have more of those more pronounced effects. But, yeah, I think, again, as in that slide where I looked at what kinds of things can affect memory in someone with epilepsy, choice of seizure medication can definitely do that. Topiramate, that's another one that tends to affect cognition pretty badly.
- Dr. Laura Lubbers: 47:18 How about zonisamide?
- Dr. Alice Lam: 47:23 It can. Again, it really varies from individual to individual. Zonisamide wouldn't be on my top list for someone who's having cognitive problems already, it would be a bit further down the list. But I would say it's not entirely neutral but it's not as bad necessarily as some other ones. But everyone is... Again, I can have one patient who's on a whopping dose of a medication, has no idea it's in their system. And have another patient who's on the same medication on a really tiny dose and is falling over because the side effects are so bad. So it's really hard to predict that unless you actually just try it and see how you feel on it.
- Dr. Laura Lubbers: 48:08 Okay. So in the same discussion, if somebody is feeling a cognitive impact and it's possibly because of their medication, are those changes reversible if patients switch medications?
- Dr. Alice Lam: 48:22 Some of them can be, yeah. Again, if it tends to be a, "I just started this medicine a couple of months ago and I and my family are all noticing that I'm a lot slower on forgetting conversations." Then yeah, in general come off that medicine. I would expect those side effects to get better as you're off the medicine. But some of these older medicines like phenobarbital, Dilantin, if you've been on them for years and years and now you're coming off them it may not be as great a benefit because there are some long-term changes from those medicines. So you might not notice as great a benefit but it might still be worth trying to come off them to see if you do get a benefit.
- Dr. Laura Lubbers: 49:06 Okay, great. Thank you. Can testing neuropsych evals tease out declines in cognition based on AED side-effects versus declines resulting from regular aging? Can testing determine the source of the cognitive decline?

Dr. Alice Lam: 49:23 Yeah, that's a great question. I use neuropsychological testing actually pretty frequently in my patients with epilepsy and memory problems. I think that there's a number of things that can be helpful with it and often I do use it for the purposes that you're talking about to try to tease apart what is actually causing this person's cognitive impairments. Because one thing that neuropsych testing allows you to do is it really... I mean, if any of you have ever done neuropsych testing it's a several hour-long cognitive test. You never knew that there are many tests for your learning and for your memory and things like that. So it's very detailed and it can get in very good detail what parts of your thinking are working well and what parts of your thinking aren't working well?

Dr. Alice Lam: 50:12 A lot of patients will say, "My memory is bad." But actually it's not their memory that's bad, it may actually be their executive function, their ability to plan and organize things that's more affected than their memory. And so neuropsych testing allows you to tease apart some of those things. And depending on what cognitive domain, whether it's memory, executive function, language, any of those things, depending on which domains are affected, that can often help us hone in on what might be causing those changes.

Dr. Alice Lam: 50:42 And so sometimes that can help me distinguish between whether it's someone's longstanding epilepsy that's causing their cognitive troubles or whether it might be something new or different, maybe they've developed dementia or maybe they've developed depression late in life. Trying to tease apart some of those factors, neuropsych testing can be helpful for that, yeah.

Dr. Laura Lubbers: 51:06 Great, thank you. Is the ketogenic diet a heart-healthy diet?

Dr. Alice Lam: 51:14 Ooh, that's a tough one, actually. I actually I don't know the answer to that. I think it's tricky because obviously it's a very fat-intensive diet and I should actually look that up, but I do not know the answer to that offhand.

Dr. Laura Lubbers: 51:34 It's a great question. Is it really-

Dr. Alice Lam: 51:36 It's a really good question.

Dr. Laura Lubbers: 51:37 Yeah, yeah. Yeah. Yeah.

Dr. Alice Lam: 51:40 I mean, I know that people who are on the ketogenic diet get monitored frequently. They have their cholesterol levels

checked, they have a lot of these metabolic things checked. But I don't know what the data is in terms of long-term, if it actually predisposes you to having heart attacks because of the high-fat content or not.

- Dr. Laura Lubbers: 52:01 Right, right. Right. Especially in an older population, right?
- Dr. Alice Lam: 52:05 Right.
- Dr. Laura Lubbers: 52:06 Okay. Does chronic microvascular ischemic change get worse with time and does it make epilepsy worse?
- Dr. Alice Lam: 52:15 Okay, that's a good question. For those who don't know what is chronic microvascular ischemic change, the best way I can describe it is let's say you have an MRI that's done. What it looks like on an MRI are these little white spots actually, these little white spots that you don't normally see but you do tend to see them more as people get older. And what we think of these little white spots is that it's reflecting damage to really small blood vessels in the brain. It's showing you that there's some disease of the small blood vessels, they're affected somehow. And sometimes that can be due to the kinds of vascular risk factors that we've been talking about, high blood pressure can definitely do that. People who smoke definitely you'll see a lot more of these microvascular changes in the brain.
- Dr. Alice Lam: 53:15 Can that worsen... I think that was the question, can it worsen epilepsy? What I'll say is, there have been studies that been done recently looking at what are the risk factors for people who develop late-onset epilepsy. And it turns out that people who have these chronic microvascular ischemic changes, again think of them almost silent changes. Most people don't know that they're there, it's something that you see on MRI, on brain imaging when you do the imaging but they're silent. Think of it as silent cerebrovascular disease. It tells you that your blood vessels are not as healthy as we'd like them to be.
- Dr. Alice Lam: 53:57 But anyhow, if you have those kinds of changes in mid-life in your 40s and 50s, that is actually a risk factor for developing late-onset epilepsy. Whether if you already have epilepsy that kind of change will worsen your epilepsy. I'm not sure if we know that or not, but again, in terms of this vascular risk I've been talking about, think about this chronic microvascular change as another sign that maybe things aren't as healthy as you want them to be.

Dr. Laura Lubbers: 54:32 Okay. Right. And then to try to manage that to the best degree possible going forward.

Dr. Alice Lam: 54:37 Exactly. Exactly.

Dr. Laura Lubbers: 54:40 We have time for one more question. And this relates to the graph that you showed with people with temporal lobe epilepsy and the age of onset and the likelihood of dementia or loss of cognitive function. Are there different outcomes on epilepsy in other areas of the brain, for example, parietal lobe? Has this been studied or has it just been focused on TLE?

Dr. Alice Lam: 55:01 That's a great question. And so a lot of the studies on cognition and epilepsy have been done in people with temporal lobe epilepsy. It's the most common focal epilepsy so there's a lot more people that have it compared to things like parietal or occipital or frontal lobe epilepsy, that's probably one of the reasons. But also we know that temporal lobe epilepsy affects the temporal lobes and we know that those are really important for memory as well. I think that historically that's been the case and it's hard to do... You need really big studies in order to make these kinds of observations or to get these kinds of insights you need a lot of patients over time too.

Dr. Alice Lam: 55:43 So you're looking at thousands of patients in that study in that graph that I showed. I think it can be challenging maybe to find enough people with certain kinds of epilepsy to be able to do those studies and to be able to make these kinds of clear inferences. But it's an area that we definitely need to work more on to understand better.

Dr. Laura Lubbers: 56:05 Right. This is definitely an area of need for more research.

Dr. Alice Lam: 56:08 Yeah.

Dr. Laura Lubbers: 56:10 Yeah. Well, I want to thank you again, Dr. Lam. We're going to wrap up our Q&A session, we deeply appreciate the answers you have provided. I know there are a few outstanding questions and we may try to get those over to you for answers at some point in time.

Dr. Alice Lam: 56:24 Sure.

Dr. Laura Lubbers: 56:26 Again, I want to thank you and I want to thank our audience for such great questions and those people who submitted in advance gave us really some great things to think about as we've been preparing for this session. For the audience

members if you have additional questions about the topic or would like to suggest a future webinar topic or wish to learn about any of your epilepsy's research programs or future webinars, please visit our website at www.cureepilepsy.org, or you can email us at research@cureepilepsy.org.

Dr. Laura Lubbers: 57:00

Please also remember to keep an eye out for the announcement for the remainder of our webinars in this series which will continue in September, we're going to take the summer off. Thank you again, stay safe, and have a wonderful summer. And thank you again, Dr. Lam-

Dr. Alice Lam: 57:14

Thanks for the opportunity, Dr. Lubbers.