



2016 Abstracts

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#1

Title: Significance of sleep as a risk factor for SUDEP

Authors: Ahmer Ali, MD, Shasha Wu, MD PhD, Sandra Rose, MD, Naoum Issa, MD PhD, James Tao, MD PhD

Institution: University of Chicago

Rationale:

Sudden unexpected death in epilepsy (SUDEP) could preferentially occur in Sleep. However, the incidence of SUDEP occurred in sleep ranges widely from 25 to 95% among the published case studies. Our goal of this systemic review and meta-analysis is to determine a more accurate incidence of SUDEP that occurs in sleep, which may demonstrate the significance of sleep as a risk factor for SUDEP.

Methods:

We conducted a systematic review and meta-analysis based on a literature search from databases PubMed and Scopus, using keywords "SUDEP" or "sudden unexpected death in epilepsy" or "sudden unexplained death in epilepsy." Sixty seven publications met all inclusion and exclusion criteria and were included in this study.

Results:

Of the 895 cases of SUDEP in the 73 publications, 608 (67.93%) cases of SUDEP were found to have occurred in sleep (defined as those found in sleep, in bed or in the bedroom), whereas 287 (32.07%) cases of SUDEP that occurred in wakefulness. In a subset of 94 SUDEP patients who died in sleep with body position defined, there were 85 cases occurring in prone position, while 9 cases occurred in supine position and 5 in other positions.

Conclusions:

Our study demonstrates a robust association of sleep with SUDEP, which suggests that sleep might be a significant risk factor for SUDEP. Meanwhile, a significant number of these cases of SUDEP occurring in sleep also showed a strong association with prone position, which may have contributed the SUDEP risk associated with sleep.

#2

Title: The missing link: Seizure-related modulation of systemic arterial blood pressure in focal epilepsy

Authors: Kevin Hampel, Jahanbekam Amirhossein, Christian Elger, Rainer Surges

Institution: Department of Epileptology

Rationale:

Alterations of cardiorespiratory function are commonly observed with epileptic seizures and may lead to syncope and sudden unexpected death in epilepsy (SUDEP). Whilst most previous research has focused on control of heart activity and respiration, little is known about seizure-related regulation of systemic blood pressure (BP). We have investigated whether periictal modulation of systemic BP depends on seizure characteristics.

Methods:

Systemic arterial BP, heart rate (HR) and peripheral capillary oxygen saturation (SPO₂) were continuously and non-invasively monitored using the ccNexfin[®] device in people with epilepsy undergoing video-EEG telemetry. Data are given as mean±SD.

Results:

Forty-four seizures in 38 patients were included. In focal seizures (FS, n=36), mean arterial BP (MAP) increased by 33±34 % and HR by 53±43 %, whereas SPO₂ remained unaltered. Increases of MAP and HR were significantly greater in FS with alterations of consciousness than in those without. In FS evolving to bilateral convulsive seizure (BCS, n=10), all ictal recordings were compromised by artefacts. However, 2 min after seizure cessation MAP was enhanced by only 16±14 % and dropped slightly below preictal levels after 5 min, whereas HR was augmented by 77±33 % and remained elevated throughout the postictal phase.

Conclusions:

Periictal regulation of systemic BP and HR displays distinct patterns depending on the seizure type. In view of the possible drop of systemic BP, BP-monitoring in the early postictal phase following BCS seems to be advisable.

#3

Title: Caffeine and SUDEP: Benefits and Risks

Authors: Hai-Ying Shen¹, Teresa Straub², Marwan Huneidi¹, Wakaba Omi¹, Detlev Boison¹

Institution: Robert Stone Dow Neurobiology Laboratories¹ and Department of Integrative Physiology and Neuroscience²

Rationale:

Epileptic seizures trigger a surge of adenosine (ADO), which is an endogenous agent required for seizure termination. The adenosine surge may also contribute to cardiorespiratory functions in the brainstem by activation of different subtypes of adenosine receptor (AR). We hypothesized that a seizure-induced increase in ADO in combination with insufficient metabolic clearance of ADO in the brainstem can cause fatal over-activation of ARs leading to brainstem dysregulation, resulting respiratory and cardiac dysfunctions. In support of our hypothesis, we have previously used a kainic acid (KA)-induced acute seizure mouse model to demonstrate that SUDEP is due to overactivation of ARs in mice with pharmacologic ADO clearance deficiency. Caffeine, a non-selective AR antagonist and the world's most popular stimulant drug is reported as habitually used in about 80% of persons with epilepsy. The caffeine use may play a critical role in susceptibility and/or prevention of SUDEP.

Methods:

To evaluate whether caffeine use can protect from SUDEP or increase susceptibility to SUDEP, we report here the benefits and risks of caffeine on lethal outcome in two kainic acid (KA)-related seizure mouse models. An intrahippocampal KA (200ng)-injection followed by a 4-week incubation period was used to create epileptic mice, and cranial electrodes were installed during latent period for electroencephalograph (EEG) monitoring. All mice were subjected to daily caffeine (or vehicle) treatment via drinking water for 21 days, and EEG monitoring was conducted throughout caffeine-treatment till 3 weeks after caffeine withdrawal. Spontaneous mortality was calculated for SUDEP susceptibility of the period of acute caffeine, chronic caffeine, and caffeine withdrawal.

Results:

First, we evaluated the effect of acute caffeine administration on a KA-induced acute seizure mouse model combined with pharmacological ADO clearance deficiency. Our data showed that (i) while insufficient ADO metabolic clearance led to a lethal outcome in mice during seizures, acute caffeine administration after onset of seizure was able to prolong animal survival time. (ii) The benefit of caffeine during seizures was linked to counteracting seizure-related cardiac arrhythmia, demonstrated by electrocardiograph (EKG) monitoring. Second, we evaluated whether changes in caffeine consumption affects SUDEP susceptibility in chronic epileptic mice. Our data showed that (i) changes in caffeine consumption were linked to increased sudden death in epileptic animals, particularly during the periods of acute consumption (31.3%) and withdraw (28.6%) of caffeine. Conversely, chronic caffeine consumption was linked to a lower mortality (20%) in epileptic animals vs acute and withdraw of caffeine. (ii) EEG analysis demonstrated that acute caffeine significantly increased seizure-onset frequency and time-on-seizure; similarly, caffeine withdrawal led to a significant increase of time-on-seizure, albeit the seizure-onset frequency dropped down. (iii) However, in the chronic caffeine period the seizure-onset frequency dropped down to a level close to non-caffeine exposed mice, which is in line with its lower mortality (20%), compared to acute- and withdraw of caffeine.

Conclusions:

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Together, our findings suggest that acute inhibition of ARs via caffeine may protect against SUDEP whereas caffeine consumption habits can affect seizure phenotype and susceptibility of SUDEP.

#4

Title: Prone sleeping and SUDEP risk: the dynamics of body positions in non-fatal convulsive seizures

Authors: Sharon Shmuelly, MD¹; Rainer Surges, MD PhD²; Josemir W. Sander³; Roland D. Thijs, MD PhD¹

Institution: Stichting Epilepsie Instellingen Nederland (SEIN)¹, Department of Epileptology, University of Bonn, University Medical Center Bonn², NIHR University College London Hospitals Biomedical Research Center, UCL Institute of Neurology³

Rationale:

Most victims of sudden unexpected death in epilepsy (SUDEP) are found prone with signs suggestive of an unwitnessed convulsive seizure (CS). Prone sleeping has been proposed as a risk factor for SUDEP. Little is known, however, about the change of body position during the course of CSs.

Methods:

We retrospectively reviewed video EEG data and assessed body positions during the course of the CSs, until there was a physical interaction by nursing staff with the subject.

Results:

We identified 180 CSs in 90 individuals. In 16 of the 180 CSs (9%) the subject started in or turned to the prone position. Of the 7 CSs that started in prone position, 3 turned to a lateral position during the CS. In 13 CSs the subject was in prone position at time of nursing intervention; nine (69%) of these started in a non-prone position.

Conclusions:

Our data suggest that the prone position occurs rarely during non-fatal and closely supervised CSs, thus strengthening the association between prone position and SUDEP. Whether prone sleeping prior to CSs increases SUDEP risk, however, remains speculative as body position during the course of a CS appeared to be dynamic.

#5

Title: Postictal apnea is the primary cause of sudden death in a Dravet Syndrome mouse model.

Authors: YuJaung Kim, Eduardo Bravo, George Richerson

Institution: University of Iowa

Rationale:

Dravet Syndrome (DS) is an infantile-onset epilepsy with severe seizures commonly due to SCN1A mutations. DS patients have a high risk of SUDEP, but the mechanisms of death are not well defined. The recent MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) reported the largest series of SUDEP cases while in Epilepsy Monitoring Units (EMUs). Most cases occurred after a generalized seizure, and were associated with both cardiac and respiratory dysfunction. In DS mouse model, death occurs after spontaneous and induced seizures. This postictal death is likely to be relevant to the mechanisms of SUDEP in DS patients. EKG recordings from DS mice have shown that postictal death after heat-induced seizures is due to progressive bradycardia and asystole [Kalume et al, 2013]. Postictal bradycardia and death can be prevented in DS mice by pretreatment with atropine at a dose of 1 mg/kg, which has led to the conclusion that massive parasympathetic cardiac inhibition is the cause of death. However, postictal breathing has not been measured during experiments studying postictal death in DS mice, so it is unknown if respiratory dysfunction, such as central apnea, contributes to postictal death. Here we studied mice with an Scn1aR1407X/+ mutation to determine the role of respiratory dysfunction in postictal death after spontaneous and heat-induced seizures.

Methods:

Spontaneous and heat-induced seizures were induced in a mouse EMU while monitoring EEG, nuchal EMG, EKG, video, whole body plethysmography (breathing), body temperature, room temperature, and humidity. To induce seizures by hyperthermia, DS mice were exposed to a heat lamp to cause a continuous increase in body temperature to 43° C. To study death after spontaneous seizures, DS mice were continuously monitored in a mouse EMU for 24 hours per day until postictal sudden death spontaneously occurred.

Results:

When severe seizures with tonic extension were induced by hyperthermia, mice invariably had apnea followed by death. When terminal apnea occurred, EKG activity continued for 3-5 minutes with progressively worsening bradycardia followed by asystole. Two DS mice died after a spontaneous seizure while being monitored. In each case, the sequence of events was identical to that which occurred after heat-induced seizures. Death could be prevented after heat induced seizures by mechanical ventilation. Bradycardia and death could also be prevented with 1 mg/kg atropine, but at that dose seizures were not followed by apnea. When this experiment was repeated 2 days later, 1 mg/kg atropine did not prevent apnea or bradycardia. Atropine given at a dose of 0.03 mg/kg, which is known to be sufficient to block peripheral muscarinic receptors, and did prevent vagus nerve-mediated heart rate variability, did not prevent apnea, bradycardia or death. Exposure of wild-type mice to anoxia led to progressive bradycardia that was not prevented by 1 mg/kg atropine.

Conclusions:

We conclude that primary respiratory arrest can play an important role in death due to spontaneous and heat-induced seizures in DS mice with a Scn1aR1407X/+ mutation. In this case bradycardia and asystole are due to the hypoxia and hypercapnia that results from the apnea, and is not due to

parasympathetic inhibition of the heart. These data may lead to an understanding of SUDEP mechanisms in DS patients, as well as shed light on possible therapeutic approaches to prevent SUDEP.

#6

Title: Targeted Self-Management for Epilepsy and Mental Illness for individuals with epilepsy and psychiatric comorbidity

Authors: Martha Sajatovic, MD, Curtis Tatsuoka, PhD, Elisabeth Welter, MA, MSc, Adam Perzynski, PhD, Kari Colon- Zimmermann, Jamie Van Doren, BA, Ashley Bukach, BS, Mary Ellen Lawless, MA, RN, Eleanor Ryan, RN, ND, Katherine Sturniolo, BA candidate, Samden Lhatoo,

Institution: Case Western Reserve University School of Medicine, Neurological and Behavioral Outcomes Center

Rationale:

Serious mental illness is disproportionately common in people with epilepsy and contributes to complications and mortality. Few care approaches specifically target individuals who have epilepsy and severe mental illness. These investigators used an iterative process to refine an existing intervention and tested the novel intervention, Targeted Self-Management for Epilepsy and Mental Illness (TIME) in individuals with epilepsy and mental illness (E-MI).

Methods:

TIME was developed with input from a community advisory board and then tested for feasibility, acceptability and preliminary efficacy in people with E-MI, using a prospective randomized controlled design comparing TIME (N=22) vs. treatment as usual (TAU, N=22) over 16 weeks. Primary outcome was change in depressive symptoms, assessed by the Montgomery Asberg Depression Rating Scale (MADRS). Secondary assessments included global psychiatric symptom severity, seizure frequency, sleep patterns and quality of life. Exploratory mechanistic elements included evaluation of stigma, social support and self-efficacy.

Results:

There were 44 individuals enrolled, mean age 48.25 (SD = 11.82) with 25 (56.8%) African-Americans. The majority, (N=31, 70.5%), were unemployed and most (N=41, 95.5%) had annual income < U.S. \$25,000. With respect to study retention, there were 36 individuals (18 in TIME /18 in TAU) assessed at 12 weeks and 35 individuals (19 in TIME/16 in TAU) assessed at 16 weeks. There was a significant treatment by time interaction effect for MADRS ($p=0.036$; effect size of 0.70), with lower MADRS at 16 weeks in TIME, while TAU MADRS did not change. Differences between most secondary measures were not statistically significant.

Conclusions:

The TIME intervention engages individuals to actively participate in self-management, and can reduce depression in people with E-MI. Given the high morbidity and mortality associated with epilepsy complicated by serious mental illness, additional research is needed to better identify how TIME might be implemented in routine care settings.

#7

Title: Occurrence of central ictal apnea in temporal lobe seizures is independent of seizure spread and laterality of seizure onset: a case study

Authors: Rup Sainju, MD, Brian Gehlbach, MD, Mark Granner, MD, George Richerson, MD, PhD

Institution: University of Iowa

Rationale:

Severe peri-ictal respiratory abnormality is hypothesized to be responsible for sudden unexpected death in epilepsy (SUDEP) in some cases. Ictal apnea is thought to be associated with spread of seizure to bilateral temporal regions or with secondary generalization. Here we report the results of comprehensive respiratory monitoring in a patient with drug resistant epilepsy undergoing video electroencephalography (EEG) monitoring who had ictal apnea without evidence of bilateral temporal spread or generalization.

Methods:

A 60-year-old right handed man was admitted to the Epilepsy Monitoring Unit (EMU) for video-EEG monitoring as part of pre-surgical evaluation for drug resistant epilepsy. We used standard 10-20 scalp EEG recording with the addition of bilateral sphenoidal electrodes and Silverman's electrodes (T1/T2). We also measured transcutaneous carbon dioxide (tcCO₂) and pulse oximetry (SpO₂), along with chest and abdominal respiratory inductance plethysmography (RIP), nasal airflow and oral thermistry. Bradypnea was defined as reduction in respiratory rate by 20% or more compared to a baseline measured two minutes prior to EEG seizure onset. Apnea was defined as absence of significant nasal airflow and RIP changes for 10 seconds or more.

Results:

Video EEG study confirmed temporal lobe epilepsy with bilateral, independent interictal epileptiform discharges and temporal seizures. A total of 5 complex partial seizures (3 left temporal & 2 right temporal) with distinct semiology depending on laterality were recorded. Bradypnea and/or apnea was noted as long as 65 seconds prior to any ictal EEG changes. These respiratory changes were the first clinical manifestation during all seizures, and were independent of seizure laterality or seizure generalization.

Conclusions:

We conclude that changes in breathing can occur before any other apparent ictal manifestations and don't require seizure spread to the contralateral hemisphere.

#8

Title: Deficits of 5-HT-Mediated Arousal Are Implicated in Seizure-Induced Respiratory Arrest

Authors: Hua-Jun Feng, Honghai Zhang, Haiting Zhao, Chang Zeng, Christa Van Dort, Carl Faingold, Norman Taylor, Ken Solt

Institution: Massachusetts General Hospital and Harvard Medical School

Rationale:

The DBA/1 mouse exhibits seizure-induced respiratory arrest (S-IRA) leading to death after generalized tonic-clonic seizures, and is an animal model of sudden unexpected death in epilepsy (SUDEP) observed in humans. Studies suggest that deficits in serotonergic (5-HT) neurotransmission contribute to S-IRA. 5-HT transmission plays an important role in modulating respiration and arousal, and our previous studies indicate that 5-HT-mediated arousal may be importantly involved in S-IRA. 5-HT neurons in the brainstem dorsal raphe (DR) mediate the arousal response. Thus, we hypothesized that a deficiency of 5-HT neurotransmission in the DR contributes to S-IRA in DBA/1 mice.

Methods:

Transgenic DBA/1 mice with 5-HT neurons selectively expressing ChR2 (TPH2-ChR2) (referred as transgenic DBA/1 mice below) were created by backcrossing the available hemizygous C57 TPH2-ChR2 mice (The Jackson Laboratory) with wild type DBA/1 mice using marker-assisted accelerated backcrossing (MAX-BAX, Charles River Laboratories). These transgenic DBA/1 mice have the same genetic background as wild type DBA/1 mice and display similar seizure pattern and incidence of S-IRA to wild type DBA/1 mice. A fiberoptic cannula was implanted through the calvarium over the DR (-4.47 mm AP, 0 mm ML, -3.5 mm V). Generalized seizures were induced either by acoustic stimulation using an electric bell (96 dB SPL) or by pentylenetetrazole (PTZ, 75 mg/kg, i.p.). The effect of photostimulation (blue light, 20 ms pulse duration at 20 Hz) of 5-HT neurons in the DR on S-IRA evoked by audiogenic seizures (AGSz) or PTZ was examined. Coupling of photostimulation with a precursor for 5-HT synthesis (5-hydroxytryptophan, 5-HTP) or a 5-HT₃-receptor antagonist (ondansetron, OND) was used to confirm the involvement of 5-HT in S-IRA reduction by photostimulation.

Results:

Photostimulation on 5-HT neurons in the DR at 9 mW for 15 min significantly reduced the rate of S-IRA from 100% (evoked by AGSz without photostimulation) to 6.7% in transgenic DBA/1 mice ($p < 0.001$, $n = 15$), and susceptibility of these mice to AGSz returned 24-72 hr after photostimulation. Increasing the energy level to 15 mW significantly and reversibly suppressed S-IRA evoked by AGSz with a shorter duration of photostimulation at 5 min ($p < 0.01$, $n = 6$). Compared with S-IRA evoked by PTZ without photostimulation (83.3%, $n = 6$), photostimulation at 9 mW for 15 min significantly reduced S-IRA evoked by PTZ in transgenic DBA/1 mice (16.7%, $n = 6$) ($p < 0.05$). Optogenetic activation of DR with the same stimulation parameters produced no effect on S-IRA in siblings of transgenic DBA/1 mice that have no ChR2 expression in DBA/1 mice ($n = 6$). While photostimulation of DR at 9 mW for 10 min exerted no effect on S-IRA (100%), pre-treatment with 5-HTP (50 mg/kg, i.p., once daily for two days), which alone produced no effect on S-IRA, significantly reduced S-IRA by photostimulation (9 mW, 10 min) ($p < 0.05$, $n = 6$). Pre-treatment with OND, at a dose (2 mg/kg, i.p.) that alone had no effect on S-IRA, significantly reversed S-IRA reduction by photostimulation (9 mW, 15 min) ($p < 0.05$, $n = 6$).

Conclusions:

Our studies demonstrated that enhancement of 5-HT neurotransmission by activating 5-HT neurons using optogenetics significantly suppresses S-IRA evoked by either acoustic stimulation or PTZ in transgenic DBA/1 mice. These findings suggest that deficits in 5-HT-mediated arousal are involved in S-IRA in DBA/1 mice.

#9

Title: Center for SUDEP Research: Morphometry Core/Pre-mortem Imaging: Preliminary Results

Authors: Lisa M Bateman, M.D, Susanne Mueller, MD, Maromi Nei, M D, Alica Goldman, MD

Institution: Columbia Comprehensive Epilepsy Center

Rationale:

The causes of sudden unexplained death in epilepsy (SUDEP) are still unknown but the respiratory and cardiac symptoms observed in witnessed cases suggest that a breakdown of the central autonomic control system plays an important role. A pilot study using quantitative image processing found evidence for brainstem damage in regions involved in autonomic control in the MRIs of two patients who later died of SUDEP that significantly exceeded the brainstem damage occasionally seen in other epilepsy patients. This indicates that it might be possible to use MRI to identify patients with a heightened risk for SUDEP. The purpose of the pre-mortem imaging project of CSR Morphometry Core is further investigate this possibility. This is done by obtaining and analyzing MRIs obtained for clinical purposes from patients who died of SUDEP. In contrast to MRIs acquired in research settings where all factors influencing quantitative image processing are strictly controlled, MRIs acquired in clinical settings are acquired on different MR platforms with different protocols and sequences. The second aim of this project is therefore to test to what degree quantitative analysis methods used in research settings can be used to process clinical data and to develop clinical imaging protocols suitable for quantitative imaging analysis and clinical needs.

Methods:

24 whole brain T1 weighted images of 10 patients (mean age: 29.7 ± 14.0 , range 12 – 59 years) who died of SUDEP within 1-9 years after the last MRI (mean 3.3 ± 2.2 years). 2 patients had several exams within a short period of time with allowing to assess the effects of different platforms, different field strength, sequences, contrast injection and noise on the detectability of brainstem lesions. Freesurfer was used generate a mask encompassing brainstem, cerebellum and thalamus/diencephalon for each that was used to extract the regions of interest. The shot toolbox from SPM12 was used to warp the brainstem images onto a brainstem atlas that had been generated from the MRIs of healthy controls who had undergone 3T MRI in a research setting. The deformation matrices were used to calculate age and ICV adjusted z-score maps of the Jacobian determinants. The resulting maps were visually inspected for volume loss (z-score ≤ -0.5) in the thalamus/diencephalon, at the level of the pontomesencephalic junction, mid pons, pontomedullary junction, medulla, lower medulla

Results:

Cerebellar and thalamic atrophy was seen in all patients and followed the pattern commonly seen in epilepsy patients. Brainstem atrophy was also found in all patients. It was most commonly found in the medulla (9/10) followed by the ponto-medullary and the ponto-mesencephalic junction with the latter showing more severe abnormalities than the former. Image noise (motion or accelerated acquisition), sequence type and field strength influenced the severity of the volume loss but not its distribution. Gadolinium injection not only changed the severity but also the distribution.

Conclusions:

These preliminary findings suggest that it is possible to use MRI acquired for clinical purposes for quantitative image analysis. However, due to the different contrast to noise behavior of the different sequences, it is necessary to assess the atrophy pattern rather than to use absolute values as it is done in images acquired in research settings. The atrophy pattern found in this data set was similar than that found in the pilot study, i.e., the most prominent findings were in the tegmentum/ponto-mesencephalic junction and ponto-medullary junction that contain structures involved in autonomic control.

#10

Title: Knowledge of SUDEP Among Pediatricians in Virginia

Authors: Madison Berl, PhD¹, Adrian Bumbut, MBA¹, Barbara Kroner, PhD², William Gaillard, MD¹, Howard Goodkin, MD, PhD³

Institution: Children's National Health System¹, RTI International², University of Virginia³

Rationale:

Neurologists are aware of the risk of mortality in epilepsy yet a minority of neurologists discuss SUDEP with all of their patients (Friedman et al., 2014). Our objective was to determine knowledge of SUDEP among primary care physicians (PCPs). We hypothesized that a minority of the sample would be aware of SUDEP and even less would discuss the topic with families.

Methods:

An electronic web-based survey was sent to 60 academic and private pediatricians and family practice physicians within the greater Charlottesville, Virginia region. The survey was comprised of 17 questions that took less than 10 minutes to complete. Questions included whether PCPs treat patients with epilepsy, are familiar with the term SUDEP and its risk factors, are aware that children and adolescent with epilepsy were at a higher risk of mortality, and expect that a pediatric neurologist will discuss seizure precautions and epilepsy comorbidities with their patients. At the end of the survey, respondents were provided online resources for SUDEP education. Descriptive statistics were calculated.

Results:

Forty-three (72%) surveys were completed. Experience ranged from 0-35 years post-residency with an average of 18 years. The majority were pediatricians (70%) with other being general or nurse practitioners and one pediatric emergency medicine doctor. Forty-two percent were private practitioners, 37% practiced in an academic setting, and 21% practiced in a medical center. Seventy percent described their practice setting as suburban, 13% as urban and 7% as rural. Ninety-three percent followed at least one patient with epilepsy; most (65%) had fewer than 10 patients with epilepsy. None had a patient die from definite or probable SUDEP. The majority (77%) was not familiar with the term SUDEP, and 86% were exposed to the definition for the first time because of the survey. None had had formal education on the topic of SUDEP, 70% were unaware that children with epilepsy were at higher risk of mortality, and 74% indicated they did not know the risk factors for SUDEP. None had ever discussed SUDEP with a patient or caregiver but 76% discussed other seizure risk factors/lifestyle modifications. Eighty-three percent expect that the patient's neurologist will discuss SUDEP with all patients with epilepsy. The majority (93%) believes that learning more about SUDEP is relevant to their practice and preferred a variety of formats (i.e., lecture, web-based, journal articles).

Conclusions:

In a community of PCPs whom almost all treat children with epilepsy, SUDEP is a largely unknown risk, and is therefore not discussed despite discussing other risk factors of epilepsy. PCPs expect that neurologists are discussing these risks with their patients. We identified a knowledge gap among PCPs regarding their knowledge of SUDEP, were able to briefly educate them about the risk by giving them their first exposure, and subsequently, they endorsed that learning more about SUDEP is relevant to their practice. Future work will expand the survey to other PCPs to determine if knowledge is different in other settings. In addition, we plan to develop educational modules and evaluate its impact on care.

#11

Title: Methyl-CpG binding-protein 2 function in cholinergic neurons mediates cardiac arrhythmogenesis
Authors: Jose Herrera, PhD¹, Christopher Ward, PhD², Xander Wehrens, MD PhD¹, Jeffrey Neul, MD PhD²
Institution: Baylor College of Medicine¹, University of California San Diego²,

Rationale:

Rett Syndrome is an X-linked neurodevelopmental disorder that is nearly always caused by loss of function mutations in Methyl-CpG-binding protein 2 (MECP2). The protein product, MeCP2, functions to regulate transcription both in as a repressor and activator of transcription. Loss of MeCP2 function leads to a complex array of neurological symptoms including developmental regression, difficulty walking, repetitive meaningless hand movements, seizures, breathing abnormalities, and a variety of autonomic problems including cardiac abnormalities. Nearly 20% of individuals with RTT have a cardiac conduction defect known as QT interval prolongation, or long QT (LQT). Furthermore, there have been case reports of severe sinus bradycardia, AV block, and possible lethal ventricular tachyarrhythmias (VT). However, the etiology of the cardiac phenotypes in RTT remains to be investigated.

Methods:

To explore the role of cardiac problems in sudden death in RTT, we characterized cardiac rhythm in mice lacking Mecp2 function. The cardiac phenotype of knockout and conditional KO mice was characterized using telemetry, surface electrocardiograms, and intracardiac programmed electrical stimulation.

Results:

Male and female mutant mice exhibited spontaneous cardiac rhythm abnormalities including bradycardic events, sinus pauses, atrioventricular block, premature ventricular contractions, non-sustained ventricular arrhythmias, and increased heart rate variability. Death was associated with spontaneous cardiac arrhythmias and complete conduction block. Atropine treatment reduced cardiac arrhythmias in mutant mice, implicating overactive parasympathetic tone. To explore the role of MeCP2 within the parasympathetic neurons, we selectively removed MeCP2 function from cholinergic neurons, which recapitulated the cardiac rhythm abnormalities, hypothermia, and early death seen in RTT male mice. Conversely, restoring MeCP2 only in cholinergic neurons rescued these phenotypes.

Conclusions:

MeCP2 in cholinergic neurons is necessary and sufficient for autonomic cardiac control, thermoregulation, and survival, and targeting the overactive parasympathetic system may be a useful therapeutic strategy to prevent sudden unexpected death in RTT.

#12

Title: Intracranial Electroencephalographic (EEG) Correlates of Surface Postictal Generalized EEG Suppression (PGES)

Authors: Luisa Londoño-Hurtado, Aman Dabir, Bilal Zonjy, Curtis Tatsuoka, Samden Lhatoo

Institution: UH Case Medical Center

Rationale:

To determine the correlation between surface PGES and intracranial EEG suppression, since intracranial EEG is a more accurate measure of neuronal activity, in patients with generalized tonic-clonic seizures. To determine seizure factors which influence the degree and duration of surface and intracranial EEG suppression in patients with generalized tonic-clonic seizures.

Methods:

We studied patients recruited to the Prevention and Risk Identification of SUDEP Mortality (PRISM) Project and its follow on study of Autonomic and Imaging Biomarkers of SUDEP who had undergone invasive presurgical evaluations, and had simultaneous surface and bihemispheric intracranial EEG recordings of seizures. Intracranial electrodes sampling grey matter were compared to surface EEG, measuring onsets and offsets of seizure phases, EEG suppression and EEG burst suppression, using amplitude criteria of 10uV (surface), 50uV and 100uV (intracranial). Statistical significance was tested using one-sample Wilcoxon Signed Rank.

Results:

86 generalized tonic clonic seizures in 42 patients were identified. 36(41%) seizures had either surface PGES (n=28, 78%), intracranial EEG suppression (n=32, 89%) or both (n=24, 67%). Mean PGES duration was 19.58 seconds for the intracranial EEG (50uV), 25.85 seconds for intracranial EEG(100uV) and 29.83 seconds for scalp. Surface PGES and intracranial suppression durations were significantly different at 50uV (p=0.019), but not at 100uV (p=0.526). Surface PGES/intracranial EEG suppression onsets and offsets (100uV) were not significantly different (p=0.078, p=0.356 respectively). However, surface PGES/intracranial EEG suppression offset using the 50uV criterion was significantly different (p=0.038). We also studied the EEG burst suppression pattern that follows PGES. There was no significant difference between surface and intracranial burst suppression durations (P=0.754).

Conclusions:

Our study shows that in 11% of seizures, surface PGES can occur without true generalized intracranial EEG suppression. Unsuppressed intracranial EEG was seen in very restricted locations such as the hippocampus, a closed field that does not appear on surface EEG. In such patients therefore, PGES does not mean true “electrocerebral shutdown”. However, in the majority (67%), surface PGES appears to reflect true generalized intracranial EEG suppression. Intracranial suppression of all brain activity to below 50uV criterion did not correlate with surface PGES suggesting that profound suppression of neuronal activity is not well reflected on surface EEG. This population may be at greatest risk of SUDEP. Our findings suggest that surface PGES is a nuanced phenomenon and reflects heterogeneity in intracranial neuronal activity, or lack thereof, in the post seizure phase.

#13

Title: Long term ECG recordings in refractory focal epilepsy: an interim analysis

Authors: Marije van der Lende, MD¹, Johan Arends, Prof, MD, PhD², Arnaud Aerts, MD³, Henk Swart, MD⁴, Roland Thijs, MD, PhD¹

Institution: Stichting Epilepsie Instellingen Nederland (SEIN)¹, Kempenhaeghe², Zuyderland Medical Center³, Antonius Ziekenhuis⁴

Rationale:

Postictal asystole and ventricular tachycardia/fibrillation (VT/VF) may contribute to SUDEP. Ictal arrhythmias seem rare during ictal EEG recordings, but it is yet unknown how often these arrhythmias occur during long term follow up. Two small-sized studies (n=19) using long term ECG monitoring yielded conflicting results: 5% versus 21% of subjects had asystole. To determine the usefulness of long term ECG recordings we assessed the two-year prevalence of all clinically relevant arrhythmias in refractory focal epilepsy.

Methods:

We recruited people with focal refractory epilepsy with at least one seizure per month and implanted a cardiac loop recorder (Reveal XT) with two year follow up. The devices automatically record arrhythmias. Subjects and their caregivers were instructed to make additional recordings during or immediately after seizures. We here report our interim results, focusing on the following arrhythmias: asystole, atrial fibrillation, supraventricular tachycardia and VT/VF.

Results:

We included 49 people, mean age 42 years (SD 12.2), with focal epilepsy and recorded over 560.000 patient hours. Over 8000 seizures were reported, the subjects managed to make additional recordings in 3286 of these seizures. Three people had an asystole: two subjects had one asystole and one subject eleven. All asystoles lasted < 6 seconds and were not reported to coincide with a typical seizure. All were considered benign and none of the subjects received a pacemaker. A supraventricular tachycardia was seen in one subject and atrial fibrillation in two. No events with VT/VF were identified.

Conclusions:

This interim analysis shows a very low yield of clinically relevant cardiac arrhythmias in subjects with high SUDEP-risk. These data do not seem to support the routine use of implantable loop recorders in refractory focal epilepsy.

#14

Title: Vigilance state dependent regulation of cardio-respiratory effects and death following maximal electroshock induced seizures in mice

Authors: Gordon Buchanan, MD, PhD¹, Michael Hajek²

Institution: University of Iowa¹, Yale School of Medicine²

Rationale:

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy. SUDEP tends to occur at night, but whether this is a simply a coincidence, or whether this speaks to a specific circadian-dependent or sleep state-dependent mechanism is unknown. Respiratory and cardiac arrest are the most commonly implicated etiologies for SUDEP. Control of both breathing and cardiac function are subject to circadian and sleep state-dependent regulation. Seizures themselves are modulated in a sleep state- and circadian-dependent manner. Here we set out to determine whether there are circadian and/or state-dependent effects of seizures on respiratory and cardiac function that contribute to seizure-related death.

Methods:

EEG, EMG and EKG electrodes were implanted in adult male mice. Seizures were induced with maximal electroshock (MES; 50 mA, 200 ms, 60 Hz) during wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep during mid-day and mid-night and EEG, EMG, EKG, and breathing were assessed. Vigilance state was determined on-line in real time based on EEG and EMG characteristics using standard parameters.

Results:

Seizures that occurred during sleep were more likely to be fatal, especially those induced during REM, and those induced during the daytime. In all instances, death ensued due to primary respiratory arrest. Non-fatal seizures induced during NREM were associated with longer duration post-ictal respiratory suppression, reduced ventilation, and increased respiratory rate variability compared to those induced during waking. All mice died when seizures were induced during REM sleep, therefore this analysis could not be conducted for REM sleep. In addition, there was increased baseline variability in the respiratory rhythm in mice that died compared to those that survived.

Conclusions:

These data indicate that seizures that occur during sleep, especially during the circadian phase associated with less activity, can have detrimental effects on breathing which may contribute to increased seizure related death.

#15

Title: Autonomic dysfunction and increased arrhythmogenic potential in mice following status epilepticus

Authors: Amber Levine¹, An Dao, PhD¹, Yi-Chen Lai, MD², Heather Born, PhD¹, Anne Anderson, MD²

Institution: Baylor College of Medicine¹, Baylor College of Medicine and Texas Childrens Hospital²

Rationale:

Status epilepticus (SE) is a prevalent disorder, which is associated with significant morbidity, including the development of epilepsy, and mortality. Studies indicate that lethal cardiac arrhythmias contribute to death following SE as well as sudden unexpected death in epilepsy (SUDEP). A wide range of potentially lethal cardiac arrhythmias (i.e. tachycardia, bradycardia, asystole, and atrioventricular blocks) are observed in patients and are indicative of underlying autonomic dysfunction. Tachycardia is the most commonly reported seizure related to arrhythmia but asystole and bradycardia have also been observed and predominantly occur ictally in people with temporal lobe epilepsy (TLE). Numerous studies have described autonomic nervous system imbalance during ictal and postictal periods but less is understood about autonomic function during interictal periods. We sought to understand autonomic changes following SE by monitoring cardiac electrical activity in a chemoconvulsant mouse model of TLE.

Methods:

Kainate is a glutamate analog which causes hyperexcitation in neurons. Intrahippocampal administration of kainate results in SE, followed by the development of chronic, spontaneous recurring seizures (epilepsy) that are associated with hippocampal neuron loss and mossy fiber sprouting and closely model what occurs in humans with TLE. Male C57BL6J mice were anesthetized with isoflurane and placed on a stereotaxic apparatus for implantation of a guide cannula and electrodes at 2-4 months of age. The guide cannula was placed into the hippocampus for the administration of kainate in a freely moving and awake animal. To simultaneously investigate alterations in electrocardiography (EKG) and video synchronized electroencephalographic (vEEG) signals following SE, six electrodes were implanted. One recording and one reference electrodes were placed on the chest to monitor EKG. Three other electrodes were implanted to record hippocampal and cortical EEG activity with vEEG. After a week of recovery, mice were recorded continuously for baseline EKG and vEEG activity. Then, animals received saline or kainate via the intrahippocampal cannula and monitored for another two weeks.

Results:

Recordings showed ictal bradycardia and post-ictal tachycardia, which had been described in other mouse models of SE, as well as humans. Interictally, no changes were seen in heart rate, R-R interval, QTc interval, and PR interval between saline and kainate treated animals. However, SE animals exhibited decreased interictal beat-to-beat variability of QTc and decreased PR intervals respectively for the full two weeks of monitoring after SE or until a death event. Sinus pause with a junctional escape beat, premature ventricular contractions, accelerated ventricular rhythm, and atrioventricular blocks were observed interictally following SE during sleep. Additionally, death events were captured and showed seizure related increases in beat-to-beat variability in the R-R, QTc, and PR intervals preceding death.

Conclusions:

Our mouse model recapitulates changes that are observed in human TLE. Although average values for heart rate, R-R interval, QTc interval, and PR interval showed no difference interictally between saline and kainate treated animals, the potentially lethal arrhythmias observed (e.g. sinus pause with a junctional escape beat, premature ventricular contractions, accelerated ventricular rhythm, and atrioventricular blocks) and beat-to-beat variations in R-R, QTc, and PR intervals indicate autonomic dysfunction not only ictally but also interictally. Interestingly, the arrhythmias were observed most commonly during sleep and more than half of all cases of SUDEP are reported to occur during sleep. Further research into the mechanisms of autonomic dysfunction following SE may be fruitful in providing greater understanding as well as treatments to prevent future cases of SUDEP.

#16

Title: Cardiorespiratory dysfunctions and sudden death in two mouse models of intractable epilepsy

Authors: Angela Bard, BS¹, Nikhil Sahai, BS¹, Sarah Hanna, BS¹, Jonathan Skibo, BS¹, Achira Roy, PhD¹, Kathleen Millen, PhD¹, Jan Ramirez, PhD², Franck Kalume, PhD²

Institution: Seattle Children's Research Institute¹, Seattle Children's Research Institute/UW²

Rationale:

Sudden unexpected death in epilepsy (SUDEP) is the most common type of death in people with intractable epilepsies associated with cognitive impairment. These life-threatening epilepsies include epilepsy associated with focal cortical dysplasia (FCD) and Dravet syndrome (DS). FCD is a developmental disorder with early childhood onset marked by intractable seizures. Recent genetic studies have uncovered that FCD type IIa is linked with missense gain-of-function mutations in PIK3CA, a critical gene involved in development and cancer. DS is an intriguing treatment-resistant epilepsy with infantile-onset and has one of the highest rates of SUDEP. DS is often caused by heterozygous loss-of-function mutation in SCN1A, the gene encoding NaV 1.1 channels. Cardiovascular dysfunctions have been identified as the main causes of SUDEP. We conducted a dual examination of cardiac and respiratory functions during interictal, ictal, and post-ictal periods to identify and characterize biomarkers of SUDEP susceptibility in a mouse model of FCD (carrying a gain-of-function mutation in *Pik3ca*) and that of DS (harboring a heterozygous knock out of *Scn1a*).

Methods:

Combined video-EEG-ECG and whole body plethysmograph were recorded from freely moving genetic mouse models of DS, FCD, and respective controls using fine silver wire electrodes. Signals were acquired on a Power Lab 8/35 using LabChart Software 8.0 (AD Instruments) during Interictal, ictal, and postictal periods.

Results:

In DS mice (n=6), our previous studies showed a substantial suppression of resting heart rate variability, increased frequency of AV blocks, and no change in resting heart rate (HR). In these studies, we observed suppressed respiratory responses to hypercapnia ($60 \pm 8\%$), hypoxia ($48 \pm 5\%$), and anoxia ($31 \pm 6\%$) in DS mice (n=6) compared to WT (n=9). In addition, these mice exhibited concurrent transient bradycardia and bradypnea during the tonic phases of thermal generalized tonic clonic seizures. Mice carrying DS-causing mutation in GABAergic interneurons alone, not excitatory neurons, revealed similar ictal and interictal dysregulations of cardiorespiratory functions. In FCD mice, resting interictal recordings also showed a decreased in HRV, but accompanied with increase in HR and absence of AV blocks. Respiratory recordings showed blunted respiratory responses to hypercapnic ($80 \pm 9\%$), hypoxic ($60 \pm 8\%$), and anoxic ($30 \pm 7\%$) conditions compared to controls (n=6). These defects were comparable to those of DS mice. Furthermore, PTZ-induced seizures caused similar but less severe simultaneous brief bradypnea and bradycardia, analogous to those of DS mice.

Conclusions:

These results suggest that regardless of the etiology of epilepsy, seizures cause similar cardiorespiratory dysfunctions leading to SUDEP. In addition, GABAergic interneurons are implicated in the mechanisms of SUDEP. Understanding the cellular and network mechanisms underlying these physiological dysfunctions may lead to better therapeutic methods for SUDEP prevention.

#17

Title: Dravet Syndrome patient-derived induced pluripotent stem cell cardiac myocytes may predict SUDEP risk

Authors: Chad Frasier, PhD¹, Helen Zhang, MS¹, James Offord, PhD¹, David Auerbach, PhD², Jack Parent, MD¹, Lori Isom, PhD¹

Institution: University of Michigan¹, University of Rochester²

Rationale:

Dravet syndrome (DS) is a severe and intractable pediatric epileptic encephalopathy that is largely caused by de novo loss-of-function mutations in the voltage-gated sodium channel gene SCN1A. Up to 17% of DS patients undergo Sudden Unexpected Death in Epilepsy (SUDEP), a major concern for patients and their families. Proposed mechanisms of SUDEP include seizure-induced apnea, pulmonary edema, dysregulation of cerebral circulation, autonomic dysfunction, and cardiac arrhythmias. Our previous work in mouse cardiac myocytes demonstrated increased transient and persistent sodium current (I_{Na}) density resulting from increased activity of a tetrodotoxin-resistant sodium channel, likely Nav1.5. DS cardiac myocytes also exhibited increased excitability, action potential prolongation, and early afterdepolarizations (an arrhythmogenic substrate). Continuous radiotelemetric electrocardiogram recordings in DS mice showed QT prolongation, ventricular ectopic foci, idioventricular rhythms, beat-to-beat variability, ventricular fibrillation, and focal bradycardia. Taken together, these data suggested that cardiac arrhythmias may contribute to SUDEP in DS patients. However, because of known significant differences between mouse and human cardiac action potentials, it was critical to test this hypothesis in a human model. The purpose of this study was to investigate changes in excitability of DS patient-derived induced pluripotent stem cell cardiac myocytes (iPSC-CMs) compared to non-epileptic controls, with the long-term goal of predicting abnormal cardiac excitability, and thus SUDEP risk, DS patients.

Methods:

To test whether cardiac excitability is altered in DS patients, we generated induced pluripotent stem cells (iPSCs) from two control patients and four DS patients with distinct mutations in SCN1A. iPSC neurons were tested previously from one of these DS patients and found to be hyperexcitable with increased I_{Na} density. For the present work, we differentiated iPSCs into cardiac myocytes (iPSC-CMs). Immunofluorescence staining showed that iPSC-CMs were positive for multiple cardiac markers, including MLC2a, MLC2v, nkx2.1, and Nav1.5.

Results:

DS iPSC-CMs showed increased intrinsic beating rates compared to controls ($P < 0.05$, $N \geq 8$ per group). Multielectrode array analysis confirmed that the beat period, the time between beats, was decreased in DS iPSC-CMs vs controls. No differences were observed in the field potential duration, which is a correlate of action potential duration. Consistent with our previous studies in DS mice, we observed a ~two-fold increase in peak I_{Na} in iPSC-CMs from 3 of the 4 DS patients ($P < 0.05$, $N \geq 9$ per group). I_{Na} density from the remaining patient, DS5, was ~3 fold higher than controls. Because of the high level of I_{Na} density recorded in DS5 iPSC-CMs, we recommended a cardiac workup. The patient presented with sinus tachycardia and repolarization abnormalities that are now being closely monitored.

Conclusions:

Our data suggest that alterations in cardiac myocyte excitability contribute to the mechanism of SUDEP via increased I_{Na} density, which may underlie cardiac arrhythmia, in DS patients. DS patient-derived iPSC-CMs provide a valuable model for advancing our knowledge of how changes in cardiac myocyte excitability contribute to the mechanism of SUDEP and may provide novel biomarkers for SUDEP risk.

#18

Title: Effects of vigilance state and genetic elimination of serotonin neurons on seizure susceptibility and the cardio-respiratory impact of seizures in two mouse models of epilepsy

Authors: Benton Purnell¹, Kumiko Claycomb, PhD², Stephen Kruse¹, Gordon Buchanan, MD, PhD¹,

Institution: University of Iowa¹, Yale School of Medicine²

Rationale:

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with chronic refractory epilepsy. SUDEP tends to occur at night, but the mechanisms of how this happens are unknown. We recently demonstrated in an acute seizure model, maximal electroshock seizures (MES), that vigilance state can impact seizure propensity, seizure severity, effects of seizures on breathing and whether or not a seizure will be fatal. We also previously showed in the same model that serotonin can influence these measures. The MES model is a model of acute seizures in a seizure-naïve brain, and not a model of epilepsy per se. Here we aimed to determine whether there is similar influence of vigilance state and serotonin on seizure susceptibility, severity, survival, and cardio-respiratory consequences of seizures in two established models of epilepsy in which the brain is rendered hyperexcitable – amygdala kindling and pilocarpine-temporal lobe epilepsy.

Methods:

EEG, EMG and EKG electrodes were implanted in adult male wildtype (WT) and serotonin neuron deficient (Lmx1bf/f/p) mice with or without a bipolar stimulating/recording electrode in the right amygdala. Seizures were induced with amygdala kindling (80-240 μ A, 1 ms biphasic square wave, 1 s, 60 Hz, twice daily stimulations until fully kindled) during wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, and EEG, EMG, EKG, and breathing were assessed. Vigilance state was determined on-line in real time based on EEG and EMG characteristics using standard parameters. A separate set of animals were made to spontaneously seize with pilocarpine (275-400 mg/kg, i.p.) induced status epilepticus and epileptogenesis. For these animals, seizures were analyzed post-hoc for vigilance state of occurrence and effects on breathing and cardiac activity were assessed.

Results:

Seizures induced during NREM in the kindling model were associated with increased respiratory rate variability and increased occurrence of apneas in both genotypes. Seizures were not readily induced during REM in the kindling model in WT mice, but could be induced during REM in Lmx1bf/f/p mice. Seizures occurred rarely during REM in WT mice the spontaneously seizing model, but occurred much more frequently in Lmx1bf/f/p mice.

Conclusions:

These data indicate that seizures that occur during sleep in animal models of epilepsy can have detrimental effects on breathing, which may contribute to increased seizure related death, and that serotonin may be involved in vigilance state dependent regulation of seizure occurrence.

#19

Title: Evidence of Seizures, Spreading Depression and SUDEP in a Murine Model of Post-Malarial Epilepsy

Authors: Fatemeh Bahari¹, Paddy Ssentongo¹, Derek G. Sim¹, Frank Gilliam¹, Steven Weinstein², Anna Robuccio¹, Ali Nabi¹, Balaji Shanmugasundaram¹, Myles W. Billard¹, Patrick J. Drew¹, Steven J. Schiff¹, Bruce J. Gluckman¹

Institution: Pennsylvania State University¹, George Washington University²

Rationale:

It is well established – though relatively unknown – that cerebral malaria (CM) leads to epilepsy in an estimated 300,000 children per year. Mortality ratios among persons with epilepsy are 2-3 times that of in developed countries, and are reported as high as six times in regions where malaria is endemic. Sudden unexplained death in epilepsy (SUDEP) serves as a major mortality risk, and is now thought to involve the interaction of seizures, spreading depression and cardio-respiratory failure. We investigated mice cured of CM for evidence of epilepsy, spreading depression, and SUDEP to identify models to both investigate the mechanisms of epileptogenesis and complex epilepsy-related phenomena and to test intervention strategies.

Methods:

We investigated four murine models of CM for evidence of post-malarial epilepsy by combining mouse strains (Swiss Webster (SW), C57BL/6, CBA) and two Plasmodium-berghei (Pb) parasites (NK65 and ANKA): SWPbNK65, SW-PbANKA, C57BL/6-PbANKA, and CBA-PbANKA. Cohorts of three-week old littermates were inoculated with infected erythrocytes, then rescued with Artesunate when they demonstrated signs of advanced CM. Controls were inoculated with uninfected erythrocytes. We developed a chronic recording system for long-term monitoring of brain and heart dynamics with DC sensitivity. Animals were implanted with EEG, EMG, and ECG electrodes 14 or more days post treatment, and video-EEG monitored continuously for 1-8 months per animal.

Results:

Post treatment death rates prior to implant were observed in some mixtures, with the largest rate in SWPbANKA. In these cases, death was typically accompanied by a single seizure-like behavioral event followed either by immediate death or a severe decrement in health. In all model combinations studied, recurrent spontaneous seizures were observed in a large fraction (50-90%) of the animals that survived to recording. Seizures were typically accompanied by clear spreading depression (SD) signatures in the DC components of the recordings. All epileptic mice with ECG recordings showed significant changes in cardiac activity associated with seizures. In 80% of the seizures, a transient preictal episode of tachycardia occurred followed by ictal and late-ictal bradycardia. AV node blocks were observed ictally and post-ictally in 66% of seizures. Putative SUDEP events were observed in all models recorded, including 5/13 SW-PbANKA and 8/20 SW-PbNK65.

Conclusions:

We have developed models of post-malarial epilepsy (PoME). In long-term chronic recordings, we observe complex interactions between seizures, heart arrhythmias, spreading depression, and death. These observations are consistent with pathologies of the human condition of sudden unexplained death in epilepsy (SUDEP). These models, which are induced from infection not genetic mutation, therefore provide a unique platform for the study of the mechanisms of SUDEP and models to

investigate the complex interactions between seizures, spreading depression, cardiac and respiratory dysfunction, and SUDEP.

#20

Title: Therapeutic Efficacy of Kv7 Channel Openers in Two Mouse Models of Sudden Unexpected Death in Epilepsy

Authors: Stephanie Villalba, MS, Nicole Gautier, BS, Edward Glasscock, PhD

Institution: LSUHSC-Shreveport

Rationale:

Prevention of sudden unexpected death in epilepsy (SUDEP) is currently hindered by a lack of available pharmacological treatment options. Here, we examine the therapeutic efficacy of the FDA-approved KCNQ channel opener retigabine in preventing seizures and sudden death in two different potassium channelopathy models of SUDEP: *Kcna1* knockout mice and *Kcnq1A340E* knockin mice. Mice lacking the *Kcna1* gene, which encodes voltage-gated Kv1.1 potassium channels, model human SUDEP by exhibiting severe early-onset seizures, brain-driven cardiac arrhythmias, and premature death. The *Kcnq1* gene encodes voltage-gated Kv7.1 potassium channels, which are mainly localized in the heart. Mice carrying the *Kcnq1A340E* mutation exhibit spontaneous seizures and cardiac abnormalities that occur concomitantly with cortical discharges. Though SUDEP is uncommon in *Kcnq1A340E* mice, the homologous mutation in humans is strongly associated with sudden death due to ventricular tachyarrhythmias related to long QT syndrome. Given the ability of KCNQ openers to reduce epileptiform activity and vagal hyperexcitability, we hypothesized that administration of retigabine would prevent seizures and normalize the interaction between brain and heart in *Kcna1* and *Kcnq1* mutant mice protecting them from SUDEP.

Methods:

The effects of retigabine (5-20 mg/kg, ip) on behavior and seizure threshold were examined in *Kcna1* knockout mice, *Kcnq1A340E* knockin mice, and their corresponding wildtype littermate controls. Behavior (4-6 weeks old; n=2-6/genotype) was examined for 40 min post-injection and the time spent vocalizing, hopping, tremoring, or lying in the prone position was quantified. Seizure thresholds (P29-31; n=6-11/genotype) were determined by measuring the latency to seizure following exposure to the volatile convulsant flurothyl. For *Kcna1* knockout mice, the effects of retigabine on lifespan were examined by performing semi-chronic daily injections (10 mg/kg/day, ip) between the ages of P15-P36 and monitoring survival. Quantitative RT-PCR was performed to measure mRNA levels of *Kcnq2* and *Kcnq3* in the hemibrains of mutant and wildtype mice (age P29-31; n>=3/genotype).

Results:

Retigabine administration caused wildtype mice of both strains to exhibit motionless, inactive behavior for a period of several minutes. In contrast, in *Kcna1* knockouts, retigabine caused unexpected, paradoxical behavioral hyperexcitability characterized by hopping, vocalization, and tremoring, phenotypes not observed in *Kcnq1A340E* mutants. In studies of flurothyl-induced seizures, retigabine was ineffective at reducing the latency to seizure in *Kcna1* knockouts suggesting no modification of seizure susceptibility. In contrast, in *Kcnq1A340E* mutants, retigabine significantly increased the latency to flurothyl-induced seizures suggesting the drug may be effective in altering seizure susceptibility in patients who have long QT-associated mutations in KCNQ1. In survival studies, semi-chronic daily injections of retigabine had no significant effect on lifespan in *Kcna1* knockout mice, further supporting a lack of effectiveness in that genetic model. Preliminary qRT-PCR analyses of *Kcnq2* and *Kcnq3* mRNA expression revealed a potential increase in *Kcnq2* levels in the brains of *Kcna1* knockout mice, suggesting a potential molecular cause for the differential drug effects.

Conclusions:

The differing pharmacogenetic interactions between retigabine and the *Kcna1* and *Kcnq1* mutations demonstrates that genetic profile may significantly alter the drug's therapeutic efficacy, highlighting the need for personalized genome-based therapy in epilepsy. Increased expression of one of the main molecular targets of retigabine (*Kcnq2*) in *Kcna1* mutant mice could explain the differential and unexpected effects of the drug in the two mutant mouse strains.

#21

Title: Mortality in Dravet Syndrome: a Scoping Review

Authors: Sharon Shmueli, MD¹, Sanjay M. Sisodiya, Professor², Josemir W. Sander, Professor², Roland D. Thijs, MD PhD¹

Institution: Stichting Epilepsie Instellingen Nederland (SEIN)¹, NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology²

Rationale:

Premature mortality is a major issue in Dravet syndrome (DS). To improve understanding of DS premature mortality, we conducted a comprehensive literature search with emphasis on SUDEP.

Methods:

We searched PubMed, Embase, Web of Science, Cochrane, CENTRAL, CINAHL, PsycINFO, Academic Search Premier and ScienceDirect. Search terms were as follows: “Dravet syndrome”, “severe myoclonic epilepsy”, “SMEI”, “mortality”, “survivors”, “prognosis” and “death”. DS cases or cohorts studies reporting mortality were included. We collected the following data: cause of death, age at death, SCN1A tested and SCN1A mutation found.

Results:

The search yielded 676 articles and 86 meeting abstracts. After removing duplicates and screening titles and abstracts, the full text of 73 articles was reviewed. Only 28 articles and six meeting abstracts met inclusion criteria. Five articles and four meeting abstracts were excluded as the case(s) were also described elsewhere. After checking the references of all included articles five additional studies were included. The 30 articles reported 177 unique cases (23 cohorts and 7 case reports). SUDEP was the likely cause in nearly half of the cases (n=87, 49%), followed by status epilepticus (n=56, 32%). Drowning or accidental death was reported in 14 cases (8%), infections in 9 (5%), other causes in six (3%) and unknown in five (3%). Age at death was reported for 142 of the 177 cases (80%), with a mean age of 8.7 ± 9.8 years (SD); 93% died before the age of 20 years and 73% before the age of 10 years.

Conclusions:

DS is characterized by high epilepsy-related premature mortality and a striking young age at death. SUDEP is the leading cause of death in DS, accounting for nearly half of overall mortality. Excess mortality may be explained by epilepsy severity, as well as genetic susceptibility to SUDEP.

#22

Title: A wristband assessment of accelerometry and autonomic activity of epileptic patients

Authors: Chiara Caborni, MEng, Francesco Onorati, PhD, Giulia Regalia, PhD, Matteo Migliorini, PhD, Rosalind W. Picard, Sc.D.

Institution: Empatica, Inc.

Rationale:

Electrodermal activity (EDA) is a physiological signal reflecting the activity of the sweat glands driven by the Sympathetic Nervous System. EDA and wrist acceleration (ACM) measurements have been used in a wearable device to automatically identify generalized tonic-clonic seizures (GTCs). Our prior work showed that using 30 features from EDA and ACM, and a Support Vector Machine approach, it was possible to obtain a detector (SVM_30) with sensitivity (Se) of 95% and false alarm rate (FAR) of 2.02 events/day on a set of 38 GTCs from 18 epilepsy patients. It is important to continue to test these methods on more patients and more seizures, and evaluate also the potential for false alarms during large periods of time in patients with epilepsy when they are not having seizures.

Methods:

In collaboration with top hospitals, we collected clinically labelled seizure data using video EEG (v-EEG), consisting of 192 recordings taken from 53 patients wearing a wrist sensor recording EDA and 3-axis ACM. The data were analyzed off-line using proprietary software (Empatica, Inc.) to clean the data and extract signal features on a 10 seconds window every 2.5 seconds (overlap: 75%). Then SVM_30 was employed in order to evaluate the Se and FAR on this testing set. The optimal decision threshold to discriminate between seizure and non-seizure epochs was selected by means of receiver operating characteristic (ROC) curve analysis on a prior-collected training set (38 GTCs from 18 patients over a total of 43 days).

Results:

This classifier has now been tested on data from five new patients not included in the training set, with GTC and focal motor (FOCM) seizures (i.e., 8 GTC and 4 FOCM seizures from the 5 patients over a total of 378 hours = 15.75 days) and on non-seizure recordings from 48 epilepsy patients over a total of 3564 hours (148.5 days) in order to mimic the realistic utilization of the wearable detector over 164 days. The classifier was able to provide an alarm before the seizure had finished in 100% of the cases, with a mean delay in the 12 cases of 29 seconds (SD=12 sec). As a percentage of the seizure duration, the detection occurred on average after 39% of the seizure had occurred. The SVM_30 was able to automatically recognize all 12/12 seizures, achieving over 164 days of recording from 53 patients, a sensitivity of 100% and FAR of 0.93 events/day. Of the 53 epilepsy patients, 6 patients had a FAR higher than 2, seven had from 1-2 false alarms per day, while 40 patients (most of them) averaged less than or equal to 1 false alarm/day. Of these, 18 had no false alarms.

Conclusions:

In this work, the performance of an automated seizure detection system based on ACM and EDA features measured from the wrist was presented using clinical data collected from a total of 53 patients having two types of seizures. The classifier we tested allows a high seizure detection rate for GTC and FOCM seizures that had never been trained by the model (Se=100% on 12 new seizures) while maintaining an acceptable false alarm rate of 0.93/day on average over 164 days. Furthermore, it is efficiently integrated into a hardware platform to provide real-time alarms of seizures while they are

occurring. In the future, the model will be tested on data collected outside the clinic, where the test conditions are expected to be much more challenging.

#23

Title: Sudden unexpected death in epilepsy (SUDEP) in children with benign childhood epilepsy with centrotemporal spikes (BECTS): a case series from the North American SUDEP Registry (NASR).

Authors: Kyra Doumlele, BA, Daniel Friedman, MD, Orrin Devinsky, MD

Institution: New York University School of Medicine

Rationale:

Benign rolandic epilepsy (BRE) or benign epilepsy with centrotemporal spikes (BECTS) is the most common focal epilepsy syndrome among children. Focal motor seizures involving the face are most common but children may also have secondarily generalized tonic-clonic seizures (GTCS). Anti-seizure drugs (ASDs) are not always prescribed because of infrequent seizures, predictable resolution, and excellent prognosis (Peters et al. 2002, Shields & Snead 2009, Camfield & Camfield 2002). Recently, the accuracy of the term “benign” has been questioned due to cognitive and behavioral problems in BECTS (Vannest et al. 2015, Verrotti et al. 2013, Goldberg-Stern et al. 2009). However, there may also be graver risks in BECTS. Children with BECTS who experience GTCS typically have them at night. Both nocturnal seizures and GTCS are risk factors for sudden unexpected death in epilepsy (SUDEP) (Lamberts et al. 2012, Hesdorffer et al. 2012). In this study, we report three cases of BECTS among a series of SUDEP cases enrolled in the North American SUDEP Registry.

Methods:

Case inclusion was based on a search of 124 decedents enrolled in the North American SUDEP Registry (NASR), a clinical and biospecimen repository established to investigate the risk factors and mechanisms for SUDEP. Cases were identified based on parental report of BECTS diagnosis during the intake interview. Further case review was conducted by clinicians at the NYU Comprehensive Epilepsy Center utilizing EEG, interview data, and medical records to confirm both the BECTS diagnosis and SUDEP determination. SUDEP classification followed guidelines proposed by Lina Nashef (Nashef et al. 2013). Criteria for diagnosis of BECTS included: age of onset 3-13 years of age, normal cognition and development prior to seizure onset, absence of remote symptomatic cause of epilepsy, and an EEG reporting discharges consistent with benign rolandic epilepsy.

Results:

Our analysis revealed three SUDEPs in patients diagnosed with BECTS. All were male with a median age 12 years (range: 9-13 years). Median age of epilepsy onset was 5 years (range: 3-11 years) and median duration of epilepsy was 4 years (range: 1-10 years). SUDEP was definite in two of the three cases, and probable in one. All experienced nocturnal generalized tonic-clonic seizures (GTCS) in and preceding the six months prior to their death. The median number of GTCS in the last year was 5 (range: 2-20), and 3 (range: 0-10) in the last 3 months. None of the three cases were treated with ASDs - per physician recommendation in two cases and by parental request in the third. None of the families were counseled about the risk of SUDEP.

Conclusions:

Our findings provide further evidence BECTS does not always have a benign course. While prior epidemiological studies have not identified SUDEP among children with BECTS, sample size was small (n = 42) (Camfield et al. 2014). A SUDEP in a child with BECTS was previously reported in an autopsy series (Tu et al. 2011), but clinical details do not confirm clinical or EEG diagnostic features. This is the first report to our knowledge of SUDEP among children with well-documented BECTS. The risk of SUDEP

should be recognized by clinicians for family counseling and treatment decisions in this and any other epilepsy where there is a risk for GTCS. Further investigation of SUDEP features and occurrence among patients with BECTS could potentially identify high-risk characteristics and inform patient care decisions.

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#24

Title: Regional Variation in Brain Tissue Texture in Patients with Generalized Tonic-Clonic Seizures

Authors: Ronald Harper, PhD¹, Jennifer Ogren, PhD¹, Rajesh Kumar, PhD¹, John Stern, MD¹, Dawn Eliashiv, MD¹, Inna Keselman, MD¹, Jerome Engel, Jr., MD, PhD¹, Beate Diehl, MD, Samden Lhatoo, MD³

Institution: University of California Los Angeles¹, University College London², Case Western Reserve University³

Rationale:

Patients with Generalized Tonic-Clonic seizures (GTCs) are at elevated risk for Sudden Unexpected Death in Epilepsy (SUDEP). We examined, using MRI-based entropy procedures, tissue texture indicative of brain changes in GTC patients relative to healthy controls to evaluate ongoing detrimental processes that may contribute to autonomic or breathing dysfunction.

Methods:

High resolution T1-weighted images were collected with a 3.0-Tesla MRI scanner from 53 patients with GTCs (from sites at Case Western Reserve, University College London, and University of California at Los Angeles) and 53 age- and gender-matched healthy controls (University of California at Los Angeles). Images were bias-corrected, entropy maps calculated, normalized to a common space, smoothed, and compared between GTC patients and healthy controls using ANCOVA (covariates age, gender; SPM12, family-wise error correction for multiple comparison, $p < 0.01$).

Results:

Decreased entropy values, indicative of neuronal swelling, appeared in relatively discrete regions. In addition to primary cortical motor and sensory areas, decreased entropy was observed in the basal ganglia, rostral-basal cerebellum (including the deep autonomic nuclei), and external surfaces of the pons. The anterior and posterior thalamus and midbrain were also affected. Caudal to the pons, the more caudal medulla was prominently affected. The ventral medial frontal cortex, the hippocampus and surrounding temporal cortex, and the insula also showed lower entropy values. Only a few isolated regions showed increased entropy.

Conclusions:

Two remarkable aspects emerged. 1) Decreased entropy (increased tissue homogeneity, potentially resulting from inflammation) appears in multiple motor regulatory areas (sensory and motor cortex, basal ganglia, cerebellum) and major autonomic regulatory areas (ventral frontal cortex, insula, hippocampus, dorsal and ventral medulla, deep autonomic cerebellar nuclei), suggesting that GTC seizures have the potential to induce long-term injury both to autonomic regulatory and motor control sites. 2) Seizures in GTC patients arise from widespread brain areas, resulting in few consistent areas of injury; hence, increased entropy, representing regions of long-lasting injury are unlikely to appear in grouped data from multiple patients. The outcome of little common injury should be compared to findings from temporal lobe epilepsy onset patients, where increased entropy appears in multiple, defined sites.

#25

Title: Autonomic Dysfunction in TLE is associated with brainstem pathology

Authors: Susanne Mueller, MD, Alix Simonson, B.A., Robert Knowlton, MD, Yee-Leng Tan, MD, Kenneth Laxer, MD

Institution: Center for Imaging of Neurodegenerative Diseases

Rationale:

Sudden unexplained death in epilepsy (SUDEP) is the leading cause of premature death in epilepsy. The symptoms in witnessed cases suggest that it might be caused by a severe, seizure-related disturbance of the autonomic system. Interestingly many epilepsy patients show signs of a mild interictal dysfunction that manifests itself most commonly by a reduced heart rate variability (HRV). One possible explanation is an impairment of the central autonomic control due to seizure induced damage to regions involved in the autonomic control. The brainstem is an interesting candidate for the site of this damage because it plays not only a crucial role in the autonomic control but also in seizure control. The overall goal was therefore to obtain evidence that atrophy in brainstem regions involved in autonomic control leads to autonomic dysfunction in non lesional mesial temporal lobe epilepsy (TLE).

Methods:

18 TLE patients (f/m:10/8 mean age: 40.2±14.1) and 11 healthy controls (f/m: 5/6, mean age: 30.7±7.8) were studied on a 3T MRI with simultaneous EEG and ECG recordings and a whole brain T1 and T2 image acquired. The ECG recording was used to calculate frequency adjusted HRV. The control group was enriched by 19 healthy controls who had been studied with the same protocol but without simultaneous EEG/ECG recordings for atlas building and the estimation corrected normal ranges. The T1 and T2 images were co-registered and the brainstem/cerebellum/diencephalon extracted. The shoot toolbox from SPM12 was used for brainstem atlas building using the T1 and T2 images of the enlarged control group and warping of the individual TLE and control brainstem images onto this atlas. The deformation matrices were used to calculate ICV and age-adjusted z-score maps of the Jacobian determinants. Group differences (t-test) and associations between brainstem atrophy and HRV reduction in the TLE group (linear regression) were assessed at the voxel level with SPM12. Mean age-adjusted z-scores were calculated from brainstem/diencephalon voxels to assess brainstem atrophy in individual subjects. Subjects whose mean brainstem z-score was below the lower 99% confidence interval calculated by bootstrapping the mean z-scores of the enlarged control group were considered to have “pathological” brainstem volume loss.

Results:

TLE had lower heart rate adjusted HRV z-scores (-0.176±1.01) compared to controls(0.318±0.94) but this difference did not reach significance. TLE had no significant brainstem atrophy (FDR p<0.05) compared to controls. Lowering the threshold for significance (p<0.01) revealed volume loss in the cerebellum and region of the superior and inferior colliculi. HRV was associated with volume loss in several brainstem regions involved in autonomic control in TLE 10 TLE (mean z-score: -1.05±0.62) but also 4 controls (mean z-score: -0.89±0.49) had “pathological brainstem volume loss in the single subject analysis. The finding in the latter might explain the unexpected mild brainstem atrophy in the comparison between TLE and controls. TLE with pathological volume loss had significantly reduced HRV z-scores compared to those within the normal range (-0.65±1.00 vs 0.42±0.69, p<0.05). The same was true for controls with pathological brainstem atrophy (-0.50±0.15 vs 0.86±0.82, p<0.05).

Conclusions:

Autonomic dysfunction manifesting itself as reduced HRV was associated with volume loss in brainstem structures responsible for autonomic control in TLE. If progressive, this lesion might lead to further autonomic dysfunction and increased risk for SUDEP. The single subject analysis confirmed this finding in TLE but also identified 4 controls with significant brainstem volume loss and evidence for autonomic dysfunction. While confirming the association between autonomic dysfunction and brainstem volume loss the finding in the control group also indicates that this brainstem “lesion” is not specific to TLE.

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#26

Title: Normal sleep EEG and malignant generalized tonic-clonic seizures trigger postictal generalized EEG suppression in children with epilepsy

Authors: Hirohi Otsubo, MD, Kazuo Okanari, MD, Elizabeth Donner, MD

Institution: The Hospital for Sick Children

Rationale:

The identification of a biomarker for sudden unexpected death in epilepsy (SUDEP) has the potential to save lives. Generalized tonic clonic seizure (GTCS) and postictal generalized EEG suppression (PGES) most often precede SUDEP and are potential biomarkers. We identify the characteristics of awake and sleep EEG, GTCS and PGES in children with epilepsy.

Methods:

A retrospective review of 977 pediatric prolonged scalp VEEG recordings performed at The Hospital for Sick Children in Toronto, Ontario, Canada, between January 2009 and December 2011 was performed. VEEG were reviewed for seizure type, duration and semiology, awake and sleep EEG features. To identify predictors of PGES we examined two cohorts: 1) 26 children with ≥ 1 episodes of PGES; and 2) 41 children with 84 GTCS. We applied multivariate logistic regression models, fitted with a generalized estimating equation (GEE) to adjust for clustering at the subject level.

Results:

26 children (mean age 9.9 years) demonstrated ≥ 1 episodes of PGES with a total of 129 seizures. PGES occurred significantly more often with primary or secondary GTCS than any other seizure types (RR 8.54; 95% CI [3.5-20.8]; $p < 0.001$). When all seizure types were considered, seizure duration was significantly longer for seizures with PGES (1.14 [1.02-1.29]; $p = 0.025$). The presence of normal sleep features significantly increased the risk of PGES (4.1 [2.3-7.3]; $p < 0.0001$). Shorter duration of the tonic-clonic phase (0.81 [0.70-0.93]; $p = 0.0024$) and clonic phase (0.89 [0.79-1.00]; $p = 0.049$) were significantly associated with PGES. All GTCS with a postictal suppression-burst pattern were followed by PGES (1.79 [1.24-2.59]; $p = 0.002$).

Conclusions:

PGES was significantly associated with GTCS including partial seizures with secondary generalization, longer seizure duration and normal sleep EEG features. Analysis of GTCS alone demonstrates shorter duration of both tonic-clonic and clonic phases and presence of suppression-burst pattern associated with PGES. These ictal features may define a pattern of malignant GTCS which, when combined with normal sleep EEG, may predispose to PGES and a potentially increased risk of SUDEP.

#27

Title: Mortality associated with epilepsy in Veterans of the Afghanistan and Iraq Wars

Authors: Mary Jo Pugh, PhD RN FACMPH¹, Megan Amuan, MPH²,

Institution: VA Epilepsy Centers of Epilepsy¹, Center for Healthcare Organization and Implementation Research (CHOIR)²

Rationale:

Recent studies have identified the prevalence of epilepsy in Post-9/11 Veterans, but no information exists regarding long-term outcomes of epilepsy in this population. In particular, mortality is a concern due to higher than expected rates of suicidality, and the lack of “health soldier effect” found in prior cohorts of Veterans.

Methods:

National VA administrative data (2002-2015) were analyzed to identify the burden of comorbidity and premature mortality in Post-9/11 Veterans with epilepsy (VWE) among those who received VA care during two different years. Inpatient and outpatient databases were used to identify diagnosis codes for comorbid conditions and diagnoses consistent with epilepsy (epilepsy: 345.0-345.5, 345.7-345.9; unspecified seizure: 780.39) and comorbid conditions. Outpatient pharmacy data were used to identify dispensed seizure medication. Individuals who met epilepsy criteria between 2002-2011 (an epilepsy-specific diagnosis or two or more unspecified seizure diagnosis codes and a seizure medication within a year) were included in the VWE cohort. Baseline comorbidities were identified through 2010 or before meeting epilepsy criteria, and date of death from vital status files 2011-2015 was used to identify mortality. Table 1 shows characteristics of the VWE and no epilepsy cohorts. Demographic characteristics, comorbidities, and mortality for individuals in the VWE compared to no epilepsy cohorts were compared using the chi-square statistic and the trend of mortality rates (censored at 60 months) were plotted and the chi-square test of trend was used to determine the statistical significance of the trend lines. Cox proportional hazard models were used to identify baseline characteristics associated with five-year mortality.

Results:

Between 2002 and 2011, 2,198 of 368,123 Post-9/11 Veterans met epilepsy criteria. VWE were more likely to be white, 30-39 years of age, and more likely to have all comorbid conditions examined. Among VWE 4.96% (N=109) were deceased compared to 1.02% (N=3,736) in the remainder of the cohort ($p < .01$). Mortality was more likely among individuals with epilepsy (Hazard Ratio [HR]=2.47; 95% confidence interval [CI] 2.01-3.02), even after controlling for cancer (HR=5.07; 95% CI 4.41-5.82), substance use disorder (HR=2.59; 95% CI 2.38-2.82), liver disease (HR=2.36; 95% CI 1.91-2.91), kidney disease (HR=1.88; 95% CI 1.41-2.51), suicidality (HR=1.77; 95% CI 1.54-2.03), and overdose (HR=1.76; 95% CI 1.36-2.28). Mortality was also more common in whites and those over the age of 50.

Conclusions:

While VWE were significantly more likely to have other physical and psychiatric comorbidities strongly associated with mortality, epilepsy was a significant predictor of mortality controlling for both physical and psychiatric comorbidity. Excess mortality associated with may be associated with accidents commonly associated with seizures, poorly controlled seizures, and sudden unexplained death. Evaluation of seizure control and patient education regarding safety and injury are epilepsy quality

indicators that are often not evident in documentation. Close evaluation of seizure control and safety issues may be targets for intervention to reduce excess mortality associated with epilepsy.

#28

Title: Mortality in Phase III studies of adjunctive and monotherapy eslicarbazepine acetate in patients with partial-onset seizures

Authors: Philippe Ryvlin¹, Andrew Cole², Eva Andermann³, Helena Gama⁴, Francisco Rocha⁴, David Blum⁵, Todd Grinnell⁵, Hailong Cheng⁵, Eugen Trinka⁶,

Institution: Centre Hospitalo-Universitaire Vaudois (CHUV)¹, Massachusetts General Hospital; Harvard Medical School², Neurogenetics Unit and Epilepsy Research Group, Montreal Neurological Institute and Hospital; Departments of Neurology & Neurosurgery and Human Genetics, McGill University³, BIAL – Portela & Ca, S.A., BIAL – Portela & Ca, S.A.⁴, Sunovion Pharmaceuticals Inc.⁵, Christian Doppler Medical Centre; Department of Public Health and Health Technology Assessment, UMIT⁶

Rationale:

Mortality and Sudden Unexplained Death in Epilepsy (SUDEP) are important issues in epilepsy. Risk factors for SUDEP are not fully understood, but may include inadequate seizure control. Adjunctive treatment of refractory epilepsy with efficacious doses of antiepileptic drugs (AEDs) may reduce the incidence of SUDEP compared with placebo (PBO) (Ryvlin P, et al. Lancet Neurol 2011;10[11]:961–8). This exploratory analysis evaluates mortality in adult patients with refractory partial-onset seizures (POS) treated with eslicarbazepine acetate (ESL) in Phase III adjunctive or monotherapy studies.

Methods:

Mortality data from six studies were included: three adjunctive studies, BIA-2093-301, -302 and -304, all of which included open-label extension phases; three monotherapy studies, 093-045 and -046, and the related open-label extension, -050. Adult (aged ≥16 years) patients with refractory POS (≥4/month) during stable treatment with ≥1 AED received adjunctive ESL at doses of 400 mg, 800 mg or 1200 mg once-daily (QD; patients continued to receive stable doses of baseline AEDs; the open-label extension was carried out according to a flexible dosing schedule and was open to patients who had received placebo), or ESL monotherapy at 1200 mg or 1600 mg QD (studies -045 and -046; previous AEDs were withdrawn), or 800–2400 mg QD (study -050; flexible dosing schedule, up to two additional, non-oxcarbazepine AEDs allowed).

Results:

1021 patients received at least 1 dose of double-blind adjunctive ESL, and 639 patients received at least 1 dose of open-label, adjunctive ESL. In the monotherapy studies, 365 patients received at least 1 dose of double-blind ESL, and 274 patients received at least 1 dose of open-label ESL. As of September 22 2014, overall ESL exposure (double-blind and open-label combined) was: adjunctive therapy, 1877.3 patient-years; monotherapy, 627.0 patient years. As of September 22 2014 there were 19 deaths overall during the adjunctive and monotherapy studies: two pre-randomization; 13 during treatment with PBO or ESL (double-blind or open-label); four post-ESL discontinuation. 11/13 on-treatment deaths occurred while patients were receiving ESL, and 2/13 occurred during treatment with PBO. 6/19 deaths were potentially due to SUDEP, three of which occurred while patients were receiving ESL (adjunctive, n=2; monotherapy, n=1). Among patients enrolled in the adjunctive studies (double-blind and open-label phases) the SUDEP rate for patients who were receiving ESL was 0.11 per 100 patient-years (90% confidence interval [CI] upper bound = 0.34). For the adjunctive and monotherapy studies combined,

the SUDEP rate for patients who were receiving ESL was 0.12 per 100 patient-years (90% CI upper bound = 0.31).

Conclusions:

Deaths were rare in Phase III studies, including deaths potentially due to SUDEP, among adult patients with refractory POS who received ESL (as adjunctive or monotherapy).

#29

Title: Population-Based Registry of SUDEP in Children

Authors: Robyn Whitney, MD, FRCPC¹, Michael Pollanen, MD, PhD, FRCPath, DMJ (Path), FRCPC², Shelly-Anne Li, MSc¹, Joel Gupta, MD¹ Candidate 2018, Elizabeth Donner, MD, MSc, FRCPC¹

Institution: Division of Neurology, The Hospital for Sick Children¹, Laboratory Medicine & Pathobiology, University of Toronto²

Rationale:

Children with epilepsy have an increased risk of death compared to the general population. Sudden Unexpected Death in Epilepsy (SUDEP) is a devastating cause of mortality in individuals with epilepsy. The incidence of SUDEP in children is up to 0.43 per 1000 patient years of epilepsy, more than 10 times the rate of sudden death in children in general. Risk factors for SUDEP have been studied in adults; however, pediatric specific factors have not been well defined. Careful evaluation of pediatric SUDEP cases is important to help better identify potential factors in children with epilepsy at risk of sudden death.

Methods:

The goal of this study was to determine potential risk factors for pediatric SUDEP through the development of a national, multi-centered, prospective population based registry for SUDEP. Children with epilepsy with an unexpected death from January 1, 2014 to December 31, 2016 were sought for enrollment. Inclusion criteria were: age at death \leq 18 years, history of epilepsy (\geq 2 seizures), death that was sudden and unexpected, death that occurred during normal circumstances and an autopsy that determined no anatomical or toxicological cause of death. Deaths due to trauma or drowning were excluded. Cases were collected from: the Canadian Pediatric Epilepsy Network (CPEN), Canadian Pediatric Surveillance Program (CPSP), and the Ontario Forensic Pathology Service (OFPS). Records were reviewed for demographics, clinical features, circumstances surrounding death and autopsy findings.

Results:

Twenty-one cases of pediatric SUDEP have been identified to date: 9 OFPS, 8 CPSP, 3 CPEN & 1 CPSP/CPEN. Nine cases were adjudicated as definite SUDEP, one as definite SUDEP plus, eight as probable SUDEP and three as possible SUDEP. Forty-eight percent were males. The median age at death was 8.3 years (range: 21 months – 16 years) and median duration of epilepsy was 5.2 years (range: 2 months – 15 years). The age of seizure onset was known in sixteen and 94% had onset before 5 years. Eighteen children (85%) were on an AED at the time of death and thirteen (62%) were on two or more. Global delay was present in fifteen. In eighteen children, the state before death was known. Sixteen children (89%) were asleep and two (11%) were awake; death was unwitnessed in fourteen (78%) and witnessed in four (22%). Seventeen children had information regarding the presence of a recent infection; eight (47%) had a recent infection, while nine did not (53%).

Conclusions:

The majority of SUDEP cases occurred in children with global developmental delay, early onset epilepsy and with seizures that required polytherapy. Almost all deaths were during sleep and were unwitnessed. Male sex and longer duration of epilepsy were not found at increased frequencies in our cohort, which have been previously described in adult SUDEP cases. Almost half of the children had a recent infection, which may potentially favour increased surveillance around the time of illness.