Plenary 7
Updates and Discussion on Select Programs in Mortality Research
June 26, 2106
9:15 a.m. - 10:15 a.m.
Moderator: Maggie Moore, MPH, Centers for Disease Control

Panelists:
- Samden Lhatoo, M.D., Case Western University
- Brandy Fureman, Ph.D., Epilepsy Foundation
- Tracy Dixon-Salazar, Ph.D., CURE
- Samuel Wiebe, M.Sc., M.D., FRCPC, International League Against Epilepsy
Plenary 7: Major Resources and Programs for Research in Epilepsy Mortality

Moderator: Maggie Moore, MPH
Centers for Disease Control and Prevention

JUNE 2016

Learning Objectives

Following participation in this activity, learners should be able to:
• Identify at least 5 organizations working in epilepsy mortality research.
• Describe select resources and programs related to epilepsy mortality research.
• Identify gaps in resources and programs related to epilepsy mortality research.

Panelists and Agenda

Panelists
Samden Lhatoo, MD, Case Western University
Brandy Fureman, PhD, Epilepsy Foundation
Tracy Dixon-Salazar, PhD, CURE
Samuel Wiebe, MSc, MD, FRCP, International League Against Epilepsy

Agenda
• Brief panelist presentations
• Audience questions
• Discussion

Disclosure
None
Learning Objectives

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

• Gain knowledge of the organization, infrastructure and scientific projects in the NINDS Center for SUDEP Research

www.sudepresearch.org
Goals

- To create a SUDEP risk index as a tool for all epilepsy patients so as to accurately determine individualized risk
- To further determine SUDEP mechanisms in order to pave the way for prevention
- To create a large SUDEP research database that contains phenotypic, genotypic, physiological (EEG, EKG, breathing, autonomic, biochemical) and imaging data.
- To mentor a new generation of researchers in SUDEP

Autonomic and Imaging Biomarkers of SUDEP

![Figure 3. Projected SUDEP events per year for every 4000 enrolled patients.](image)

Center for SUDEP Research

![Center for SUDEP Research](image)


Wandschneider and Diehl 2014
**Molecular Diagnostics Core**

PI and Core Director:
Alicia M Goldman, MD, PhD
Assistant Professor
Neurology
Baylor College of Medicine
Houston, Texas

http://codifiedgenomics.com/

**CORE GOALS**

- Molecular diagnostics of SUDEP cases and at risk patients with epilepsy
- SUDEP gene/variant research database
- Identify novel SUDEP genes and molecular biomarkers
- SUDEP Genetics Clinic

**Morphometric Core**

**MORPHOMETRIC CORE (MMC) GOALS**

SUDEP centered morphometric analytical network aimed to facilitate SUDEP brain collection and to correlate brain morphometric studies with clinical, electrophysiological, and autonomic investigations.

**SA 1:** Precision brainstem ANTEMORTEM morphometric analysis

(Dr. Susanne Mueller)


Troy 1983-2014
Left-Insular Damage, Autonomic Instability and SUDEP
Nuria Laccuyi1,2, Bilal Zonjy1, Wanchat Theerannaew1,2, Kenneth A. Loparo3, Curtis Tatsuoka3, Jayakumar Sahadevan4 and Samden D. Lhatoo1,2.

Neuropathology of SUDEP
Biomarkers & Physiology, Cortex & Brainstems
Maura Boldrini, MD, PhD
Columbia University School of Medicine
Orrin Devinsky, MD
NYU Langone School of Medicine
Maria Thom, MD
University College London

Biomarkers & Mechanism: The Neuropathology of SUDEP
• Link: biomarkers & mechanisms with surgical tissue, surgical tissue with postmortem tissue: correlate physiology to brainstem
• Potential Biomarkers of SUDEP Risk
  — Living – PGES, MRI, EKG, genetic, etc
  — Deceased – neuropathological (serotonergic & adenosine activity), cardiac pathology, genetic
• Understanding mechanisms of SUDEP
  — Pathophysiological autopsy

Cardiac Gene and Circuit Mechanisms
Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy (SUDEP)
Edward Dibyajyothi1, Jung W. Yoo1, Tim Y. Chen1, Tara L. Klassen1, and Jeffrey L. Wagshul
1Department of Neurology, Baylor College of Medicine, Houston, TX 77030
2Department of Neuroscience, Baylor College of Medicine, Houston, TX 77030
3Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030
4Arhythmia in Heart and Brain: KCNQ1 Mutations Link Epilepsy and Sudden Unexplained Death
A. M. Goldman, E. Grasseck, J. Yoo, T. T. Chen, T. L. Klassen, and J. L. Noebels
Department of Neurology, Baylor College of Medicine, Houston, TX 77030
Project: Center for SUDEP Research: Respiratory and Arousal Mechanisms

Project leader
George Richerson, MD, PhD
University of Iowa

Other personnel
Brian Gehlbach, MD
Mark Granner, MD
Gordon Buchanan, MD, PhD
Doug Nordli, MD (Lurie Children’s Hospital)

Project Goal: To define the neurobiological basis by which seizures cause respiratory arrest and post-ictal coma.

Scope: Adults (Iowa) and children (Lurie Children’s) with epilepsy; synergistic with animal experiments & Human Physiology Network

SA #1: Characterize interictal and ictal respiratory control and arousal in patients with Dravet Syndrome and other forms of epilepsy
SA #2: Determine the relationship between post-ictal respiratory depression and baseline central chemosensitivity as assessed by the inter-ictal hypercapnic ventilatory response (HCVR)
SA #3: Investigate the relationship between peri-ictal respiratory depression, the HCVR, and other clinical phenomena

iPSC and Mouse Neurocardiac Models

Control

DS

Number of Publications vs PUBMED search terms: Epilepsy, Sudden Death, SUDEP (1,319 hits)

Total vs CSR PI-Co-I publications for 2014-2015
Project Title: Electrical Disturbances in the Brain and Heart in LQTS: A Dangerous Synergy
PI: David Auerbach MD PhD
University of Rochester

Project Title: Role of S-HT in seizure-induced cardiorespiratory inhibition in two mouse models of SUDEP
PI: William P. Schilling, Ph.D.
Co-PI: Diana L. Kunze, Ph.D.
MetroHealth Hospitals and CWRU

Project Title: Combating SUDEP with HTR2C agonists
PI: Chen Liu PhD
UT Southwestern Medical Center

Project Title: Peri-ictal respiratory dysfunction: A multi-modality analysis of sleep and breathing in adults with pharmacoresistant epilepsy
PI: Nancy Foldvary-Schaefer MD
Cleveland Clinic Foundation

Project Title: High resolution heart and lung structural MR imaging of intractable epilepsy patients
PI: Chris Flask PhD
Case Western Reserve University
Mortality Research Programs: Perspective from the Epilepsy Foundation
Brandy Fureman, PhD
Epilepsy Foundation
JUNE 2016

Learning Objectives
Following participation in this activity, learners should be able to:
• Describe outcomes from the EF Targeted Program in Morbidity and Mortality, and other related programs
• Apply for the SUDEP Institute Biomarker Challenge

Mortality and Mortality in Epilepsy
• Targeted Grant Program:
  – 2015 Buchanan "NE and 5-HT in seizure-induced respiratory arrest and death"
  – 2014 Mueller "Brainstem atrophy: A SUDEP Biomarker"
• Fellowships/Career Development awards
• New devices supported in New Therapy Commercialization Grants, Shark Tank awards
• Research Roundtable in Epilepsy meeting May 19-20: "Reducing placebo exposure in epilepsy clinical trials"

SUDEP Institute Challenge Initiative: Predictive biomarkers of epilepsy seizures
• Level One Goal: identify human biomarker(s) that can predict and allow development of interventions for people at high risk of SUDEP (up to 10 prizes worth a total of $150,000)
Impact on Clinical Care and Practice

- Identify those at high risk
  - Act on modifiable factors: seizure control, safe sleep, wellness practices
  - Find targets for prevention
- Identify those at low risk
  - Reduce burden of fear for individuals and families

Director, SUDEP Institute and Targeted Programs

- Read the Position Description and Apply –
  http://www.epilepsy.com/director-sudep-institute-targeted-projects

Are you passionate about ending SUDEP?
- Can you drive a project forward?
- Can you rally diverse stakeholders to the cause?

We are looking for YOU!
Learning Objectives

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

• Understand CURE’s SUDEP Research Efforts

Our Mission

is to CURE epilepsy, transforming and saving millions of lives. We identify and fund cutting-edge research, challenging scientists worldwide to collaborate and innovate in pursuit of this goal. Our commitment is unrelenting.

1 in 26 Americans Will Develop Epilepsy in their Lifetime.

Research Programs for a CURE*

73% Investigator Directed Grants
20% Epilepsy Genetics Initiative
5% Epilepsy Epilepsy Etiology
2% Conference Support & Seminars
Efficiency of Expenditures*

More than 92% of CURE’s grant expenditures are spent on Seizure control research. This among the highest percentage of dollars awarded for research spent on Seizure control.

CURE has funded 204 grants

CURE EPILEPSY
CURE Funded Breakthroughs

- Respiratory arrest established as a leading cause of SUDEP and studies suggest this may be helped with caretaker intervention or use of serotonin reuptake inhibitors (SSRI).
- Revealed link between SUDEP and genes found in both the brain and heart.
- Funded SUDEP registries in Canada, Sweden and the U.S.
- Six new animal models of SUDEP now exist and are being extensively studied to further our understanding of the mechanisms that underlie SUDEP.
- Generalized tonic-clonic seizures have been established as a clear risk factor for SUDEP.
- Increases in SUDEP awareness and research funding overall.

SUDEP Awareness Metrics

- News Articles (Google Trends) 2004-2015
- News Articles (RePORTER) 2004-2015
- NIH SUDEP Funding History
- NIH SUDEP funding over time

SUDEP Awareness Metrics

- Children Death in Epilepsy Publications 1940-2015
- Publications per Year
- 0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500
- 0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000
- Source: NIH RePORTER
Impact on Clinical Care and Practice

- Patient organizations can significantly help advance the research efforts
Advocacy and Research Perspective
International League Against Epilepsy

Samuel Wiebe, MD, MSc
Executives Board, International League Against Epilepsy
University of Calgary, Canada

JUNE 2016

Disclosure

Served advisory boards:
- Electrocore
- Sunovion

Sponsored lecture and seminar:
- UCB

Learning Objectives

Following participation in this activity, learners should be able to discuss:
- Epilepsy burden of disease and mortality in global context
- Research/advocacy in non-US non-European countries
- Role of international organizations (ILAE) in research/advocacy

Lost years due to epilepsy (death + disability) per 100,000 people

Global cause of death 2012 – by income group

Global epilepsy research
Rest of the world


Source: global burden of disease, WHO 2012

PARTNERS AGAINST MORTALITY IN EPILEPSY

INTERNATIONAL LEAGUE AGAINST EPILEPSY
Vehicles for Advocacy – Education – Research

World View

INTERNATIONAL - REGIONAL Congresses, courses, workshops
Vehicles for Advocacy – Education – Research

Task Forces

MORTALITY, EPIDEMIOLOGY, THERAPEUTICS

Collaboration

INTERNATIONAL - REGIONAL Congresses, courses, workshops
Wikipedia

AWAWARENESS, EDUCATION, RESEARCH, CARE, EDUCATION

3 Journals

Epilepsia, Epileptic Disorders, Epilepsia Open

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