Plenary 1
Mortality in People with Epilepsy: Epidemiology and Surveillance
June 24, 2016
8:30 a.m. -10:15 a.m
Moderator: Vicky Whittemore, Ph.D., NINDS

- Epidemiology of Epilepsy-related Mortality – Dale Hesdorffer, Ph.D., Columbia University

- Suicide Among People with Epilepsy: A Population-based Study Results from the Data of U.S. National Violent Death Reporting System, 17 States, 2003-2011 - Niu Tian, M.D., Ph.D., Center For Disease Control

- Case Ascertainment and Registries: What Information Is Currently Being Collected in US/UK/Australia? - David Fowler, M.D., Chief Medical Examiner for Maryland and Margaret Warner, Ph.D., Centers for Disease Control

- The Sudden Death in the Young Case Registry: Updates and Progress – Heather Macleod, M.S., CGC, Sudden Death in the Young Registry

- Panel Discussion:
  - Are we getting at the right data?
  - What populations aren’t we exploring?
  - What additional information should be collected?
  - How do we improve case ascertainment?
Epidemiology of Epilepsy-Related Mortality

Dale C Hesdorffer, PhD
Columbia University
JUNE 2016

Learning Objectives

- Understand the differences between status epilepticus (SE) in the old and new classifications of SE
- Describe risk factors and outcomes of Prolonged Refractory Status Epilepticus (PRSE) and new-onset refractory status epilepticus (NORSE)
- Describe the number of SUDEP deaths and consider similarities between drowning deaths, SUDEP and SE

"Old" definition of status epilepticus

A seizure lasting more than 30 minutes or a series of seizures lasting more than 30 minutes without intervening recovery of consciousness.

In-hospital mortality in 399 of 11,580 US patients with generalized convulsive SE, 2000-2004

Koubeissi & Alshekhlee Neurology 2007

Incidence of SE in Rochester, Minnesota

Hesdorffer et al, Neurology 1998;50:735-741
New Conceptual ILAE Definition of Status Epilepticus

**Time 1** indicates when treatment should be initiated (5 minutes)
**Time 2** indicates when failure to terminate or from the initiation of mechanisms which lead to abnormally prolonged seizures after time 1.**

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic SE</td>
<td>5 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Focal SE with impaired consciousness</td>
<td>10 minutes</td>
<td>&gt;60 minutes</td>
</tr>
<tr>
<td>Absence SE</td>
<td>10-15 minutes</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Currently information to define T1 and T2 | **No information to define T1 and T2**

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New ILAE classification of SE: Four Axes

- **Semiology**
- **Etiology**
- **EEG correlates**
- **Age**

New ILAE classification of SE: Semiology and Etiology

- Presence/absence of prominent motor symptoms
- Degree (quantitative or qualitative) of impaired consciousness
- Known (i.e. symptomatic)
- Acute
- Remote
- Progressive
- Unknown

New ILAE classification of SE: EEG correlates and age

- **EEG correlates**
- Location
- Name of the pattern
- Morphology
- Time-related features: (e.g., prevalence, frequency)
- Modulation
- Effect of medication on the EEG
- Age groups
  - Neonatal (0-30 days)
  - Infancy (1 month – 2 years)
  - Childhood (2 to 12 years)
  - Adolescence and adulthood (>12-59 years)
  - Elderly (>60 years)
New compared to old ILAE SE definition:
SE with motor signs in hospital-based adults

Comparing mortality in the \textit{old} and \textit{new} SE classification

Conclusions: Prolonged Refractory Status Epilepticus

- Two-thirds survived to discharge
- One-fifth had a good outcome ≥6 months after Prolonged Refractory Status Epilepticus
- One-tenth of those without significant disability had a good outcome

- Good or excellent outcomes occurred
  - 3 months after PRSE
  - Up to 35 years of age

Prolonged refractory status epilepticus (PRSE)

- SE that persists despite at least one week of induced coma
- PRSE consecutive patients with PRSE from medical and neurointensive care units of 3 academic medical centers over 9-years
- Complete PRSE control was associated with:
  - Persistent features (clinical or electrographic during treatment)
  - Recurrent seizures within 48 hours of discontinuation of anesthetic infusions
New-Onset Refractory Status Epilepticus (NORSE)
A state of persistent seizures with no identifiable etiology in patients without prior epilepsy that lasts longer than 24 hours despite optimal therapy.

Gaspard et al, Neurology 2015

Conclusions: Treatment and complications in positive etiology and no etiology

- Immune system therapies greater in positive etiology
  - Plasma exchange (p=0.02)
  - IV immunoglobulin (p=0.01)
  - Rituximab (p<0.001)

- Complications greater in no etiology
  - Need for vasopressors (p=0.03)
  - Severe acidosis (p=0.04)
  - Uncontrolled SE at death (p=0.04)

50% unknown etiology
50% known etiology after investigation
20% autoimmune, non-paraneoplastic
18% paraneoplastic
8% infection-related
4% other causes

In those with unknown etiology
62% poor outcome
22% died

Annual number of SUDEP deaths
- Age-adjusted incidence of SUDEP in the US
  - 1.11 SUDEPs per 1,000 people with epilepsy
  - Adjusted for the 2000 standard population

Using the US and European population estimates in 2013, there were:
- 2,750 SUDEPs per year in the United States
- 3,994 SUDEPs per year in the 28 nations of the European Union

Thurman et al, Epilepsia 2014

Cumulative incidence of SUDEP: By year of epilepsy onset
Distribution of SUDEP by population and by age

Drowning deaths

Prevalence of drowning in bathtubs in the US 1979-81

SMRs of drowning deaths in epilepsy by study

SMR of drowning death in epilepsy by population

Autonomic Nervous system: effects on drowning, SUDEP, and SE

Drowning risk factors are similar to SUDEP:
- Learning disability
- Living in an institution
- Temporal lobe surgery
- Entered in a drug trial
- Tertiary clinic
- ALL INDICATORS OF HIGH SEIZURE FREQUENCY

Autonomic Nervous System regulates involuntary body functions:
- Activity of the heart, respiration, intestinal tract and glands

Sympathetic nervous system:
- Accelerates heart rate
- Constricts blood vessels
- Increases blood pressure

Parasympathetic nervous system:
- Slows heart rate
- Increases intestinal and gland activity
- Relaxes muscle sphincters
Autonomic Nervous System in Epilepsy: Drowning, SUDEP, and SE

<table>
<thead>
<tr>
<th>Death in Epilepsy</th>
<th>Sympathetic NS</th>
<th>Parasympathetic NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowning</td>
<td>Cold water receptors inhibit the respiratory center, leading to apnea &amp; vasoconstriction</td>
<td>Atrial and pulmonary stretch receptors and apnea, leads to slowed heart rate</td>
</tr>
<tr>
<td>SUDEP</td>
<td>Increased heart rate and blood pressure</td>
<td>Impaired respiration, apnea, slowed heart rate, hypotension, and bradyarrhythmia precede death</td>
</tr>
<tr>
<td>SE</td>
<td>Tachycardia, hypertension, pulmonary edema, ventricular arrhythmias</td>
<td>Hypotension and generalized circulatory collapse</td>
</tr>
</tbody>
</table>

Might drowning deaths be similar to SUDEP?

- Exclusion of drowning from cases of SUDEP may be inappropriate
- Both sympathetic and parasympathetic changes are seen with water emersion in normal populations and with seizures in epilepsy
- Aberrant control of cardiac or respiratory function may occur more in PWE as demonstrated in SUDEP and drowning
- Similar findings are seen in SE

Impact on Clinical Care and Practice

- Old and new classifications of SE
  - Seizure types are better represented in the new classification
- Prolonged Refractory Status Epilepticus
  - Survival to discharge in 66%
  - Good outcome 6 months post PRSE in 22%
- New-onset Refractory Status Epilepticus
  - Almost half have an autoimmune/paraneoplastic etiology after investigation
  - May survive and do well, despite NORSE
  - Epilepsy develops in 57%
Suicide among People with Epilepsy

Niu Tian, MD, PhD
Epilepsy Program
Centers for Disease Control and Prevention (CDC)

June 2016

Learning objectives
Following the participation of this presentation, learners should be able to:

- Have an overview of epidemiology on the suicide among people with epilepsy in the general population
- Improve the knowledge about risk and risk factors of suicide among people with epilepsy
- Prepare for the suicide prevention in this special group

Suicide, # 1 cause of violence-related deaths and one of the major causes of death in the U.S. population

- In 2013, an estimated 57,786 persons died in the United States as a result of violence-related death
- 41,149 of deaths (71%) were suicides, followed by homicides and deaths involving legal intervention
- Suicide deaths among all causes of deaths
  - 2nd leading cause of death for people aged 15-34
  - 3rd leading cause of death for people aged 10-14
  - 4th leading cause of death for people aged 35-44
  - 5th leading cause of death for people aged 45-54

Source: Available at http://www.cdc.gov/injury/wisqars/fatal.html

Suicide among people with epilepsy is an increasing public health concern

- Most epidemiologic studies showed that people with epilepsy have stronger tendency toward suicide than health controls
- It has been proposed that suicide, epilepsy, and psychiatric disorder may share common pathophysiological mechanisms
- Depression, anxiety, and suicidality could relate to negative SDOH (unemployment etc.) and the lifestyle changes imposed by sudden seizure and increased stigma perception among people with epilepsy

2. Hesdorffer DC, et al. Epilepsia 2011;52:77-84

The gold standard for studies on mortality (including suicide) in people with epilepsy

- Population-based cohort of incident cases

- Only this type of study permits a complete collection of data and the observation of the clinical phase of the disease from the diagnosis of epilepsy to the outcome of the study, death


Disclosure

- The authors have no conflicts of interest
- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention
Limitations/problems in most epilepsy-suicide studies

- Suicide burden is calculated by cause-specific mortality ratio
- Results vary significantly
  - Different countries
  - Different populations
  - Different selected patient groups
  - Different study designs
  - Usually small sample sizes

Suicide epidemiology among people with epilepsy in the general population is not clear/unknown

- Population-based surveillance systems including both epilepsy and suicide have not been routinely available
- No studies have described both suicide rates and the characteristics of people with epilepsy who died from suicide in a large general population setting

Data Source

- Source: U.S. National Violent Death Reporting System (NVDRS)

<table>
<thead>
<tr>
<th>Components: detailed information on the circumstances of violent deaths including suicides</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 unique variables for each death from individual information sources</td>
</tr>
<tr>
<td>Abstractors also compose text narratives that describe further details about the death</td>
</tr>
<tr>
<td>Monitored by CDC with high quality control</td>
</tr>
<tr>
<td>Purpose: accurate, timely, and comprehensive data to better understand and ultimately to prevent the occurrence of violent death including suicide in the U.S.</td>
</tr>
</tbody>
</table>

Study objectives

- To analyze suicide data among those with epilepsy in the general population from the U.S. National Violent Death Reporting System (NVDRS):
  - Describe suicide burden (suicide rate and trend)
  - Investigate risk factors associated with suicide
  - Suggest measures to prevent suicide in this special group

Study design and sample

<table>
<thead>
<tr>
<th>States</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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</tbody>
</table>

Source: CDC, NCHS and CDC Mortality and Morbidity Weekly Report (MMWR), 2014:63/No. 11-3-15
**Identify suicides with and without epilepsy**

Identified 8,529 suicides from NVDRS by using ICD-10 codes X60–X84 and Y87.8 at ages 10 years or older in 17 states from 2005-2011

Searched epilepsy/seizure-related key words and phrases: “epilepsy”, “seizure”, “convulsion”, “drop attack”, “fainting out spell”, “staring spell” from:
- death certificates
- medical examiner/coroner records
- law enforcement reports

Search code for epilepsy/seizure related ICD-10 codes: G41, G41, Y00 and X16 from:
- death certificates

Excluded 43 drug-induced seizures by reading abstractors’ narratives.

1,015 suicides with epilepsy/seizure.

972 suicides with epilepsy.

81,529 suicides without epilepsy.

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**Trends of suicide in people with and without epilepsy in the general population**

- Trends of the proportions of suicides deaths among people with and without epilepsy in 16 states (all but Ohio) with continual data from 2005 through 2011

- The annual proportion of suicide deaths = number of suicides each year / the total number of suicides for all years from 2005 through 2011

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**Calculation of suicide rates among people with epilepsy in the general population**

- Epilepsy prevalence
  - U.S. children aged 10–17 years old from the U.S. National Survey of Children’s Health (8.1/1,000 persons)
  - U.S. adults 18 years old or older from the U.S. National Health Interview Survey (10.0/1,000 persons)
- Estimate the expected number of people with epilepsy in each state for each study year
- Suicide rate = total number of suicide cases in people with epilepsy in each year / total expected number of people with epilepsy each year


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**Other sociodemographic characteristics (covariates)**

- NVDRS collects information about characteristics such as:
  - Age, gender, race/ethnicity
  - Education, and marital status
  - Location of injury
  - Month of injury
  - Method of injury

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**Statistical analysis**

- For suicide burden
  - Rate calculation—described before
  - Trend analysis
    - Cochran-Armitage trend test
    - Compared the proportions of suicide deaths between people with and without epilepsy

- For suicide risk
  - Compared the proportions of suicide deaths between people with and without epilepsy
    - by month, the location of death, and the method of injury
    - by sex, age, race/ethnicity, education, and marital status

- Defined statistically significant differences in proportions of deaths whose two-sided 95% binomial confidence intervals did NOT overlap

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**Estimated Annual Suicide Mortality Rates among People with Epilepsy in the General Population**

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate per 100,000</th>
<th>Sex</th>
<th>Race/Ethnicity</th>
<th>Education</th>
<th>Marital Status</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>9.4</td>
<td>Male</td>
<td>White</td>
<td>High</td>
<td>Married</td>
<td>18-24</td>
</tr>
<tr>
<td>2013</td>
<td>8.9</td>
<td>Male</td>
<td>White</td>
<td>High</td>
<td>Married</td>
<td>25-34</td>
</tr>
<tr>
<td>2014</td>
<td>8.5</td>
<td>Male</td>
<td>White</td>
<td>High</td>
<td>Married</td>
<td>35-44</td>
</tr>
<tr>
<td>2015</td>
<td>8.2</td>
<td>Male</td>
<td>White</td>
<td>High</td>
<td>Married</td>
<td>45-54</td>
</tr>
<tr>
<td>2016</td>
<td>7.9</td>
<td>Male</td>
<td>White</td>
<td>High</td>
<td>Married</td>
<td>55-64</td>
</tr>
</tbody>
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<td>Female</td>
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<td>High</td>
<td>Married</td>
<td>55-64</td>
</tr>
</tbody>
</table>

X = data not available
Trends of the proportions of suicides deaths with and without epilepsy from 2005-2011 in the 16 states (excluding Ohio)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>With Epilepsy</th>
<th>Without Epilepsy</th>
<th>With Epilepsy</th>
<th>Without Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>100</td>
<td>15.9 (13.1-19.0)</td>
<td>44</td>
<td>12.8 (9.5-16.8)</td>
</tr>
<tr>
<td>10-17</td>
<td>11</td>
<td>1.7 (0.9-3.1)</td>
<td>1,749</td>
<td>2.7 (2.6-2.9)</td>
</tr>
<tr>
<td>40-49</td>
<td>173</td>
<td>27.5 (24.0-31.2)</td>
<td>13,472</td>
<td>21.1 (20.8-21.4)</td>
</tr>
<tr>
<td>70 and Above</td>
<td>51</td>
<td>8.1 (6.1-10.5)</td>
<td>7,506</td>
<td>11.7 (11.5-12.0)</td>
</tr>
</tbody>
</table>

Exploration of Risk factors
Comparing the percentages of suicide death between with and without epilepsy by sex and age

<table>
<thead>
<tr>
<th>Sex</th>
<th>With Epilepsy</th>
<th>Without Epilepsy</th>
<th>With Epilepsy</th>
<th>Without Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both Sexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Exploration of Risk factors
Comparing the sex-specific percentages of suicide death with and without epilepsy by marital status

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>With Epilepsy</th>
<th>Without Epilepsy</th>
<th>With Epilepsy</th>
<th>Without Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Married</td>
<td>234</td>
<td>37.8 (34.0-41.8)</td>
<td>2,211</td>
<td>34.9 (33.6-36.2)</td>
</tr>
<tr>
<td>Married</td>
<td>216</td>
<td>34.9 (31.1-38.8)</td>
<td>23,666</td>
<td>37.4 (37.0-37.8)</td>
</tr>
<tr>
<td>Separated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed/Divorced</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Summary of major findings (for suicide burden)
- The annual suicide mortality rate among people with epilepsy in a large general population was 16.89/100,000 persons per year, 22% higher than that in the general population
- Of those total suicide deaths, 1.2% was from people with epilepsy
- Both annual rate of suicide and the annual percentage of suicides among all suicides in those with epilepsy increased steadily from 2005, peaking significantly in 2010 before falling
- Compared to those without epilepsy, those with epilepsy were more likely to die from suicide in homes, apartments, or residential institutions (81% vs. 76%)
- Twice as likely to poison themselves as those without epilepsy (38% vs. 17%)
- More of those with epilepsy aged 40-49 died from suicide than those at same ages without epilepsy (29% vs. 22%)
- Marital status (being unmarried) was related to the increased risk of suicide in people with epilepsy
Strengths of this study

- For the first time, we systematically researched the basic epidemiology of suicide among people with epilepsy in a large, general population in the U.S.
  - Suicide rate, trend, risk and risk factor
- Data from NVDRS, a unique, large population-based surveillance system with high quality control and data collection consistency, and inclusion of all suicides from 2003 through 2011 in 17 U.S. states (about one-third of the U.S. population)
- Multiple methods to identify those suicide deaths with epilepsy/seizure.

Limitations of this study

- The identification of epilepsy / seizure among suicide cases could have misclassified some suicide cases
  - Overestimate suicide cases with epilepsy
    - “falling out spell”, “staring spell”, “drop attack
  - Underestimate suicide cases with epilepsy
    - Identification of epilepsy in persons who died from suicide is usually overlooked
    - Identification of suicide deaths in persons with epilepsy is difficult

Limitations of this study (Cont.)

- NVDRS includes data from only 17 States, not the whole or a necessarily representative segment of the U.S. population.
- The calculation of the expected number of people with epilepsy in each state was based on two national age-specific prevalence estimates, which may not accurately represent these states because socioeconomic factors that may affect epilepsy prevalence may differ across the states.
- Finally, information about associations between epilepsy related suicide and prior history of mental illness is unknown.

Impact on clinical care and practice

(Cont.)

- For suicide burden
  - Based on this large community data, people with epilepsy have a slightly higher suicide rate (22%) than that in the general population and suicides with epilepsy take a small portion (1.2%) of all suicide deaths
  - The recent U.S. economic recession may have impacted the trends of annual suicide rate and proportion of annual suicide deaths among people with epilepsy.
    - The economic crisis and its consequence
      - Unemployment, poverty, debt, and diminished public welfare, and depression

Impact on clinical care and practice

(for suicide risk factors)

- Compared to general population, people with epilepsy are more likely to die from suicide in their residence, and by poisoning themselves
- People with epilepsy aged 40-49 years old are the most vulnerable group
- Family/social support are crucial to prevent suicide risk among people with epilepsy

Recommendations

- People with epilepsy may benefit from having caregivers, relatives, and friends supervise the availability of potentially harmful materials including drugs to prevent suicide
- Suicide prevention efforts should focus on people with epilepsy aged 40-49 years, especially in their residences
- Epilepsy health and social service providers, caregivers and other members of the public should be aware of the importance of screening and treatment of depression and other mental illness in people with epilepsy to prevent suicide
- Population-based surveillance or registry targeting both epilepsy and mortality including suicide needs to be enhanced to allow further epidemiology study among people with epilepsy in the U.S. nationwide
Acknowledgments

CDC Epilepsy Program

• Wanjun Cui
• Matthew Zack
• Rosemarie Kobau

Collaborators

• Katherine Fowler
• Matthew Gladden
• Dale Hesdorffer

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Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Challenges and Opportunities to Understand Sudden Unexpected Death in Epilepsy (SUDEP) Using Death Certificate Data

Margaret Warner, PhD
National Center for Health Statistics
Partners Against Mortality in Epilepsy Conference
June 2016

Mortality data
- Death is a key health outcome
- Death certificate mortality data uses include:
  - Monitor to health of nation
  - Understand causes of death
  - Identify risk and protective factors
  - Define public health response priorities
  - Evaluate the impact of interventions
  - Determine what public health messages to deliver

National Vital Statistics Mortality Data
- Based on information from all death certificates filed in the States and Territories
- Data include:
  - Demographic information such as age, sex, race, place of residence
  - Disposition information
  - Causes of death coded using the *International Classification of Diseases, Tenth Revision* (ICD-10)
- Data used to monitor the health of the nation, including leading causes of death, life expectancy

US Standard Death Certificate
- **Demographic information**
  - Completed by the funeral director using information from the best qualified person: spouse, parent, child, another relative, or other person who knows the facts.
- **Medical information**
  - For natural causes, completed by attending physician, nurse practitioner, physician’s assistant.
  - For sudden and unexplained deaths, completed by medical Examiner, coroner, Justice of the Peace.
  - For demographic information.
Vital Statistics Cooperative Program

- Federal-State cooperative arrangement
  - Federal government provides funding, coordination, standards, and cause of death coding
  - States maintain autonomy in their operations, but collect and provide data according to standard specifications and agreed upon timelines

Promoting Consistency and Uniformity

- Model State Vital Statistics Act and Regulations
- Standard Certificates and Reports

- Training materials – handbooks, videos, instruction manuals
- Technical assistance – ICD 10
- Software – automated coding

Cause of death coding

- Deaths coded using the Tenth Revision of the International Classification of Diseases (ICD-10)
- ICD-10 in use since 1999*
- ICD-11 revision in progress
- All WHO Member States use the ICD
- Developed by international workgroups
- Translated into 43 languages
- Many countries use ICD to report mortality data as their primary indicator of health status

* ICD-10-CM (the clinical modifications) are not used for mortality coding
Some “example” (simplified) certification statements for SUDEP

- Sudden death associated with epilepsy
- Epileptic seizure
- Complications of seizures
- Probable seizure
- Seizure disorder
- Complications of seizures
- Undetermined

ICD-10 Codes for sudden unknown deaths involving epilepsy and seizures

- G40.9 (Epilepsy, unspecified)
  - Includes:
    - Epileptic seizure
    - Complications of epilepsy
    - Sudden death associated with epilepsy
- R56.9 (Other seizures and convulsions)
  - Includes:
    - Probable seizure
    - Seizure disorder
    - Complications of seizures
- R99 (Other ill-defined conditions)
  - Includes:
    - Unknown
    - Undetermined
- Many other ICD-10 codes for epilepsy and seizure

Using death certificates for public health research

Methods to retrieve information from death certificates

- Manual review of death certificates
- Multiple Cause of Death (MCOD) file
- Text searches of the literal text from the death certificate
- Combination of methods

National Death Index

- Assists investigators in determining whether persons in their studies have died
- Provides the names of the states in which those deaths occurred, the dates of death, and the corresponding death certificate numbers
- Investigators can arrange to obtain copies of death certificates or specific statistical information such as cause of death from state offices
Expert panel on Investigation, Diagnosis and Certification of SUDEP

- Researchers from:
  - National Association of Medical Examiners
  - North American SUDEP Registry
  - Epilepsy Foundation SUDEP Institute
  - American Epilepsy Society
  - Centers for Disease Control and Prevention (CDC)
- Review literature to recommend state of the art practice for the investigation, diagnosis and certification of sudden death in epilepsy
- Convened May 2016 with work on-going

Questions?

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Summary

- Death certificates provide information on the causes of death to help researchers to understand underlying disease mechanisms, and risk and preventive factors
- Death certification practices for SUDEP vary
- There are many ways to review the information on death certificates
- Work on-going to improve certification and access to information for researchers

"Let conversation cease, let laughter flee, for this is the place where death delights to help the living."

Inscribed on the wall of the NYC Medical Examiner’s Office,
Translated from Latin, Giovanni Morgagni
The Medical Examiner Perspective
David Fowler, MD
Chief Medical Examiner, Maryland

Death Investigation Considerations

• ME/C sudden unexpected natural death cases mostly cardiovascular
• 20% or less are CNS pathology
• Many deaths have “terminal seizure activity”
• Some deaths during a seizure or during post ictal period may appear to be cardiac.

Death Investigation

Essential Elements and data collection

• The Scene circumstances
  • ME/C equivalent of history
  • Found dead
  • Witnessed event
  • Present with symptoms
    • Pre hospital care death
    • Hospital death

Disclosure

No commercial interests.
Essential Elements and Data Collection

- Screening for seizures or epilepsy in sudden death form
- Screening for epilepsy in other forms of unexpected deaths (suicide, accidents)
- NASB and SDY: Death Scene Investigation forms

Death Investigation

- Body Examination positive
  - Trauma
  - Cardiovascular
    - Infarct, congenital, aortic rupture/dissection
  - CNS
    - Meningitis, hemorrhage
  - Other organs
    - Perforation, hemorrhage, PE etc.

Autopsy Protocol

- Full Autopsy
  - X-ray/advanced imaging
  - Full external examination
  - Internal gross organ dissection
  - Full histology
    - Toxicology
    - Metabolic studies
    - Culture
      - Viral and bacterial

Death Investigation

- Body examination negative
  - Full Microscopic exam
    - All essential organs association with sudden death
  - Heart
    - Cardiovascular pathologist
      - Conduction system
      - Additional gross exam
      - Additional histology
  - Other studies
  - Brain malformations
  - Additional histology
  - Other studies
  - Vitreous electrolytes/glucose
  - Rule out metabolic
    - Electron microscopy
    - Metabolic studies
    - Hold blood for genetic studies (card or tube)

Death Investigation

- Body examination negative
  - Consultant Neuropathologist
    - Brain malformations
    - Additional histology
  - Other studies
    - Vitreous electrolytes/glucose
    - Rule out metabolic
      - Electron microscopy
      - Metabolic studies
      - Hold blood for genetic studies (card or tube)

Toxicology

- Rule out intoxication
- Identify therapeutic medication(s)
  - Levels
  - PM levels may well be difficult to interpret and not representative of ante mortem levels
Role of Molecular Autopsy

- Genomic testing for
  - Long QT
  - Catecholaminergic polymorphic ventricular tachycardia
  - Hypertrophic cardiomyopathy

Challenges with Determination of Death
A cause of death vs. The cause of death

Cause of Death

- Many seizure deaths go unrecognized.
  - Trauma (single occupant motor vehicle impact)
  - Drowning
  - Be consistent
    - Seizure disorder or seizure
  - Due to
  - You can use contributory causes section
    - E.g. In MVC trauma if seizure was witnessed or thought to play a part
  - It is acceptable to use “probable” on a DC if needed

ICD Codes

- There is no SUDEP Code in ICD 10
- ICD 10 Epilepsy Codes Include:
  - G40.0 to G40.9 and G40.A, G40.B
- ICD 9 Epilepsy Codes Include:
  - 780.39 and 345.0-345.9

Consent for Further Studies?

- Know your local laws
  - Consent for molecular study if needed
- In Maryland the ME is authorized to retain and do any tests that “determine the cause of death within a reasonable degree on medical certainty”
  - There is no time limitation
  - That allows further testing even years later should a new technology come up.

Limited Resources

- To autopsy or Not to autopsy that is the question?
  - MEC with resources do
  - DX of seizure disorder is often a diagnosis of exclusion
    - Exclude occult trauma, toxicology etc.
    - Exclude natural disease
    - Identify congenital abnormalities
    - Best specimens: Toxicology, Histology, culture, molecular
**Efforts to Advance our Understanding of SUDEP**

- NIH Center for SUDEP Research
- NIH-CDC Sudden Death in Young Registry
- North American SUDEP Registry
- Sudden Unexpected Death in Childhood Registry & Research Collaborative (SUDC-RRC)

**Center for SUDEP Research**

- Human physiology – EMU recordings and prospective ascertainment
- Neuropathology – insights from pathology in mechanisms linking clinical biomarkers to epilepsy surgery tissue to brainstems
- Experimental physiology – neurorespiratory and neurocardiac mechanisms and models
- Molecular diagnostics - genetics

**Sudden Death in Young (SDY) Registry**

- Collaboration of NHBLI, NINDS, CDC
- Cardiac & epilepsy focus
- 10 States/Counties
- Prospective surveillance
- Ages 0-19
- Surveillance and DNA

**Rationale for a SUDEP Registry**

- SUDEP is rare – >2,750 SUDEPs in US annually.
- Insufficient cases to study at one center
- Epilepsy center-based case ascertainment biases towards “high risk” patients
- Need more population-based approach
- Large numbers of cases are needed to evaluate what are likely heterogeneous mechanisms
- Prevention strategies may not be generalizable
- Contribution of cardiac channelopathies (eg, new onset)
- Collaborative effort involving multiple investigators from multiple disciplines

**North American SUDEP Registry**

- Registry for SUDEP cases in the United States and Canada
- Create a repository for clinical, imaging, tissue, genetic and epidemiological data
- Population based referrals of all decedents with epilepsy (SUDEP cases and controls with epilepsy)
- Partnering with Medical Examiners
- Referral through Cardiac Patient Community (EP), neurologists
- Eligible patients currently include
  - Cases with DKA or Brain tissue
  - Cases with EEG recorded seizures, EKG, MRI
- Tissue/gene material will be freely available to any investigator after review by independent advisory board

**How Can You Support NASR and SDY?**

- Medical Examiners, Forensic Pathologists, and Coroners are crucial partners for NASR’s success. To collect high-quality clinical information, tissue, and DNA from as many epilepsy-related SUDEP cases as possible - we need your help!
  - Epidemiology – all SUIDS, suicide, drowning – consider epilepsy
  - Awareness - inform encourage families to contact NASR.
  - Tissue donation – collect tissue and genetic material from as many epilepsy-related mortality cases as possible.
  - Blood cards – collect genetic data and de-identified clinical data
  - Prospective tissue collection - we can accept brain tissue or DNA from previous cases with de-identified medical records.
How NASR Can Support ME/C

- Exome sequencing
- Neuropathology reports
- Imaging
- Independent review by experts in epilepsy
- Seizure/Seizure-onset in all SUDs, single passenger AVAs
- Valuable screening form
- Field Investigator forms

Field Investigator Form

- Mission
  - To prevent Sudden Unexpected Death in Epilepsy (SUDEP)
  - Support people confronting the fear and loss caused by SUDEP
- Supports Death Investigators
- Training
  - Support with finding death review teams
  - Coordinating with family for consent and explaining death investigation process
  - General bereavement support
- To learn more or refer a family:
  - Call 855-832-1000 or email sudep@efa.org

Epilepsy Foundation SUDEP Institute

- Family member calls 24 hour registry hotline (855-832-8555)
  - Screened for history of epilepsy & possible tissue donation
    - If candidate for tissue donation, transferred to brain banking affiliates to coordinate donation
  - 45-60 minute interview with research coordinator
  - Referral to grief counseling networks and peer support groups (SUDEP Institute)
  - Consent for release of medical records
  - We can provide Genetic testing from DNA and Neuropath reports from donated brains

PAME

- PARTNERS AGAINST MORTALITY IN EPILEPSY
- pameAESnet.org
Learning Objectives

Following participation in this activity, learners should be able to:

- Describe the goals of the SDY Case Registry
- Share the progress of the SDY Case Registry
- Identify future research opportunities in SUDEP

What Causes Sudden Death?

**Autopsy Positive**
- Aneurysm
- Cardiomyopathy
- Congenital Heart Disease
- Coronary Artery Disease
- Infection
- Metabolic Disease
- Stroke
- Other

**Autopsy Negative**
- Arrhythmia
- SUDEP
- Unexplained

Sudden Death Incidence Estimates

- The sudden death of a child is a tragic event
- Estimates for SCD and SUDEP vary greatly
- Incidence SCD in the young
  - 0.6 – 2.3 per 100,000
- Incidence of SUDEP
  - about 2600-3500 cases/year (all ages)

Goals

- Establish the incidence of sudden death in the young in the United States
- Investigate etiologies and risk factors for sudden death in the young

Multidisciplinary Approach

- The Family with Sudden Death
- Medical Examiner
- Family Physician
- Patients’ Support Groups
- Genetic Testing Labs
- Genetic Counselor
- Cardiologists/Neurologists
- Researchers
Focus on the Family

- Developing protocols and processes to include:
  - Saving appropriate samples
  - Consenting procedures focused on the family
  - Providing recommendations and referral information for family screening, genetic counseling and psychosocial support

SDY Case Information Collected

- Medical records
- Symptoms
- Previous serious injury
- Exercise
- Previous diagnoses
- Medications
- Family history
- Genetic testing
Challenges

• “...barriers exist. One is cost, but just as significant is the ability of the medical examiner to order the right test and communicate the results to the family of the deceased person.”
  – Arch Pathol Lab Med Vol 138 November 2014

Diagnostic Genetic Testing

Genetic testing to elucidate cause of death in autopsy negative cases for the Sudden Death in the Young (SDY) Case Registry:

A collaboration between Invitae, the Michigan Public Health Institute and the University of Michigan.

Process for Diagnostic Genetic Testing

1. If no cause of death determined through autopsy = autopsy negative
2. Family consented to diagnostic genetic testing option
3. gDNA sample meets minimum requirements
4. SDY Autopsy Summary or equivalent
5. SDY Field and Family Form or equivalent
6. Medical Examiner places online order with Invitae

Funded Researchers: Sudden Death in the Young Initiative

• Channelopathies and cardiomyopathies among sudden deaths in the young; PIs: Alfred George and Elizabeth McNally (Northwestern)
• Role of genetic variants in sudden death in the young; PI: Prince Kannankeril (Vanderbilt)
• Integrating genomic and clinical approaches to sudden death in the young; PIs: Martin Tristani and Mark Yandell (University of Utah)

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SDY Ethicists: Amy McGuire and Sonia Suter

Questions?

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