

Partners Against Mortality in Epilepsy
Conference
Minneapolis, Minnesota
June 19–22, 2014.

A Plain Language
Conference Summary



For additional details and to view archived versions of the sessions presented at the PAME 2014 conference please visit <http://pame.aesnet.org/>

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For a more detailed summary of the sessions, including references to journal articles, or to view the PowerPoint slides of each presentation, visit <http://pame.aesnet.org>.

NOTE ABOUT THE GLOSSARY OF TERMS: This document includes a number of complex medical terms. Many of these terms are included in a Glossary of Terms at the end of this document. Each glossary term is defined within the document the first time it is used this document. In addition, each glossary term is bolded and underlined the first time it is used in any of the document sections.

Introduction

By Jeffrey Buchhalter MD, PhD and Gardiner Lapham RN, MPH

The second Partners Against Mortality in Epilepsy conference took place in Minneapolis, Minnesota, on June 19–22, 2014. Presenters summarized the latest research on death in people with epilepsy, especially sudden unexpected death in epilepsy (SUDEP). **SUDEP** is a death that is sudden and unexpected and that isn't due to an injury, drowning, or another known cause. The audience included people who had lost a loved one to SUDEP, those living with epilepsy, families of people with epilepsy, doctors, nurses, basic and clinical scientists, and representatives of advocacy and research organizations.

In addition to the topics presented at the first Partners Against Mortality in Epilepsy in 2012, the 2014 meeting focused on major causes of death in people with epilepsy other than SUDEP, grief related to epilepsy, how often SUDEP happens, and guidelines for health-care providers. Speakers included some of the most prominent scientists in the field.

The conference included several plenary sessions designed to be easily understood by attendees with different levels of scientific knowledge and experiences with epilepsy. Attendees also joined small discussion groups offering in-depth reviews of certain scientific topics.

This conference was made possible by the hard work of many partner organizations and agencies, including the American Epilepsy Society, Epilepsy Foundation, Citizens United for Research in Epilepsy (CURE), Finding a Cure for Epilepsy and Seizures, Danny Did Foundation, and National Institute of Neurological Disorders and Stroke. Ms. Cyndi Wright (SUDEP Institute of the Epilepsy Foundation) and Mr. Jeffrey Melin (American Epilepsy Society) coordinated the conference. The organizers wish to thank all of the speakers and moderators who so graciously gave their time and knowledge to make the conference successful and meaningful.

A list of sponsors and the PowerPoint slides presented at the conference are available at <http://pame.aesnet.org>.

Overview of Death in Epilepsy

Moderator: David J. Thurman, MD, MPH

Overview: Premature Deaths Due to Epilepsy

People with epilepsy are two to three times more likely to die prematurely than people without the disease. But the risk that a specific person with epilepsy will die at a young age depends on several issues, including the cause of the epilepsy and types of seizures.

Some premature deaths might be due to other disorders of the brain and nervous system, like strokes and brain tumors, that also cause the epilepsy. But epilepsy is directly responsible for many early deaths.

For example, some people with epilepsy who are otherwise healthy die of **SUDEP**. Epilepsy is also responsible for premature death in some people with **status epilepticus**, a seizure that lasts at least 30 minutes. Other people with epilepsy die from accidents and drowning.

Experts don't know for sure how many people die prematurely of epilepsy each year. But according to a study by medical examiners (physicians who figure out causes of death), about 1 in 1,000 people with epilepsy die of SUDEP each year. This rate comes out to about 2,800 deaths from SUDEP in the United States per year.

The risk of dying from SUDEP is lowest among young children and rises with age through early middle age. Having **generalized tonic-clonic seizures**, previously called grand mal or convulsive seizures, also increases the chance of dying from SUDEP. These seizures, which often last a couple of minutes, frequently begin with a sudden fall and rigid muscles, followed by jerky movements and shallow breaths.

Estimates of death rates due to status epilepticus vary, but according to one calculation, about 1 of every 4,000 people with epilepsy die of status epilepticus. So fatal status epilepticus is much less common than SUDEP.

Causes of Epilepsy That Also May Cause Death

Presented by Roland D. Thijs, MD, PhD

Some diseases that cause epilepsy can also cause death. For example, brain tumors, strokes, central nervous system infections, and some inherited disorders can cause both epilepsy and death in people with epilepsy. People whose epilepsy is related to one of these causes have a much higher risk of early death, especially in the first few years after diagnosis.

Estimates of how common these deaths occur vary a lot. But studies consistently show that the risk of death is highest in the first year after an epilepsy diagnosis. Most deaths that happen in the first two years after diagnosis are probably due to these underlying causes of epilepsy. However, people with a recent diagnosis of idiopathic epilepsy (meaning that the disease's cause isn't known) don't have a high risk of early death.

The age of a person with epilepsy affects the risk of premature death. Younger people with epilepsy have a higher risk of early death than people of the same age who don't have epilepsy. Older adults with epilepsy aren't much more likely to die prematurely than older people without the disease. This is probably because older people in general have a higher risk of dying than younger people.

Risk of Injury and Death from Accidents in People with Epilepsy

Presented by W. Allen Hauser, MD

One reason why death rates are higher in people with epilepsy than those without the disease is the higher rate of accidental injuries due to seizures. Most of these injuries are minor. But seizures can cause serious injuries, including broken bones, traumatic brain injury, drowning, and burns.

Several studies in the United States, Sweden, and Iceland show that the risk of dying from injury is about two to six times higher in people with epilepsy than those without it. But other studies have found that the risk of death from injury isn't higher in people with epilepsy.

Only a few studies have evaluated causes of accidental death in people with epilepsy. More research is needed on traffic injuries. These studies need to figure out which injured people are drivers, passengers, or nearby pedestrians.

People with epilepsy often get accidentally burned. If these people live in a developed country, they aren't likely to die of an accidental burn. But this is not true in underdeveloped countries, where up to one-fifth of all deaths in people with epilepsy are due to burns.

Several studies have shown that people with epilepsy are more likely to die of drowning. They also have a higher risk of traumatic brain injury as a result of falls, which are often triggered by seizures. Little information is available on the size of this risk.

New Definition of Sudden Unexpected Death in SUDEP

Presented by Dale C. Hesdorffer, PhD

Measuring the rates and risk of early death in people with epilepsy requires careful explanation of the causes of these deaths. This is especially true of **SUDEP**.

In 1997, two experts, Lina Nashef and Fred Annegers, each developed a SUDEP definition. These two definitions had a few differences. Nashef and other researchers recently published a single definition that combines elements from the 1997 Nashef and Annegers definitions.

Some components of the new definition include:

- The definition of SUDEP uses the term “unexpected” instead of “unexplained.”
- In SUDEP, the death occurs within 1 hour from the start of an epileptic seizure that caused the person's death.
- A deadly seizure that lasts 30 minutes or more is **status epilepticus**, not SUDEP.

The definition classifies SUDEP cases based on factors that might have played a role in the death:

- Possible SUDEP: Another cause might have played a role in the death; includes deaths in water when there is no evidence that the person was under the water.
- SUDEP plus: The person had a preexisting condition that might have contributed to his or her death and the death otherwise fits the SUDEP definition.
- Near-SUDEP: With resuscitation, the person was revived after cardiac arrest and survived for more than an hour.

Causes of Sudden Unexpected Death in Epilepsy Related to Breathing

Moderators: George B. Richerson MD, PhD & Lisa M. Bateman, MD, FRCPC

This session summarized research on the effects of seizures on breathing control in people and laboratory animals. The presenters described similarities between the causes of breathing problems in **SUDEP** and sudden infant death syndrome (SIDS). SIDS is the sudden and unexpected death of an otherwise healthy baby. The session also offered data on defects in cells and genes that could increase SUDEP risk. These data might help explain why seizures often lead to breathing problems. The data could also help scientists develop new strategies to reduce SUDEP risk.

Biological Processes Involved in Breathing During Seizures

Presented by: Lisa M. Bateman, MD, FRCPC

People with **SUDEP** or **near-SUDEP** often have breathing problems. Experts suspect that many factors are responsible for breathing problems during seizures.

Neurons (nerve cells) in the brainstem help control breathing. The brainstem is a part of the brain that controls blood pressure, heartbeat, and other basic functions in addition to breathing. Neurons the brain cortex can also influence breathing. The cortex controls certain higher-order functions, such as thought and deliberate action.

Oxygen levels are often low in the blood during seizures. About 1 in 3 focal seizures (which start in one region of the brain) lead to breathing problems during seizures. The breathing problems typically start about a minute after the seizure begins and last, on average, more than a minute.

People with breathing problems often have too much carbon dioxide gas in the blood. Low oxygen and high carbon dioxide levels interfere with heart and brain function, so they may play a role in SUDEP.

Sudden Unexpected Death in Epilepsy, Sudden Infant Death Syndrome, and Serotonin

Presented by George B. Richerson, MD, PhD

Studies in laboratory animals are evaluating treatments that target the 5-HT receptor of serotonin, a brain chemical that controls sleep, wakefulness, and breathing.

Specially bred mice with defects in the serotonin system often have breathing problems due to seizures and a high risk of **SUDEP**.

Treatment with a drug that blocks the absorption of serotonin in the brain reduces the risk that breathing will stop after a seizure in some laboratory mice. In people with epilepsy, this type of drug lowers the severity of oxygen decreases in blood during and after seizures.

The link between deaths due to seizures and serotonin systems that don't work properly in mice shows that SUDEP might have some of the same causes as **SIDS**. Both SUDEP and SIDS are more likely to happen while the person is lying down. And both conditions might be due to defects in breathing, wakefulness of the brain, and/or heart mechanisms.

Breathing Rhythm Control and Long QT Genes

Presented by Daniel Mulkey, PhD

Long QT syndrome (LQTS) is a rare disorder of the heart's rhythm. People with LQTS may have abnormal electrical activity in the **brainstem** (part of the brain that controls breathing, blood pressure, heartbeat, and other basic functions). They also have a high risk of sudden death due to irregular heart rhythm.

Experts have linked some genes that cause LQTS to epilepsy and **SUDEP**. SUDEP in patients with LQTS gene mutations is probably due to abnormal heart rhythms caused by seizures. A gene mutation is a permanent change to a person's DNA sequence that makes up a gene, making this gene sequence different from what is found in most people.

Serotonin, a brain chemical that controls sleep, wakefulness and breathing, provides instructions for making channels that transport potassium and sodium in and out of cells. By changing the activity of certain brain cells through receptors that act on these channels, serotonin affects breathing. Mutations in the genes that control these channels might increase the risk that a person will stop breathing during a seizure in the brainstem.

Figuring out what makes the network that controls breathing stable or unstable and how serotonin affects this network may lead to new drugs that can prevent SUDEP.

Adenosine, a Brain Chemical, in the Brainstem

Presented by Detlev Boison, PhD

Adenosine is a chemical substance that helps control the activity of certain **neurons**. These neurons transmit information throughout the body to control breathing, sleep, and wakefulness.

During a seizure, adenosine levels rise and the kidneys lose their ability to clear adenosine from the blood. The adenosine surge lowers neuron activity and can stop a seizure. But high amounts of adenosine also cause breathing problems. This combination might trigger **SUDEP**.

If SUDEP is due to high levels of adenosine, then chemicals that block adenosine receptors (proteins that transmit signals from adenosine), such as caffeine, should prevent SUDEP. When laboratory mice have seizures and are treated with a drug that blocks adenosine clearance from

the body, the mice stop breathing and die. But just one injection of caffeine as soon as the seizure starts prevents these effects. Caffeine blocks the activity of adenosine receptors (proteins that transmit signals from adenosine) in mice.

Genetically engineered mice that can't clear adenosine out of their bodies die of seizures, whereas their normal littermates don't. So low clearance of adenosine from the blood might help cause SUDEP.

Description of Laboratory Mice that Stop Breathing During Seizures

Presented by: Hua-Jun Feng, PhD

A laboratory breed of mouse, the DBA/1 mouse, develops **SUDEP**. These mice have seizures in response to certain sounds. During these seizures, they stop breathing and die.

One cause of breathing problems in DBA/1 mice seems to be too little transmission of nerve signals from **serotonin**.

Researchers created a breed of DBA/1 mice, DBA/1 TPH2-ChR2 mice, to understand the causes of breathing problems during seizures. The researchers used a new technology, optogenetics, which combines genetics and optics to control certain activities in tissue. These experiments showed that the DBA/1 TPH2-ChR2 mice have similar seizures and similar breathing problems to regular DBA/1 mice.

Monitoring Causes of Death in Epilepsy and Guidelines for Health-Care Providers

Moderator: Orrin Devinsky, MD

Presented by: Lindsey Thomas MD, Vicky Whittemore PhD, Cynthia Harden MD, Cyndi Wright, BS

Of the 1,891 people with epilepsy who died in Sweden in 2008, 163 (about 9%) died of causes that seem to be related to their epilepsy. **SUDEP** was the cause in 65 deaths (40%).

Medical examiners and coroners establish the cause and manner of death in patients with epilepsy. To do this, they rule out other potential causes of death (such as a drug overdose or heart disease). Medical examiners listed epilepsy as the main cause of death on the death certificates of just 15 (23%) patients who died of SUDEP in Sweden in 2008. They mentioned epilepsy in the death certificates of 49 people (75%) who died of SUDEP and 285 people (15%) who died of epilepsy.

Efforts are underway in the United States and Canada to improve SUDEP monitoring and the collection of biological samples from patients with SUDEP. These efforts include:

- **The North American SUDEP Registry:** Stores data and tissue specimens from patients who die of any epilepsy-related cause. The registry identifies causes of death based on brain specimens, when possible, and on information from imaging, genetics, and witness reports. The registry encourages all families affected by SUDEP to participate.

- The Sudden Death in the Young Registry: Collects information on rates of sudden death in young people from epilepsy, heart disease, and other causes. The registry also establishes causes of death and risk factors for sudden death in young people.

SUDEP is rare—it accounts for about 3,200 deaths each year in the United States and Canada. So it's impossible to get enough data from a single center.

To keep track of SUDEP, some states are educating medical examiners and coroners about SUDEP. Other states require state medical examiners to monitor and report cases of SUDEP. In addition, the SUDEP Institute is working with partners to improve SUDEP monitoring by increasing awareness of SUDEP and developing death investigator training programs.

The American Academy of Neurology is developing guidelines on SUDEP. Some moderately strong evidence is available on many aspects of SUDEP.

Causes of Sudden Unexpected Death in Epilepsy Related to Sleep and Wakefulness

Moderators: Gordon F. Buchanan, MD, PhD and Hal Blumenfeld, MD, PhD

A lot of the research on causes of **SUDEP** focuses on breathing and heart function. But lower levels of awareness (physical and mental alertness) and wakefulness play a role in many types of seizures, especially **generalized tonic-clonic seizures**.

Scientists are recognizing that awareness and wakefulness might play a role in SUDEP. They are also realizing that SUDEP is much more common during sleep and, possibly, during certain stages of sleep.

The Biology of Shutdown and Wakefulness Systems During Seizures

Presented by Hal Blumenfeld, MD, PhD

Seizures affect the brain's **cortex** and **brainstem**, and these effects last a long time. The cortex controls certain higher-order functions, such as thought and deliberate action. The brainstem controls breathing, blood pressure, heartbeat, and other basic functions. Dr. Blumenfeld's team developed an experimental breed of laboratory rats to study the long-term effects of seizures on the cortex, brain systems that control wakefulness, and brain systems that control breathing.

This research could help explain why low levels of wakefulness and breathing problems that lead to **SUDEP** involve disruptions in the serotonin system.

Processes of Brainstem Invasion Based on Studies in People and Laboratory Mice

Presented by Brian Dlouhy, MD

Researchers recorded the electrical activity of the brains of people with epilepsy at the beginning of a study. The researchers then stimulated participants' amygdalas. The amygdala is the part of the brain that controls emotions and motivations.

One participant developed breathing problems and a lower supply of oxygen to the blood during a seizure that spread into the patient's amygdala. But stimulation outside the forebrain, which contains the amygdala, did not cause breathing problems or reduce oxygen levels in this patient's brain.

This research sheds light on the amygdala and the brain regions that control breathing and breathing problems caused by seizures. Similar processes might control sleep and wakefulness after a seizure.

Serotonin, Breathing after Seizures, Wakefulness, and Sleep

Presented by Gordon F. Buchanan, MD, PhD

Levels of **serotonin** drop after a seizure. When people don't breathe properly, they can't breathe in oxygen and breathe out carbon dioxide, so the oxygen levels in their blood go down and their carbon dioxide levels go up. Normally, these changes tell the brain to start breathing again and increase wakefulness.

How much trouble a person has breathing after a seizure might depend on whether they were asleep or awake during the seizure. In addition, right after a seizure, people don't have the normal breathing and wakefulness responses to high carbon dioxide levels. These abnormal responses are related to serotonin levels.

Understanding how a person's sleep stage and nighttime seizures might increase the likelihood of **SUDEP** could lead to strategies to prevent SUDEP.

Role of Adenosine in Sleep and Cessation of Breathing after Seizures

Presented by Carl Faingold, PhD

Researchers are using two experimental breeds of laboratory mice, DBA/1 and DBA/2 mice, to understand how seizures stop people from breathing and the role of breathing in **SUDEP**. The studies showed the importance of the **serotonin** system in stopping breathing during seizures.

The team is also using DBA mice to study the link between another brain chemical, **adenosine**, to breathing and wakefulness in causing SUDEP. Adenosine, like serotonin, helps control breathing, sleep, and wakefulness. Adenosine also affects a person's ability to control seizures, so it's likely to play a role in SUDEP.

Giving adenosine or blocking the breakdown of adenosine seems to increase the proportion of animals that stop breathing as a result of a seizure. Blocking adenosine receptors (proteins that transmit signals from adenosine) with drugs, like caffeine, reduces the proportion of mice that stop breathing after a seizure.

These studies could help scientists find ways to prevent SUDEP.

Abstract Presentation Winner-Association Between Lying Down and Sudden Unexpected Death in Epilepsy

Presented by James Tao, MD, PhD

Dr. Tao statistically analyzed data from studies to find out whether **SUDEP** is more common at night because of the person's position during sleep. Lying down increases the likelihood that the nose and mouth will be blocked. If this happens during a seizure, the person cannot breathe. Blockage of airflow while a person is lying down is also one of the main causes of **SIDS**.

Deaths in Epilepsy Not Due to Sudden Unexpected Death in Epilepsy

Moderator: Dale C. Hesdorffer, PhD

Epilepsy-related causes of death other than **SUDEP** affect many people. These causes of these deaths include:

- **Status epilepticus**
- Acutely provoked seizure (resulting from an injury to the central nervous system)
- Suicide
- Heart disease caused by epilepsy drugs
- Not taking epilepsy drugs as instructed

These deaths are often unexpected, but some might be preventable.

Status Epilepticus and Acute Symptomatic Seizures

Presented by Dale C. Hesdorffer, PhD

A person's first episode of **status epilepticus** is deadly in 24% of cases. These deaths are six times more common in people with acute symptomatic seizures than people with other types of seizures. An acute symptomatic seizure is a result ("symptom") of a brain injury, such as a stroke or trauma.

The risk of dying from status epilepticus is highest in people with a traumatic brain injury or with alcohol or drug withdrawal. People are most likely to die in the first 30 days after an acute symptomatic seizure if the seizure was due to diseases affecting blood flow in the brain or a brain injury. People whose status epilepticus is due to an unknown cause rarely die during the first 30 days. The risk of death is 14 times higher when status epilepticus is due to brain damage caused by lack of oxygen than other causes.

Older people are about twice as likely to die of status epilepticus than younger people. After the first 30 days, death rates are highest in people with diseases that tend to get worse over time (such as Alzheimer's disease).

Frequency and Risk Factors for Suicide in Epilepsy

Presented by Nathalie Jette, MD

People with epilepsy are about three times more likely to commit suicide than other people. The reasons (risk factors) include lifelong brain abnormalities, mental illness, use of certain drugs, developing epilepsy before age 18, and alcoholism.

In a large study in Denmark, people with mental illness and epilepsy were almost 14 times more likely to commit suicide than those with epilepsy, but not mental illness. People with epilepsy were more likely to commit suicide if they had a mood disorder (such as anxiety or depression) or misused alcohol than people with other mental illnesses. But people who don't have epilepsy are most likely to commit suicide if they have a mood disorder or schizophrenia.

In a study of 1,877 Finnish people who committed suicide, those with epilepsy tended to be female, usually did not have an alcohol-related disorder, and often had a mental illness, especially depression.

The risk of suicide-related behavior is higher in the 2 months before epilepsy drugs are first prescribed. The risk drops after the person starts taking the medicine. So the drugs may help make people's moods more stable.

Health-care providers who have patients with epilepsy need to identify their mental illnesses, know what might raise the risk of suicide in people with epilepsy, and work with psychiatrists to reduce suicide risk in these patients.

Heart Disease, Epilepsy, and Antiepileptic Drugs

Presented by Scott Mintzer, MD

People with epilepsy are more likely than other people to die of a heart condition, such as a heart attack, heart disease, or stroke.

The body processes certain epilepsy drugs using P450 enzymes. Drugs that increase P450 enzyme activity, such as carbamazepine, seem to affect the formation of cholesterol. So these drugs might have long-term effects on heart health.

Cholesterol levels are higher in people treated with carbamazepine than people who get no treatment or are treated with other types of epilepsy drugs. In one study, patients were treated with a drug that increased P450 activity and then a drug that didn't have this effect. Six weeks later, levels of cholesterol, triglycerides (fatty acids), and other substances dropped. People with heart disease often have high levels of these substances. In another study, the risk of a heart condition and death due to a heart condition was lower in patients treated with valproate (which lowers P450 activity) than in those on carbamazepine.

These studies suggest that epilepsy drugs that increase P450 activity may raise the risk of a heart attack or other heart condition. Health-care providers should screen patients taking drugs that increase P450 activity for risk of heart disease.

Failure to Take Epilepsy Drugs Correctly and Risk of Death in Epilepsy

Presented by Daniel Friedman, MD

Many people with epilepsy don't take their prescription antiepileptic drugs (AEDs) as instructed by their doctor. In one study, only half of patients with epilepsy took at least 80% of their prescribed AEDs as instructed over a year.

People who don't take their AEDs correctly (known as non-adherence) are more likely to be admitted to a hospital or visit an emergency room for problems related to seizures. They are also more likely to have accidents and injuries. Most importantly, people who don't take their AEDs correctly are three times more likely to die than those who take their drugs as instructed.

Records from medical examiners' and coroners' offices show that people with **SUDEP** often have no AEDs or low levels of these drugs in their bodies. Some other studies have had similar results, but other research has not found any difference in AED levels in people with epilepsy who did or did not die of SUDEP.

Poor adherence could be due to memory problems, lack of health insurance, AED side effects, and mental illnesses. So it's not clear if patient adherence to AEDs could be improved. Another important research question is whether improving AED adherence would lower the risk of SUDEP and other causes of death in people with epilepsy.

Causes of Sudden Unexpected Death in Epilepsy Related to the Autonomic Nervous System and Heart Function

Moderators – Jeffrey W. Britton, MD and Jeffrey Noebels, MD, PhD

People with epilepsy that isn't successfully controlled with medicine sometimes have long-lasting changes in the control of the heart by the autonomic nervous system. This autonomic nervous system controls basic body functions, such as breathing and digestion, without conscious effort. Poor control of heart function by the autonomic nervous system due to seizures might lead to SUDEP.

The influence of epilepsy on heart function is an example of a phenomenon known as the "heart-brain connection." Heart disease has many of the same risk factors as brain diseases, such as stroke and dementia. The heart and brain might also share certain biological features. For example, genetic disorders in proteins known as ion channels can affect both the heart and central nervous system. Ion channel disorders might lead to the increased activity in the brain and heart that could cause **SUDEP**.

This session focused on the control of heart function by the autonomic nervous system and its relationship to epilepsy.

Structure and Functions of Heart Control by the Central Autonomic Nervous System

Presented by Jeffrey W. Britton, MD

For centuries, scientists have known that seizures disturb the control of heart function by the **autonomic nervous system**. This system controls basic body functions, such as breathing and digestion, without conscious effort.

By stimulating the **cortex** in brains of people and laboratory animals, scientists have studied the roles that different parts of the cortex have in controlling heart function by the autonomic nervous system.

Parts of the **brainstem** play a role in the control of heart function by the autonomic nervous system. These brainstem parts are involved in the sympathetic nervous system and the parasympathetic nervous system. Both of these systems are part of the autonomic nervous system. The sympathetic nervous system prepares the body for action by increasing blood pressure and heart rate and slowing down digestion. The parasympathetic nervous system saves energy by slowing down the heart rate, relaxing muscles, and promoting digestion.

Seizures can affect the control of heart function by the sympathetic and parasympathetic nervous systems. For example, during a seizure, electrical activity in the heart is abnormal. This abnormal activity in the heart could trigger **SUDEP**

Studies of Dravet Syndrome in Stem Cells from Patients and Genetically Engineered Mice

Presented by Lori L. Isom, PhD

Dravet syndrome is a rare brain disorder caused by genetic mutations. People with Dravet syndrome usually start having seizures as babies, and these seizures can last a long time or happen over and over.

Studies in specimens from the brains of patients with Dravet syndrome who had mutations in the *SCN1A* gene showed that their stem cells had abnormal electrical activity. Genetically engineered mice with the *SCN1A* gene mutation associated with Dravet syndrome have irregular heart rhythms and abnormal electrical activity in the brain.

These findings suggest that people with Dravet syndrome have more electrical activity in both brain cells and the heart. This activity could explain their high risk of **SUDEP**

Mutations in Sodium Channel Genes, Stoppage of Heartbeat, and Deadly Seizures in Laboratory Mice with Dravet Syndrome

Presented by Franck Kalume, PhD

The genetically engineered Nav 1.1 channel knock-out mice have a gene mutation that is common in people with **Dravet syndrome**. These mice die suddenly during seizures triggered by exposure to heat. The mice have less heart rate variability than healthy mice. Lower heart rate variability is a sign of sudden cardiac death.

At the start of their seizures, the mice have a very slow heart rate. Atropine, a drug that blocks the action of the vagus nerve in the brain, speeds up the heart rate. The vagus nerve connects the heart to the brain and helps keep the heart rate steady.

These findings show that a drug that stimulates the vagus nerve in the brain might help prevent seizures in people with Dravet syndrome.

Effects of Seizures on the Heart

Presented by Rainer Surges, MD

During most seizures, the resting heartbeat is faster than normal (tachycardia). So people with epilepsy often have an overactive **sympathetic nervous system**, which prepares the body for action by increasing blood pressure and heart rate and slowing down digestion.

Bradycardia, a very slow heart rate, is rare in people with epilepsy. When the heart stops beating altogether during a seizure, the stoppage is usually temporary. So bradycardia might not play a role in **SUDEP**.

Some early studies raise questions about whether epilepsy drugs are responsible for the abnormal transmission of electrical signals in the heart during seizures. The possibility that these drugs are a potential risk factor for SUDEP should be explored in future studies.

Non-inherited Risk to the Heart and Potential Treatment to Protect the Heart

Presented by Yi-Chen Li, MD

Abnormal electrical activity in the heart starts early in an experimental breed of laboratory rats that have seizures in response to pilocarpine, a drug used to treat dry mouth. In the experiments, the rats had an abnormally fast heart rate. Treatment with a beta-blocker lowered their heart rate.

If the abnormal electrical activity in the heart during seizures can be recognized quickly, beta-blocker treatment might help some people with epilepsy.

Conclusions

Some seizures might disturb heart function and contribute to **SUDEP**.

Components of the heart-brain connection, including disturbances in control of heart function by the **autonomic nervous system** and gene mutations linked to both brain and heart disorders, probably play a key role in SUDEP.

Epilepsy and Grief

Moderator: Jeanne Donalby

The learning objectives of this session were:

- Identify the typical stages of grief
- Understand the differences between complicated and uncomplicated grief
- Learn about the causes of grief complications

- Identify when or whether a person needs grief counseling
- Become familiar with grief support resources

Use of Advocacy to Heal from Grief

Presented by: Lisa Riley

Jordan Buisman, Lisa Riley's son, was diagnosed with epilepsy as a child. He was treated with anti-seizure medication and eventually stopped having seizures. But he started having seizures again as a young adult and had to retire from active duty in the Marines because of his epilepsy.

One day, Jordan had a seizure. He immediately contacted his local Department of Veterans Affairs health-care facility but couldn't get an appointment for several months. Jordan died of **SUDEP**, a few weeks before his appointment, at age 24 years.

Since her son's death, Lisa has struggled to cope with her grief. On the first anniversary of Jordan's death, Lisa made a public service announcement to honor her son's memory and increase awareness of SUDEP. Lisa now gives presentations about SUDEP and epilepsy to help deal with her grief in a positive way.

From Normal to Extreme Grief: Recognizing the Causes

Presented by Andres Kanner, MD

Most people experience normal grief after the death of a loved one. They might feel intense sadness and be unable to stop thinking about their loved one's death. They often have trouble sleeping, don't feel like eating, and lose weight. As a person adjusts to the loss, the grief becomes less intense.

But some people have complicated grief, which lasts at least 6 months. They feel very distressed and emotionally numb. They can't feel pleasure when something good happens.

When people with epilepsy have their first seizure, they and their families feel a deep sense of loss. Physicians need to understand this loss and help patients accept their diagnosis by going through the grief process. They should ask patients if they have accepted their diagnosis and if they have any fears or concerns. If a doctor ignores this responsibility, patients and families might have trouble dealing with their grief, and could increase the chances of grief complications in the event SUDEP.

Doctors should talk to newly diagnosed patients about the risk of **SUDEP**.

Grief Counseling or Not: Navigating the Grief Journey

Presented by: Linda Coughlin-Brooks, RN, BSN, CT

The stages of grief are denial, anger, bargaining, depression, and acceptance. Grief is normal, but today's society doesn't give people time to grieve. People expect those who are grieving to "buck up" and move on quickly.

When normal grief becomes **complicated**, it might be time to seek professional help. Signs that a grieving person needs to see a grief counselor include poor coping skills and a sense of hopelessness. The person might stop seeing friends or family members or avoid his or her regular activities. People with complicated grief sometimes become depressed or mentally ill, and they might even consider suicide. Some symptoms of complicated grief are physical, and the person's behaviors might be self-destructive.

Doctors, including neurologists (who diagnose and treat nervous system diseases) can help patients with symptoms of complicated grief by suggesting that the patient get grief counseling or grief therapy. Grief counseling helps people who've recently lost a loved one go through the "tasks of mourning" so that they can better adapt to the loss. Grief therapy helps people whose grief is too intense, lasts a long time, or causes physical symptoms. This therapy helps people identify and overcome the barriers to going through all of the stages of grief.

Referring People to Grief Support Services: Resources and Recommendations

Presented by: Paul Scribner, MSW, LCSW-C

Healthcare providers are in an ideal position to refer people who have lost a loved one from an epilepsy-related cause to helpful grief support resources. To make the right referrals, providers must take time to understand the basic values, beliefs, and practices of the family that might affect how family members deal with death and loss.

When working with a family that has suddenly lost a loved one to epilepsy, providers need to understand and respect the views and wishes of the family. A deep understanding of the family's unique needs, values, and customs (including family and religious customs) surrounding death and grief can help providers support family members through this tough experience without upsetting anyone. But very few families volunteer the information without prompting. So providers can only understand a family's attitudes and rituals around death by asking about these issues.

Questions that healthcare providers might ask to understand the values and beliefs of family members include:

- Does your family have traditions that are important in your grieving process?
- Over the next 6 months or a year, what kinds of things do you expect to do as part of your family or religious traditions or that will help your grieving process?
- What traditions will your family use to commemorate your loved one's life?

Providers need to develop a list of trusted referral resources and keep this list handy. These resources should include the social work, counseling, and other grief support resources at the provider's institution; grief and loss resources in the community; and national resources that provide grief-related support.

Genetic Causes of Sudden Unexpected Death in Epilepsy

Moderators: Daniel Lowenstein, MD and Alica M Goldman, MD, PhD

This session summarized key advances in genetic research that could improve diagnoses of **SUDEP** and identify the causes of early death in people with epilepsy.

Use of Genomics to Study Sudden Unexpected Death in Epilepsy in People

Presented by Alicia M Goldman, MD, PhD

Little is known about which factors affect a person's risk of **SUDEP** or could lead to preventive strategies. Assessing a given person's risk of SUDEP requires knowing which genes drive the complicated heart and breathing problems in SUDEP.

Experts have identified genes that might play a role in causing SUDEP. Some of these genes control breathing and wakefulness. Others are part of the connection between the brain and heart or the **autonomic nervous system**. A child with **Dravet syndrome** and SUDEP had a mutation in the *SCN1A* gene. About 80% of people with Dravet syndrome have a mutation in the *SCN1A* gene, but this study was the first to find the mutation in a patient with both Dravet syndrome and SUDEP. Because SUDEP is more common in people with Dravet syndrome than in most types of severe epilepsy, *SCN1A* mutations might have been linked to SUDEP.

The ability to diagnose SUDEP and predict a patient's likelihood of SUDEP based on genetics will require research collaborations among families, physicians, forensic pathologists, and scientists.

Lessons from the Epilepsy Phenome/Genome Project and Epi4K

Presented by Daniel Lowenstein, MD for the EPGP and Epi4K Investigators

The Epilepsy Phenome/Genome Project (EPGP) is an international consortium of 27 institutions in the United States, Canada, and Australia funded by the National Institute of Neurological Disorders and Stroke (NINDS) of the U.S. National Institutes of Health. EPGP has collected data on more than 4,100 patients with different types of epilepsy and their family members. EPGP has detailed information on the physical characteristics of each participant, including details on their seizures, test results, and blood samples. Researchers are now studying the genomes (complete sets of genes) in EPGP participants.

The Epi4K Genetics and Genomics Center Without Walls, also funded by NINDS, is identifying the genetic risk factors of epilepsy and developing tailored treatments and preventive strategies for epilepsy. An Epi4K research project found that gene mutations are common in the genes that control ion channels (which help minerals enter cells) and genes that cause seizures, autism, or intellectual disability.

Key factors in the successes of EPGP and Epi4K are the teams' broad scientific expertise, strong commitment to collaboration, and focus on patients.

Finding and Confirming Genes Linked to Sudden Unexpected Death in Epilepsy in Laboratory Mice

Presented by Jeffrey L. Noebels, MD, PhD

Identifying and understanding the genes that increase a person's risk of **SUDEP** is critical to develop strategies to prevent or treat SUDEP.

Two breeds of laboratory mice have two different mutations in the *KCNQ1* gene. Both genes are associated with an abnormal heart rhythm known as **LQTS**. The gene is active in the heart and brain. Both breeds of mice die of SUDEP.

Type 1 SUDEP is associated with mutations in genes that control the central nervous system (brain and spinal cord) and peripheral nervous system (nerves connecting the central nervous system to the arms, legs, skin, and organs). Type 2 SUDEP involves genes that are active in both the central and **autonomic nervous systems**, but not the heart. Some people with Type 2 SUDEP have mutations in the gene controlling the Kv1.1 ion channel, which helps potassium enter cells. This gene is active in the **vagus nerve** in the brain. Atropine, a drug that blocks the action of the vagus nerve, reduces heart problems during seizures in mice lacking the *KV1.1* gene.

Sodium Channel Mutations and Sudden Unexpected Death in Epilepsy

Presented by Miriam Meisler, PhD

The *SCN1A* gene provides instructions for making sodium channels, which help sodium go in and out of cells. Mutations in this gene are linked to **SUDEP**.

The *SCN8A* gene is a closely related to the *SCN1A* gene. *SCN8A* plays a role in epilepsy, memory problems, and SUDEP. A new experimental breed of laboratory mice has a mutation in the *SCN8A* gene. These mice start having severe seizures at an early age which results in SUDEP. This new mouse model offers a unique opportunity to study the role of *SCN8A* in SUDEP.

Abstract Winner Presentation: Studying Sudden Unexpected Death in Epilepsy and Stress in Rats that Develop Epilepsy Due to Gene Mutations

Presented by Srinivasa Kommajosyula

Genetically engineered rats with mutations in the *GEPR-9* gene have seizures but rarely die of them. For this reason, they are ideal for studying factors in the environment that influence the risk of a seizure-related death.

Adenosine is a chemical substance that helps control the activity of certain **neurons**. These neurons transmit information throughout the body to control breathing, sleep, and wakefulness. Surges in adenosine levels after a seizure seem to play a role in reducing electrical signaling in the brain.

Treating the rats with chemicals that block adenosine prolonged the reduction in electrical brain activity and oxygen levels after seizures. This treatment also increased rates of seizure-related deaths. This finding shows that adenosine seems to play a role in death due to seizures.

Alcohol changes levels of adenosine in the brain. Alcohol withdrawal in rats triggered an increase in brain adenosine levels and deaths due to seizures. These results offer a possible explanation for the increase in **SUDEP** risk in people who have been drinking alcohol heavily for a long time.

Summary

Researchers are identifying genes and biological activities involved in **SUDEP**, and new technologies are speeding up these discoveries. Detailed data on patients will be critical for identifying which genes are linked to different features of epilepsy.

Sudden Unexpected Death in Epilepsy: Devices, Treatments, and Prevention Strategies

Moderator: Elizabeth J. Donner, MD, FRCPC

Overview

Right now, the best way to prevent **SUDEP** is to reduce its risk. The best-known risk factor for SUDEP is frequent **generalized tonic-clonic seizures**. Any treatment that stops these seizures from happening often could reduce a person's risk of SUDEP.

Other risk factors for SUDEP include having epilepsy for a long time, not using treatments as instructed, and having diseases and conditions other than epilepsy. Treatments that change these risk factors could reduce the risk of SUDEP and deaths from any cause in people with epilepsy.

This session explored devices to detect seizures and behavior changes that might prevent SUDEP.

Accuracy and Usefulness of Devices

Presented by Daniel Friedman, MD

A device that tells caregivers that someone has begun to have a seizure could give them time to use a treatment that shortens the seizure, minimize harm from the seizure, or both.

People with epilepsy can wear certain devices that detect the kinds of motion that trigger seizures. Other devices use video cameras to detect movements that might indicate seizures while the person is sleeping.

One type of device measures changes in heart rate, oxygen in the blood, and other markers that might signal a seizure. This type of monitoring might be less comfortable than devices that measure physical activity. But it could detect seizures that might be more dangerous, such as those that lead to low levels of oxygen in the brain for a long time.

The devices on the market today sometimes send out alerts when the person isn't having a

seizure. False-positive alerts like these could have a negative impact on the quality of life of both caregivers and people with epilepsy.

Devices to Monitor Seizures: What to Know and What to Ask

Presented by Tom Stanton

Several devices on the market in North America can detect motions that could trigger seizures.

People with epilepsy and families thinking about buying a device to detect seizures at home should ask their doctor these questions:

- Which device is most useful and appropriate for the patient?
- Which types of seizures should the device monitor?
- Are any physical signs particularly important to detect?
- Would the data from a device help the doctor choose treatments to recommend?

Other factors to keep in mind are the costs, comfort, and ease of use of each device.

Research hasn't proven that devices can prevent seizures or **SUDEP**.

Night-Time Supervision and Stimulation During Seizures

Presented by Lisa Bateman MD

SUDEP usually happens at night or while the person is in bed. SUDEP usually happens after a seizure with convulsions.

Sleep might affect the **autonomic nervous system**. The brain might lose its ability to respond to the lack of oxygen, high carbon dioxide levels, and lower heart rate variability (a sign of sudden cardiac death) during a seizure.

A study evaluated SUDEP deaths among young people with epilepsy and learning difficulties at a boarding school in the United Kingdom. All of the deaths happened while students were away from the school. So a supervised environment might protect people with epilepsy from SUDEP.

Early intervention during a seizure can reduce breathing and heart problems and shorten seizures. But which interventions can best prevent SUDEP in hospitals and homes needs more research.

Changing Behavior

Presented by Martha Sajatovic, MD

The Managing Epilepsy Well Network (<http://web1.sph.emory.edu/ManagingEpilepsyWell>) advances epilepsy self-management through research, collaborations with network and community stakeholders, and spreading the word about research findings. The network is evaluating several self-management programs.

Challenges in developing effective self-management tools include:

- Finding ways to customize self-management strategies to each person with epilepsy

- Developing formats that are acceptable and appealing to people with epilepsy
- Using approaches that are practical and can become a routine part of epilepsy care

SUDEP Prevention from a Public Health Perspective: Changing Behaviors

Presented by Tanya Spruill, PhD

People with poorly controlled seizures have a higher risk of **SUDEP**. So maximizing people's ability to manage their own epilepsy might be a powerful way to reduce SUDEP risk.

Behaviors that could prevent people from controlling their seizures and increase their risk of SUDEP include not getting enough sleep, using alcohol, and not taking epilepsy medicines as instructed. In particular, not taking epilepsy medicines correctly increases the risk of dying.

People may not take their epilepsy medications correctly for several reasons. For example, they might not fill a prescription, skip some doses, or take extra doses. They may also take their medicines at the wrong time or with foods that they aren't supposed to eat while on the medications. Well-designed strategies to help people take their epilepsy medicines target memory problems, depression and anxiety, and negative feelings about medicines.

Patient education alone isn't enough to help people take their medicines as instructed. Patient education tools need to be customized to each patient. They also need to be combined with memory aids, reminders, social support, and other strategies.

Conclusion

The best way to reduce the risk of **SUDEP** is to make seizures happen less often. As we wait for the development of devices and strategies that can reduce death rates in people with epilepsy, everyone with epilepsy needs to work with their healthcare providers to reduce the effects of seizures. Epilepsy self-management tools should be combined with epilepsy medicines. Finally, talking about SUDEP with people with epilepsy is important to save lives.

How Organizations Are Increasing Understanding of Sudden Unexpected Death in Epilepsy

Moderators: Jeffrey Buchhalter MD, PhD and Cyndi Wright, BS

A variety of organizations are advocating for people living with epilepsy and those who have lost a loved one to **SUDEP**.

SUDEP Action (www.sudep.org) provides information on SUDEP and its risk in people with epilepsy, supports people who have lost a loved one to SUDEP, sponsors SUDEP research and education, and collects data on epilepsy-related deaths in the United Kingdom.

In 2005, Epilepsy Australia (an epilepsy advocacy organization) and Epilepsy Bereaved (which focuses on SUDEP) published the first edition of "Sudden Unexpected Death in Epilepsy: A

Global Conversation” (www.sudepglobalconversation.com). This collection of essays describes SUDEP, death, and epilepsy in a way that is understandable to everyone. These organizations published a second edition of the report in 2011 with two more advocacy organizations, SUDEP Aware and the International Bureau of Epilepsy.

The Canadian organization SUDEP Aware (www.sudepaware.org) created the first online information repository on SUDEP. SUDEP Aware also provides support services for people affected by SUDEP and encourages families to participate in research.

The SUDEP Institute (<http://www.epilepsy.com/sudep>), part of the Epilepsy Foundation, provides SUDEP education and awareness programs for lay and professional audiences, supports research, provides counseling, and works with other epilepsy organization to increase knowledge of SUDEP. The institute also works with medical examiners and coroners to better understand how many people die of SUDEP.

The Danny Did Foundation (<http://www.dannydid.org>) sponsors local educational and awareness efforts and research on seizure-detection devices. Danny Did also helps fund seizure detection devices for families who cannot afford them.

Citizens United for Research in Epilepsy (CURE) has added SUDEP to its research initiatives (<http://www.cureepilepsy.org>). CURE has funded research on the causes of SUDEP and its risk factors. CURE has also collaborated in national and international SUDEP education and research activities with federal government agencies.

The last two decades have seen a tremendous international effort to increase awareness, education, and research on SUDEP. Organizations have made important gains in rallying human and financial resources to prevent, and to support those affected by this tragedy.

Glossary of Terms

Adenosine: a chemical substance that helps control the activity of certain nerve cells (neurons)

Autonomic nervous system: controls basic body functions, such as breathing and digestion, without conscious effort

Brainstem: part of the brain that controls breathing, blood pressure, heartbeat, and other basic functions

Complicated grief: grief that lasts at least 6 months

Cortex: part of the brain that controls certain higher-order functions, such as thought and deliberate action

Dravet syndrome: rare brain disorder caused by genetic mutations and associated with seizures that begin in infancy and can last a long time or happen over and over

Generalized tonic-clonic seizures: seizures that often last a couple of minutes and typically begin with a sudden fall and rigid muscles, followed by jerky movements and shallow breaths

Long QT syndrome (LQTS): rare disorder of the heart's electrical activity

Near-SUDEP: with resuscitation, the person was revived after cardiac arrest and survived for more than an hour

Neurons: nerve cells in the brain

Possible SUDEP: The person had a preexisting condition that might have contributed to his or her death and the death otherwise fits the SUDEP definition

Serotonin: brain chemical that controls sleep, wakefulness, and breathing

Status epilepticus: seizure that lasts at least 30 minutes

Sudden infant death syndrome (SIDS): death of an otherwise healthy baby

Sudden unexpected death in epilepsy (SUDEP): death that is sudden and unexpected and that isn't due to an injury, drowning, or another known cause

SUDEP plus: death in a person with a preexisting condition that might have contributed to his or her death and the death otherwise fits the SUDEP definition

Sympathetic nervous system: prepares the body for action by increasing blood pressure and heart rate and slowing down digestion

Vagus nerve: connects the heart to the brain and helps keep the heart rate steady