Epilepsy and Neurodegenerative Disorders: The Relationship Between Stroke and Seizures
A CURE Epilepsy Webinar
(Transcript)

Laura Lubbers: Welcome everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer of CURE Epilepsy. Since our founding in 1998, 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 advance the search for cures and more effective treatments.

Today's webinar is focused on the relationship between stroke and seizures. Some stroke patients suffer from early seizures and status epilepticus and are prescribed anti-seizure medications. Despite these medications, many people still suffer from seizures. In fact, a study published in 2013 found that 7% of people who suffered a stroke went on to develop epilepsy. Advances in acute stroke management have led to improved survival after stroke, and therefore more people are expected to develop post-stroke epilepsy.

Post-stroke seizures are often associated with significantly increased mortality and severe disability in patients. Thus, it's really critical to talk to stroke patients about this issue to create awareness about the complications of stroke, including epilepsy, and understand how this condition affects their care and quality of life. Today, you'll learn about the epidemiology of post-stroke epilepsy, the complications of post-stroke epilepsy, and the international efforts to promote research on this topic.

This will be the first of a number of webinars this year that will discuss epilepsy in older adults. In subsequent webinars, we'll learn about the association of epilepsy with conditions that often affect older adults such as neurodegenerative disorders. 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. This webinar is presented by Dr. Nishant Mishra, who will share his independent views on post-stroke epilepsy in this webinar. He's the stroke director at the West Haven VA Medical Center and is a stroke neurologist at Yale New Haven Hospital. He's also the convener and co-founder of the International Post-Stroke Epilepsy Research Consortium. He's been an active stroke researcher over the last two decades and currently focuses on understanding the mechanisms of post-stroke epilepsy.

As full-time faculty at Yale University, he conducts clinical research to improve the care of stroke patients. Before Dr. Mishra begins, I'd like to encourage everyone to ask questions. We'll address the questions during the Q&A portion of the webinar. Keep in mind, you can submit your questions anytime during the presentation by typing them into the Q&A tab located on your Webex panel and click send. 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 and not specific to a loved one's epilepsy. So with that, I'll turn it over to Dr. Mishra.

Dr. Mishra: Thank you, Ms. Lubbers. So my name is Nishant Mishra. I'm a stroke doctor and I typically manage patients with acute stroke and their stroke-related complications. For instance, if someone is having a new stroke-like symptom, for instance, the vision is going off, face is turned to one side. Arm, legs are going weak, and if they are within the time window for offering the clot-busting therapy, which we call TPA, and the time window is four and a half hours of the symptom onset, I select those patients talk to them or their family members and offer them the clot-busting therapy, the TPA or the TNK these days.

Some of these patients may have a vessel occlusion in their brain and I refer them or bring them in to the hospital to offer them what we call endovascular therapy. What that means is our colleagues from the neuro-intervention side, they go ahead find the clot in the brain and pull it out hoping for re-canalization of the vessel. I also manage patients who have bleeding the brain unfortunately. And there I seek support and help from our colleagues from the neuro-critical care side.

So this is the kind of job that I do. And one of my first patients, in fact, the very first patient who I offered TPA, the clot-busting therapy, he was texting my supervisor in about an hour or so that, "Hey, Dr. XYZ, I'm able to use my left hand, which was weak and that was a great outcome." And I was a young doctor several years ago, and I was really excited to see that outcome. Fast forward few months later, the same gentleman in his early 50s started coming to our hospital that was back in the days when I used to work in India.

He started coming to our hospital with some neuropsychology behavioral manifestations. He would be walking with his wife and he would have some delusions and hallucinations that people are saying unnecessary things. He would be driving his car and at the zebra crossing, the intersection as we call them in America, he would see as if people's faces are really coming in front of his driveway, and that really affected his quality of life. I'm telling you this story. We actually published this case report in Journal of Neuropsychiatry and Clinical Neurosciences.

So this is out in public domain. And the reason why I'm telling this is because the common perception about seizures is that there should be jerky movement, jerking off certain body muscles, body parts, but patients can also have behavioral manifestations, psychosis, delusions, hallucinations, and all these manifestations, even like someone may have a transient short duration seizure, which can lead the person to fall. And these events really significantly and adversely affect the quality of life of the patient population that I treat. Therefore, this topic post stroke epilepsy is really, really very important and needs to be addressed.

And thanks, Laura, for creating this opportunity for me to speak to our patient population. I'm really, really looking forward to also learning what is it that's most important to this patient population through organizations like yours and understand what we can do so that we can really contribute from research and also from clinical standpoint to the felt need of this patient population.

I'm employed by certain organizations, and anything I say in this meeting are my personal opinion. Typical disclaimer that I must say before I move on to the next slide. So why post stroke epilepsy should be studied? So there are many reasons from the scientific standpoint. I gave you an example from the patient standpoint the kind of manifestations that someone can have and the way it can affect the quality of life of these patients.

From the American Epilepsy Society standpoint, National Institute of Health standpoint, there's a lot of interest and focus in understanding the mechanism of epileptogenesis. What that means is that if somebody has had a stroke or a traumatic brain injury or some other kind of injury to the brain, there are certain pathways that get activated, which we don't really understand that well at this time. But if we have a good understanding of those pathways, we'll be able to develop some drugs, some interventions, which will really prevent the seizures from happening in these patient population.

And that will be really great because if you can prevent somebody from having seizures, then patient population don't have to be on the medications for seizure control and not have to suffer from the side effects and other complications that come from this. So this is indeed a very important topic. And from a physician standpoint, the strokes are interesting and topic to study epileptogenesis because in this condition, the lesions, the stroke lesions are very discreet. So one can better investigate that from the scientific angle.

When we look at the new onset epilepsy in the older population, we recognize that almost 50% of the patients, of the individuals in age group 60 and above, they suffer epilepsy or seizures secondary to cerebral vascular disease, ischemic stroke and hemorrhagic stroke. As you can see here in this... And it's jumping fast. Okay, let me go back.

So as you can see in this figure, there are two peaks. There's one peak in the early age, and then the second peak is in the older age. So older age group patient population, almost 50% of their seizures or the late onset epilepsy, new onset epilepsy is actually attributed to the ischemic stroke and hemorrhagic stroke. When we started studying this topic, the question is why is this important? Why should we study this topic?

So we started by looking at all the published data from around the world and conducted a systematic review and meta-analysis in which we identified almost 6,000 plus papers, eventually selected 71 studies that were eligible for this study and we were looking at the outcomes in this patient population, and we

found that the post stroke seizure was associated with double the risk of death in this patient population. And then if you go on to look at the other... Sorry.

Okay, when we go on to look at the other outcomes. So here, poor outcome on the ranking three to six, it means that patients are less independent and these data suggest that patients or individuals who have post stroke seizures are more likely to be dependent or likely to have disability. And there were some data to suggest that they are more likely to have dementia as well. So the systematic review and meta-analysis that we did, it supported the hypothesis that post stroke seizures are associated with increased mortality, poor outcomes, more disability, greater risk of having cognitive problems, dementia, and therefore this is an important topic that should be investigated and we need to put in efforts to reduce the risk of this condition.

But we also recognize that there are many challenges. On this slide, I have listed many technical items, but in short, what we recognize is that there have been a lot of variations in the methodology which need to be tackled and better research should be conducted in the future. Stroke and epilepsy doctors typically work in their own silos. It's jumping fast. What happened? Can we go back, Laura? It's automatically jumping. Okay, thank you.

So stroke and epilepsy doctors, we are so much focused in our own specific subspecialties that the interdisciplinary topics wherein there is a need for an epileptologist and stroke doctors work together. At times we may be missing that. And it's very important that at a global level we begin to work together, understand what is more important to our patient population, and also it's important for us for bodies like CURE and also the patient, patient advocates to highlight this problem to the various representatives including the federal bodies to promote this topic of investigation.

When we are doing that systematic review, the one that I just showed a few seconds ago, we recognized that there was actually a lot of global effort already ongoing in terms of the research on looking at outcomes from stroke-related seizures. We could find papers from almost every continent, almost every country in the world, but the sample size was smaller in each of these studies, in each of these centers. And as a result, we felt that there was a need for us to bring collaborators, colleagues from around the world together so that we could pull these data and make some more meaningful analysis and guide the research forward.

And that led us to launch the International Post-Stroke Epilepsy Research Consortium in which we have colleagues leading epileptologist and stroke doctors joining forces together. We have been having our annual meeting at the American Epilepsy Society Conference wherein we have our epilepsy doctors, the researchers, the stroke docs joining hands, discussing ways to better understand this topic and talk about how the epileptogenic pathways can be suppressed both in the humans and also the preclinical research.

We have some special interest groups wherein our colleagues are looking at how to best design the clinical trials, what drugs may be useful or meaningful in preventing occurrence of seizures, late seizures in this patient population. What biomarkers may be able to help, select the patients who are at a higher risk of developing seizures after the stroke to their colleagues who are interested in understanding the biological mechanism in the animal models, electrophysiology, brain imaging.

It goes without saying that these are important investigations which will contribute to our advanced understanding of the epileptogenesis, the mechanism by which the seizures develop in humans, and then the equity. The world is so big. Epilepsy is such a big problem worldwide. It has not only the consequences from quality of life. When we talk about seizures, there are stigma. There are so many other aspects of epilepsy that needs to be tackled, and equity is very close to our heart and we are trying to understand how the seizures and epilepsy can be prevented in other parts of the world, and for which we have our colleagues collaborating with our fellow colleagues in different parts of the world.

We have started pooling data from previously conducted research on post-stroke epilepsy and are building this repository. The idea here is that by pulling the data from the previously published the research and then identifying the common data elements, having a larger sample, we will be able to make better sense out of a larger data and guide the future research.

So let me come back to some clinical aspects. So how do we diagnose post-stroke epilepsy? So from a clinical standpoint, anyone who has had unprovoked seizure and is at a risk of 60% or more of having another seizure in the next 10 years, we call that individual to be suffering from epilepsy. The general understanding in the field is that if somebody has had a stroke and then a late seizure, the seizure that happened after seven days of the stroke onset, then that person is at a greater risk of having seizure recurrence and therefore we call that individual suffering from post-stroke epilepsy.

Anyone who develops a seizure soon after the stroke in the first seven days, we call it early seizures. Individuals who suffer from early seizures who have had seizure after the stroke in the first seven days, they are at a greater risk of having late seizures.

So what are the risk factors? So there are certain risk factors which we cannot change. I cannot stop aging. I cannot stop getting older. I cannot stop my hair turning gray, but there are other aspects of my life which I can modify. For example, if I stay healthy, if I exercise, if I control my cardiovascular risk factors, my brain will stay healthy and I will hopefully not develop stroke. And then hopefully then I will not have a cerebral vascular disease and not suffer from the consequences of epilepsy or seizure if that were to happen to me.

So risk factors for post-stroke epilepsy include age, the kind of stroke somebody has had. So if somebody had, for example, a bleed in the brain, so we know that blood is more epileptogenic compared to the ischemic stroke. So people who have bleed in the brain, they're at a greater risk of having late seizures. Not everyone who has bleed will develop seizures, but the odds of that population having seizures is higher.

Similarly, somebody who has had a stroke and his stroke severity was greater like more significant handicap, that individual is more likely to have late seizure seizure after seven days. Somebody, as I said earlier, somebody who had an early seizure, seizure that happened in the first seven days after the stroke, that individual is at a greater risk of having late seizures. And then there are some emerging data that there may be a role of genetics, family history, which also contributes to increased risk of late seizures.

So what are the clinical manifestations? So I started by telling you the story of one patient about whom actually I published long time ago that the seizures can manifest with behavioral symptoms. Usually the patients will have otherwise focal seizures. That's the common pattern that we see. But as I'm showing in the slide, almost 43% of the patients will have non-motor seizure which means they will not have the jerky movement of the body tonic-clonic, that kind of seizure. They will have more the behavioral changes.

This slide is actually very clearly showing what I mean to say here. So motor seizures and non-motor seizures. Motor seizures mean jerking up the body parts tonic-clonic sometimes. And as you can see, almost 30% of the patients will have focal stiffening. So stiffening of the muscles or about 20% will have focal rhythmic jerking.

But if we go down in this row, cognitive, so some patients will have problem with their language, positive features such as hallucinations, and that is about 24, 25% of the patient population. There are other manifestations as well that have been reported. So the summary is that post-stroke epilepsy patients can have behavioral manifestations about which we should be aware. These are the symptoms that go unnoticed, uncaptured. They don't contribute to the epidemiology data. So when we say that about eight or 10% of the stroke patients develop post-stroke epilepsy, we are potentially missing this patient population who may be going totally unnoticed and not captured in the epidemiological data.

Why this is important? So our stroke patients are on a range of medications to prevent stroke recurrence. We offer them medications like aspirin, Plavix. We Back in the days we used to use warfarin or Coumadin. Many of you would remember Coumadin as the rat poison. That medication used to be used for keeping the blood thin so that the stroke doesn't happen again. These days we use medications which we call DOAC or NOAC like Eliquis, Pradaxa, those kind of medications. And they do interfere or the anti-seizure medications by some

mechanism influence the functioning of some of the medications that we offer to the stroke patients.

Also, they modifies the risk factors for stroke like the cholesterol, lipoprotein carotid intima-media thickness. Impact of the effect of the anti-hypertensive, the blood pressure medications. So it's very important. In fact, certain medication can also influence the way the heart is running like cardiac arrhythmia. So we have to be mindful and there is a really need for us, the stroke doctors to better understand about the safety and efficacy and which medications are the best for this unique population.

How do we go about preventing post-stroke epileptogenesis? What can we do to prevent an individual who suffered a stroke from developing a seizure later on in his life? So this picture is actually showing bleeding in the brain. There are some biological mechanisms, certain inflammation, certain factors which accumulate they lead to more epileptogenic processes. Similar mechanisms can also be spoken about for the ischemic stroke, the stroke that happens from a clot that occludes a vessel.

I want to show you this picture. It looks a little complicated, but let's see. So let me explain one picture at a time. So this one on the very left, X-axis, this shows the time. This is when the stroke happened at the onset. And then Y-axis, this vertical line is showing the seizure threshold. So when the stroke happens at this time, the first insult, the seizure threshold was high. So the person is not likely to develop seizure at that time, but because of the biological process, the epileptogenesis gradually the seizure threshold comes to a line to a point where there is an increased propensity for the person to have the seizure.

So even though the epileptogenesis, the epileptogenic biological pathways have already started at the onset over time there comes a point when the seizure threshold has gone below this red line and the person starts developing seizure. And our mission, our goal is to prevent this line going down. If we can do that, we can prevent the person from having a first late seizure of his life after the brain injury, in this case stroke.

If we are not able to do that, then that person will go through progression, which means the precipitating factors, the mechanisms, M1, M2, M3 will keep influencing the seizure threshold. And it may be that this line goes down and person keeps having seizure or some unknown mechanisms, which we don't fully understand yet. Once the precipitating factor has disappeared, some patients may go into remission.

What that means is this line may go up. Who develops this? What causes this pathways to get activated? We don't really know at this time, and that's why it's very important to understand the biology of epileptogenesis so that we can develop drugs. If we can develop a drug that prevents this line from going down below this threshold line, then we would have a win. We would have success in preventing a person from being on lifetime of anti-seizure medication. And

because despite anti-seizure medication use, patients still at times unfortunately have recurrent seizures for a variety of reasons.

So on the one hand, the goal is prevention, where we offer a medication. Here it says intervention, right? So intervention means medication. So we offer the medication somewhere around this time after the stroke in a patient in whom we are confident that that patient is going to go the direction of developing seizures. We don't want to give this medication to an individual who is not going to have seizures later on.

So first step is to figure out which patient is going to develop seizure and then use the drug, a future drug, a drug with anti-epileptogenic characteristic and use it in a study such that we are able to keep this line above this red line and prevent any future seizures from happening.

Cure. Cure means disease has already started. So here this person, this patient population has started having seizures and then we are offering the medication, the intervention around this time so that this medication is able to pull this green line above this red line and cure it for good so that again, the patient is not going to have seizures and have better quality of life.

So what are the interventions? What are the things that we can do? So statins, these are your atorvastatin, rosuvastatin, the cholesterol medication. So there are some data from a systematic review, meta-analysis that this medication actually helps with preventing post-stroke seizures. This hasn't been tested in clinical trials, but this is a typical medication which we give to our stroke patients regardless to control their LDL, the cholesterol.

So there are some data that suggest that this may work, whether the existing anti-seizure medications that we use in this patient population will work, we really don't know. We know that inflammation after the stroke can contribute to epileptogenesis. Which ones? We don't know. In the stroke world, we have tested several neuroprotective agents. The trials were mostly negative almost. We don't have any neuroprotective agent in the stroke world that is associated with improved outcomes in the stroke population.

But could there be one that would have an effect in preventing epileptogenesis? We still don't know. So VNS is vagal nerve stimulation. TMS is transcranial magnetic stimulation, and then there may be interventions which are not invented yet. So there are potential things that can be tested, but we don't really know whether they will work in the patient population. We need to test that in a clinical trial setting.

And as we go from top to bottom, as you can see the trial, the research study will become complex and it will also contribute to increasing cost. As you can see when we say that, say for example, I usually cite a number like seven to 10% patients having post-stroke epilepsy. So say there is a 5% risk in control and we

offer a drug and then to an active one, the patients with post-stroke epilepsy and then placebo, and then follow these patients for almost five years, we'll be needing like 2,500 patients, which is a huge number and that will make the trial very, very expensive.

So what we need, we need a way to determine early on after the brain injury, after the stroke, which patient is more likely to develop seizures. And how do we do that? So there has been some work done in the field, but let me first show you the cost. So cost of enrolling about 502 patients is this number, 35 what million? And that's really guided by the risk reduction. So if the 50% risk reduction... Essentially these numbers suggest that if the risk of epilepsy is higher in the population in which we are investigating doing the trial, if it's higher, then we are able to reduce the cost.

So how do we select a patient population with higher risks of having post-stroke epilepsy? If you're able to do that, we'll be able to reduce the cost and that means that we will end up needing some scoring systems or selecting patients based on their ED features or the biomarkers that will guide us which patients are more likely to have seizures after seven days.

So there are some data that are already available. For instance, person with larger stroke, bleeding in the brain, disruption in their blood brain barrier. Again, like iron deposition in the brain, these patients are more likely to have post-stroke epilepsy.

There are certain EEG features, the brain wave test, which can guide us which patients are more likely to have seizures after seven days. And these approaches can then help us better select the patient population at risk of post-stroke epilepsy.

So if we select any stroke patient in a trial, we need almost 2,500 patients. But if we use an existing scoring system, for example, one that we know has been published a few years ago, in which person with greater severity of stroke with this particular feature on their brain vessel imaging, the person who had an early seizure, seizure within the seven days, person with specific part of the brain, which we call cortices or cortical involvement and particular brain vessel stroke.

If we add up these points as we can see the person who had early seizure, he gets the highest point. So we are able to select based on this scoring system, the patients who are more likely to have seizures. And if we were to select a number seven, the individuals who had this particular score more than seven, we are able to enrich patient population in a study such that we need only 300 patients. So we need some reliable methodology to select patients who are more likely to have seizures so that we can control reduce the cost of a future trial.

So with that, I will stop. I thank you all for joining today and I'm happy to tackle any questions.

Laura Lubbers: Thank you so much, Dr. Mishra. That was very informative. We really appreciate all the information you've shared. So now we can open up the webinar to Q&A portion of this time. Just a reminder, if you have questions, you can put them into the Q&A tab, click send and we can read them off and get them addressed. And while we wait for questions to come in, you made a really important point about the challenges of doing clinical trials in this population. And even though stroke is quite prevalent and therefore there are more people who are likely to develop epilepsy, there are still challenges in terms of developing those clinical trials and the number of people you have to enroll.

So you shared at the very end about how if we select the right patient population based on some scores, we might be able to enrich those trials. How is this community thinking about that biomarker selection? Are you considering algorithms to help figure out what are the right markers to track? How are you approaching this? I think it's an important question. I know that there is some folks interested in post-traumatic epilepsy that are on the call and they might be interested in your perspective from the stroke community.

Dr. Mishra: So for now, there are two scoring system. One is the select score, which is for ischemic stroke that I just showed in one of the slides. From the hemorrhagic stroke standpoint, there's a scoring system called CAVE score. These scoring systems include clinical variables only. There have been some studies in which our colleagues have previously looked at the biomarkers in the blood. Unfortunately, no biomarker has been proven to be valid because those studies haven't been really conducted for discovery and then validation of the biomarkers.

So one approach could be that we select patients with post-stroke epilepsy and the controls follow them up over time and collect their blood sample genetics material, which again can come from the blood itself and do a comparison of the features which are very unique to the patient population with post-stroke epilepsy. For instance, one can apply a proteomics approach wherein one can look at the trajectory of proteins which are uniquely expressed in this patient population.

One can look at the genetic variables, can conduct some studies using GWAS or something like that to determine which patient population is more likely to have post-stroke epilepsy risk. This really requires a concerted effort, colleagues from different parts of the world with their unique expertise and we need to be able to collect enough samples to build a reliable valid prediction model and integrate the biomarkers from the serum. And then there are certain features on the EEG that may also contribute to better selection.

We are living in the days when we are able to analyze multi-dimensional data. Artificial intelligence is something that is really influencing our lives on the day-

to-day basis, which wasn't the case several years ago when our senior colleagues were trying to investigate this topic. So we are really at a time period in our history when we have resources and analytical skills that can help really tackle some of these questions. So it hasn't been answered yet. That's a topic for investigations and we really need to work on that.

Laura Lubbers: Great. It's a hot topic. I know for many different epilepsies, again, traumatic epilepsy as a result of traumatic brain injury. This is a hot topic I think across many different epilepsy sub-fields. It's quite a topic and we're figuring out how do we address that. So for people who have had a stroke and they're concerned about what the consequences of that could be, how would you recommend having a discussion with the doctor?

Because often you're seen by a stroke doctor and then you move on to somebody else. So who's the right person to bring these concerns to, and how does somebody who's had a stroke have this conversation? What are your recommendations?

Dr. Mishra: I think this is a very important question and I think so commonly when patients develop stroke and they come to our clinics, we typically deal with the medications. We talk about aspirin, Plavix, or the need for anti-coagulation test to look for a presence of atrial fibrillation, more of these kind of questions. We don't typically discuss mood, cognition, fatigue, post-stroke epilepsy, which I think are also important topics that we as stroke physicians should be tackling, discussing to offer a comprehensive care to our stroke population.

Same goes to, in terms of questions around driving, for instance. We want to know which patient population is at a higher risk of having a post-stroke epilepsy and are they able to or should we let them drive or not? So there are many questions that linger in the mind of patients and through the effort like this, thanks to your organization, we need to really promote this topic so that our clinic follow-ups from the stroke standpoint are really more comprehensive wherein we are tackling not only the medicine aspect but also cognitive post-stroke epilepsy.

I think stroke doctors are the right doctors who should be tackling it early on. Obviously, we send patients for rehab and our MDs with physical medicine and rehabilitation training experience, another set of colleagues who should be able to guide this patient population. Epileptologist as well. I'm really delighted to see a lot of discussion on cardiovascular disease management in the epilepsy conferences these days. So I think even though our specialties are different, our mission is same, which is to promote outcomes in our patient population. So we should feel comfortable tackling these questions.

Laura Lubbers: Great points. And I love that you mentioned comprehensive care. It's something that some groups in our epilepsy community are familiar with and then others are not, and we really need to seek to get holistic care for those who are at risk of epilepsy or struggling with epilepsy. So we have a good question here. This is

coming from somebody who is an occupational therapist and a parent of a child with nocturnal epilepsy has witnessed the degree of disability across the lifespan. Would you consider the genesis of epilepsy as a type of TBI.

I think this person thinks that this could be off-topic, but I think it's a really important piece too, this concept of epileptic genesis and brain injury, and perhaps you can talk a little bit about maybe how neuroinflammation plays a role in these epilepsies. Yeah, let's start there.

Dr. Mishra: Thanks for asking this question and my sympathies for what this particular individual is going through, particularly in the pediatric age group. From the stroke standpoint, after a stroke, there are some animal data, some research from various colleagues that suggest that there is activation of the inflammatory pathways. There is a damage to blood brain barrier. There are certain molecules like TGF beta which seep into this blood-brain barrier, disrupted regions, accumulation of albumin.

There are some biological mechanisms which have been talked about and linked to the occurrence of post-stroke epileptogenesis. One would imagine that because inflammation is the cause and if we use anti-inflammatory agents, we should be able to prevent post-stroke epilepsy. It's very simplistic, however, because as we know the inflammation is on the one hand it's useful because it helps repair the bodies once it's undergoing the effect of the injury.

On the other hand, if it persists long enough can be detrimental. And where exactly is the right balance? We don't know. Unfortunately, we don't have targeted therapies for this. There are some studies which... For instance, there is a study in which people have... There's this one person investigator who has looked at the newer and anticoagulant dabigatran inhibiting some of these pathways and is associated with reducing the risk of epileptogenesis in the animal models.

Dabigatran is an anticoagulant. There is a possible way to remove the anticoagulant effect of these molecules and retain the potential anti-epileptogenic, anti-inflammatory pathways. But the research of that kind needs to first go through the animals, needs to be validated. It has to go through phase one, phase two studies, and then eventually. There is also some talk on the topic that there are already some anti-inflammatory agents, which we are used to using and may potentially be repurposed.

But those medications are for really other inflammatory diseases to safely offer them to a patient population which is suffering from other cardiovascular risk factors. We really need to do a thorough thinking and test them in a safe way in clinical trials before anything like that would be available for patients. There is one colleague who is looking at the fact of Losartan, which is an antihypertensive agent. And based on some animal model studies, it may have some effect in saving the blood-brain barrier from getting worse or securing the blood-brain barrier.

We use Losartan for blood pressure management anyways, but it again hasn't been tested in the clinical trials. Same would go with the statins, the medications like atorvastatin about which I showed you in one of the slides, that there is a systematic review and meta-analysis which suggested that it's associated with reduced risk of post-stroke epilepsy that again needs to be tested in clinical trials.

We know that the statins have a pleiotropic effect, which means that in addition to reducing the levels of the cholesterol in the blood, it also keeps the blood vessels healthy and reduces the inflammation there. So in short, it seems like there is a need for more investigation from understanding the inflammatory pathways, which again requires more collaborative global effort.

Laura Lubbers: Great point. It feels like this is still very much in the forefront, in the very cutting edge trying to move this research forward and how critical more work is to understand this. And in that light, can you talk about the group that you have convened and what you hope to achieve in the next few years?

Dr. Mishra: So the need for the consortium came from the realization that on the one hand I showed you in one slide that the risk of having post-stroke epilepsy is very high in the older population, age above 60. We also know that stroke is a global problem. A large number of patient population have stroke, but the estimates for post-stroke epilepsy is around 10%, eight to 10% depending on which study we look at. So no single center would be able to accumulate significantly large number of patient population to allow meaningful analysis of their data to reach conclusions.

So for instance, the select score, the study that I showed those colleagues, they accumulated collected data from multiple centers in Switzerland and few other countries in Europe. So our goal with this consortium is to bring in colleagues with range of different expertise in stroke epilepsy, animal model, data mining and first highlight the important questions, show that this question is important and also write collaborative grants so that we are able to, number one, detect the meaningful biomarkers, which can be used for clinical trial design and also discuss the design issues potentially also start running some clinical trials using some drugs which appear to have some signal of anti-epileptogenesis for instance, my colleague and co-convener, Patrick Kwan, who's an epileptologist in Monash, Australia leading figure in the field.

He and his colleagues are doing an investigation looking at Perampanel. Perampanel is a medication for a seizure management. They're doing a pilot study. And there is another colleague, senior colleague, Dr. Matthias Koepp. He's testing one anti-seizure medication. But we need to really come together so that we are able to design trials, which really serve the purpose because we would not want our effort to go waste doing running trials, which are poorly designed. One more mission that I have, and I would like the support of everyone here is what is it about this condition that makes most sense to our patient population? Why is it so important? Right?

Dr. Mishra doing a research on a topic that is not meaningful to patient population, does no service to the field. So we are interested. We are creating writing surveys, which soon we will be spreading across in different countries, trying to understand what is it that's meaningful in terms of patient reported outcomes to the patient, their caregivers, family members. So these are the kind of question which we need to tackle and create a framework so that we can have larger future studies which are more meaningful and really advance the field.

Laura Lubbers: I'm so glad you mentioned that having the voice of the patient involved is critical and it's one of the tenets of CURE Epilepsy is to make sure that that lived experience voice is a part of the research process. So I'm so glad that are wrapping your arms around that. And of course we'd be happy to help spread the word about surveys and really understanding what do patients need, what are their greatest concerns, and how can the research address those. Thank you so much.

Dr. Mishra: Thank you.

Laura Lubbers: Seems like there's probably no other questions, but this has been an incredibly informative dialogue and presentation. Thank you so much for making the time to start to spread even greater awareness of this issue. And again, the older population is a group that we really haven't talked much about, so I think it's really, it's been great to have you here to share more about that. I also want to thank our audience for participating. As always, we always enjoy having you and seeing familiar names in our list of participants. So thank you for joining us. The researchers who are on the call as well to learn more about this.

If you have any additional questions about the topic or wish to learn about any of CURE Epilepsy's research programs or other webinars, please visit our website or emails at research@cureepilepsy.org. Also, stay tuned for the announcement of our May webinar, which will focus on childhood epilepsy syndromes such as childhood absence epilepsy and juvenile myoclonic epilepsy, and the potential genetic causes of these forms of epilepsy based on the largest international genetic research study to date.

So look for more details in our CURE Epilepsy emails and our social communications. Thank you all. Thank you again, Dr. Mishra and everyone, please have a great day.