

Report of the NIH/NINDS-sponsored multidisciplinary workshop on Sudden Unexpected Death in Epilepsy (SUDEP)

[THIS IS THE COMPLETE ON-LINE VERSION]

Workshop held November 12-14, 2008, Bethesda, Maryland, U.S.A.

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[complete list of participants attached]

ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is a devastating complication of epilepsy and is not rare. The NIH and NINDS sponsored a three-day multidisciplinary workshop to advance research into SUDEP and its prevention. Parallel sessions were held; one with a focus on the science of SUDEP, and the other with a focus on issues related to the education of health care practitioners and people with epilepsy. This report summarizes the discussions and recommendations of the workshop, including lessons learned from investigations of sudden infant death syndrome (SIDS), sudden cardiac death, autonomic and respiratory physiology, medical devices, genetics, and animal models. Recommendations include educating all people with epilepsy about SUDEP as part of their general education on the potential harms of seizures, except in extenuating circumstances. Increasing awareness of SUDEP may facilitate improved seizure control, possibly decreasing SUDEP incidence. There have been significant advances in our understanding of the clinical and physiologic features of SIDS, sudden cardiac death, and SUDEP in both people and animals. Research should continue to focus on the cardiac, autonomic, respiratory and genetic factors that likely contribute to the risk of SUDEP. Multicenter collaborative research should be encouraged, especially investigations with direct implications for the prevention of SUDEP. An ongoing SUDEP Coalition has been established to facilitate this effort. With the expansion of clinical, genetic, and basic science research, there

is reasonable hope of advancing our understanding of SUDEP and ultimately our ability to prevent it.

Introduction:

Throughout the world, approximately 0.5-1% of the population has epilepsy. One-third of people with epilepsy have persistent seizures despite appropriate treatment. Each year, slightly less than one of every one thousand people with epilepsy dies of sudden, unexpected, unexplained death. In those with refractory epilepsy, this occurs in 1 in 150 people *each year*. The risk is particularly high in those with uncontrolled tonic-clonic seizures.

In 2007, the American Epilepsy Society and the Epilepsy Foundation formed a joint task force to address the research and educational issues concerning the phenomenon of Sudden Unexpected (Unexplained) Death in Epilepsy (SUDEP). Among the published recommendations of the task force was that a multidisciplinary workshop on SUDEP be convened (So et al, 2008). The goal of the workshop was to bring together a multidisciplinary group of professionals and lay advocates with diverse expertise to further our understanding of SUDEP and our ability to prevent it. The depth and breadth of the participants included epileptologists and other neurologists, patient and professional educators, advocates from the bereaved community, and experts in guideline development as well as experts from related fields, such as sudden cardiac death (cardiology), neurocardiology, the autonomic nervous system, sudden infant death syndrome (SIDS), genetics, animal models of sudden death, respiratory physiology, and pathology (medical examiners/coroners).

In November 2008, a unique, 2.5 day multidisciplinary SUDEP workshop was convened by the National Institutes of Health (NIH) and the National Institute of Neurological Disorders

and Stroke (NINDS) in Bethesda, Maryland. Invited participants were experts from the many disciplines related to the issue of sudden death. We also invited patient and professional educators, advocates from the bereaved community, and experts in guideline development. The workshop included parallel sessions, one with a focus on the science of SUDEP, and the other with a focus on education of health care practitioners and people with epilepsy.

The objectives of the workshop were as follows:

- 1) Design methods to raise awareness of the risk of SUDEP in the medical and lay communities. Investigate when, what, and how to best discuss SUDEP with patients and caregivers
- 2) Involve experts from other disciplines related to sudden death.
- 3) Identify possible preventive strategies for SUDEP
- 4) Develop a research agenda for SUDEP that includes basic and clinical directions
- 5) Formulate and establish a SUDEP research consortium

This report summarizes the discussions and recommendations from the workshop. In general, references are not included. Most references can be found in one of several excellent recent related review articles. (Blum 2009; Kinney and Thach 2009; Lathers et al, 2008; Schuele 2009; So 2008 and 2009; Samuels 2007; Tester and Ackerman 2009; Tomson et al, 2008).

Disclaimer: This report is a workshop summary, not a guideline, practice parameter or evidence-based review. While some of the suggestions involve clinical practice, these recommendations only represent the views of the majority of the workshop participants at this time. Further study is required to develop future evidence-based guidelines.

The definition of SUDEP used in this document is based on that of Nashef and Brown (Nashef and Brown 1996):

“Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus.”

- *Definite SUDEP* requires a postmortem examination showing no definite alternative cause of death (such as high levels of illicit drugs or acute myocardial infarction).
- *Probable SUDEP* fulfills all of the above criteria for definite SUDEP, but without a postmortem examination.
- *Possible SUDEP* is applied to less clear cases that might have been SUDEP, but where there is inadequate information to be certain or competing possible causes of death.
- *Near-SUDEP*: For this workshop and summary, the term *near-SUDEP* is used to describe cases in which death would have been likely if resuscitation or other intervention had not been applied.

This report is organized as follows:

I. Developing a research agenda to understand and prevent SUDEP

- A) Lessons learned from Sudden Infant Death Syndrome
- B) Lessons learned from sudden cardiac death, neurocardiology and studies of the autonomic nervous system.
- C) Lessons learned from respiratory physiology

D) Recommendations

- i) Animal models
- ii) Clinical investigations
- iii) Genetics
- iv) Medical Devices
- v) Case-identification
- vi) Collaborative research/SUDEP Coalition

II. Educating people with epilepsy and their families about SUDEP

- A) Ethics: The right to know vs. the right not to know
- B) When and how to provide information
- C) Recommendations

III. Educating health care providers about SUDEP

- A) Recommendations

IV. Prevention of SUDEP

V. Future directions

VI. Conclusions

I. **DEVELOPING A RESEARCH AGENDA TO UNDERSTAND AND PREVENT SUDEP**

A. Lessons learned from Sudden Infant Death Syndrome (SIDS)

- i) Role of sleep position and environment

- a) The prone sleep position is associated with autonomic dysfunction, decreased arousability, heat trapping and rebreathing of exhaled gases. Many patients with SUDEP are found prone, although this position could occur secondary to a seizure.
 - b) The “back to sleep” campaign, which promotes placing infants to sleep on their back, was highly successful; SIDS rates were reduced by about 50% in developed countries. This demonstrates that an educational campaign geared to the public can prevent a form of sudden death even without full understanding of the mechanism involved. This specific recommendation is not likely to work for prevention of SUDEP as older patients do not stay in one position while sleeping, and seizures may cause the person to turn prone.
 - c) SIDS risk is decreased if an adult sleeps in the same room (but not in the same bed) as the infant. Preliminary evidence suggests that having another person (adult or older child) in the bedroom may also be protective for SUDEP.
 - d) Exposure to cigarette smoke is a risk factor for SIDS. The primary risk is related to maternal smoking during pregnancy, with some incremental risk associated with postnatal exposure. In both animal and human infant studies, smoke exposure decreases ventilatory responses to hypoxia and decreases arousal from sleep.
- ii) Physiologic considerations
- a) Autonomic dysfunction, primarily increased sympathetic or decreased parasympathetic activity, appears to be associated with a higher risk of SIDS; there is similar evidence that this may be associated with higher risk for SUDEP.
 - b) Decreased sighs, gasps, spontaneous arousals and arousability are associated with higher risk for SIDS.

- c) Recent infection has been reported in about half of SIDS infants, but the causal relationship is unclear.
 - d) Brainstem serotonin dysfunction appears to play a significant role in SIDS, possibly explaining up to half of cases.
 - e) There is pathological evidence of repeated or chronic hypoxia in SIDS cases.
 - f) SIDS is associated with higher CSF vascular endothelial growth factor (VEGF) levels. These elevations may be secondary to episodes of prior hypoxia, but gain-of-function polymorphisms in VEGF have also been reported.
- iii) Genetics
- As many as 10% of SIDS cases appear to be associated with genetic variations known to be associated with cardiac arrhythmias and sudden death, or linked to regulation of central nervous system serotonin levels. Some of the more common examples of these pro-arrhythmic polymorphisms include multiple long QT syndrome genes; the *RYR2* gene, associated with catecholaminergic ventricular tachycardia syndrome and encoding a cardiac ryanodine receptor; and *SCN5A*, associated with long QT and Brugada syndromes. . Twenty-six genes have been reported to have polymorphisms that occur more frequently in SIDS infants than controls. In addition to genes associated with cardiac ion channelopathies (both sodium and potassium), genetic variants have been reported in genes relating to serotonin transport, autonomic nervous system and brainstem development, cytokines (up-regulation of pro-inflammatory or down-regulation of anti-inflammatory cytokines), and energy production (mitochondrial function).

The factors reviewed above that are associated with SIDS have either not been investigated in SUDEP (cigarette smoke exposure, infection, arousability, brainstem physiology, CSF findings) or will require additional investigations (sleep position, nocturnal supervision, autonomic and respiratory physiology, genetics).

B. Lessons learned from sudden cardiac death, neurocardiology and studies of the autonomic nervous system

i) Physiologic considerations

a) In general, increases in sympathetic activity and decreases in parasympathetic activity are markers for increased risk of cardiac arrhythmia. Heart rate variability (fairly well studied in relation to epilepsy, its treatment and SUDEP) and baroreflex sensitivity (not well studied in relation to SUDEP) are reasonable measures of autonomic system dysfunction that might predispose to sudden cardiac death.

Baroreflex sensitivity may be more relevant to SUDEP, as it is a measure of an acute, reactive vagal response rather than chronic vagal tone as measured by heart rate variability.

b) Inflammation, fever and high C-reactive protein appear to be associated with an increased risk of sudden cardiac death.

c) The following agents may help prevent sudden cardiac death in a variety of different cardiac patient populations: beta blockers, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, fish oil, and exercise. Statins may improve autonomic function.

ii) Genetics:

It is now established that many of the known cardiac arrhythmia genes associated with either long or short QT syndromes, Brugada syndrome or catecholaminergic polymorphic ventricular arrhythmia are dually expressed in heart and brain. There is growing evidence that these genes are associated with SUDEP, including the following genes:

a) *KCNQ1*: Encodes the α subunit of an inward rectifier potassium channel expressed in cortical and hippocampal circuitry as well as in the dorsal motor nucleus of the vagus, mediating parasympathetic innervation of the heart. Mutations in this gene are the most common form of human long QT syndrome (LQT1). Human LQT1 mutations in mice produce epilepsy and malignant arrhythmias, including asystole, and sudden unexpected death. Almost one quarter of humans with LQT1 mutations have 'seizure-like' episodes.

b) *RyR2*: Codes for a ryanodine receptor involved in intracellular calcium regulation. In a mouse model of a human *RYR2* mutation linked to exercise-induced cardiac arrhythmias, there is independent co-existence of cardiac arrhythmias and seizures; there is also sudden cardiac death in these mice when challenged by exercise and epinephrine infusion.

c) *KCNH2* (or *HERG*): Another potassium channel gene associated with long QT syndrome type 2 (LQT2); also expressed in the hippocampus and likely plays a role in glial potassium buffering. Other potassium channel genes associated with long QT syndrome and expressed in brain include *ANK2* (LQT4), *KCNE2* (LQT6), and *KCNJ2* (LQT7; short QT).

d) *SCN1A*: codes for an α subunit of a voltage-gated sodium channel that is dually expressed in brain and heart, and is known to be affected in generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (Dravet syndrome). Preliminary evidence indicates an increased rate of SUDEP in patients with severe myoclonic epilepsy of infancy.

e) Other genes for channels that predispose to arrhythmias and are expressed in brain include sodium channel genes (e.g., *SCN5A*, associated with LQT3 and Brugada syndrome), and calcium channel genes (e.g., *CACNA1C*, associated with LQT8).

iii) Clinical conditions associated with sudden cardiac death

The following conditions are associated with sudden unexpected cardiac death in young, otherwise healthy people, usually with structurally normal-appearing hearts:

a) Long QT syndrome: mostly related to potassium channel gene mutations, but can also be associated with sodium channel gene mutations, and others. Syncope and seizure-like events are not uncommon in this syndrome.

b) Brugada syndrome: associated with a specific EKG pattern of a right bundle branch block and ST elevation in leads V1-V3. It is most common in males (8:1).

Most reports have been from Asia (especially southeast) and Europe. Fever may be a trigger for arrhythmia. About fifteen percent of patients with Brugada syndrome have a mutation in *SCN5A* (a sodium channel gene).

c) Arrhythmogenic right ventricular “dysplasia” or cardiomyopathy (ARVC): a progressive cardiomyopathy (note that the meaning of the term “dysplasia” as used here is distinct from the meaning when used in neurology for static, developmental

brain malformations) associated with sudden death in 20-40 year olds, especially athletes. Half of ARVC cases are familial, with 30% due to a PKP2 gene mutation. The condition is possibly due to desmosome dysfunction. ARVC is detectable with MRI or cardiac CT; echocardiography is less sensitive. Diagnosis is challenging in early stages of the disease. Although there is no known relationship between ARVC and epilepsy, several individuals with this cardiac condition have been reported to have had a seizure at the time of sudden death.

d) Catecholaminergic polymorphic ventricular tachycardia (CPVT): Associated with sudden death in healthy young adults, especially during adrenergic stimulation such as exercise. Resting EKG is usually normal. Ryanodine receptor gene (RYR2) mutations have been found in some patients with CPVT. The RYR2 gene is also expressed in the brain, including the hippocampus. A rare familial form is related to a mutation in calsequestrin (*CASQ2*), a gene related to calcium homeostasis.

e) Short QT syndrome: This is an uncommon condition defined by a QTc < 330 ms on EKG. Mutations in potassium channel genes have been reported. (Of clinical note, rufinamide should be avoided in these patients).

f) Wolff-Parkinson-White: Short PR interval is seen on resting EKG, associated with the presence of an accessory atrio-ventricular pathway. Increased risk of sudden death has been recognized in a small subpopulation with rapid accessory pathway conduction.

iv) A single standard EKG may not detect all patients with long QT syndrome or Brugada syndrome. 35% of patients with long QT syndrome have normal or borderline corrected QT intervals (QTc; normal <0.44s for men, 0.46s for women).

- v) Mechanisms of sudden cardiac death or myocardial injury during seizures or epileptiform discharges may include the following:
- a) Hyperadrenergic state associated with coagulative myocytolysis (also known as contraction band necrosis), as can occur in subarachnoid hemorrhage and “scared-to-death” syndrome (also known as “voodoo death” or “broken heart” syndrome). This can be associated with apical ballooning on echocardiography, or Takotsubo cardiomyopathy. Other acute autonomic changes that may occur in “voodoo death” (including hyperparasympathetic activity and possibly acute adrenal failure) may play a role as well.
 - b) The lock-step phenomenon: When this occurs, brain discharges are directly linked to activity of small intracardiac autonomic nerves, which is not normally the case and which predisposes to arrhythmias in animal models.
 - c) Evidence suggests that intracardiac release of catecholamines is an important cause of cardiac injury. Cumulative injury may occur over time via this mechanism.
 - d) Hyperactive parasympathetic activity, including asystole and possibly hyperactive baroreflex activity or similar neurocardiogenic mechanism (although these are typically benign).
 - e) Ischemia/coronary artery occlusion, particularly in patients with known coronary artery disease (not typically considered SUDEP, but still a potentially preventable cause of sudden seizure-related death in epilepsy patients).
 - f) Arrhythmias/channelopathies.
 - g) Conduction or autonomic effects of antiepileptic drugs or their withdrawal.

h) Combinations of the above, or combinations of the above and pulmonary issues, especially hypoxia.

C. Lessons learned from respiratory physiology:

- i. Serotonin plays a role in respiratory drive and the response to hypercapnia. In sheep and mouse models of SUDEP, seizures are associated with death due to respiratory arrest. In one strain of mice (DBA), pharmacologically increasing serotonin or its action can prevent SUDEP by preventing seizure-related respiratory arrest, and blocking serotonin activity increases seizure-related death. In other studies, increasing serotonin may decrease sleep apnea and death after stroke. See discussion on serotonin in SIDS section above as well.
- ii. In one animal model, administration of oxygen prevented seizure-related sudden death.
- iii. Possible respiratory mechanisms contributing to SUDEP
 - a) Central apnea, either related to serotonin as above, other substances released during seizures such as adenosine or opiates, or to “cerebral shutdown” of all brain activity after a seizure. This “shutdown” may be due to ictal or post-ictal dysfunction of monoamine neurons, including serotonergic neurons. Inactivity of monoamine neurons could lead to simultaneous central apnea and decreased arousal – both thought to occur in SUDEP
 - b) Obstructive apnea

- c) Pulmonary edema, especially neurogenic edema, as seen in a sheep model of SUDEP
- d) Ictal hypoxia, frequently observed with seizures, including complex partial seizures without generalization. Hypoxia can be present without obvious respiratory distress or dysfunction. It typically involves a component of central apnea, but may also involve ventilation-perfusion mismatch or pulmonary edema.
- e) Aspiration (not typically considered SUDEP, but another potential cause of sudden non-traumatic, non-drowning, seizure-related death)
- f) Laryngospasm, perhaps induced by aspiration. This often leaves no obvious findings on autopsy, and therefore is likely to be classified as SUDEP.
- g) Also see SIDS discussion for other respiratory-related issues.

D. Recommendations to advance research in SUDEP (see Table 1 for summary)

i. Animal models

- a) Continue the search for and development of genetic models of SUDEP.
- b) Sudden death, typically seizure-related is known to occur in animal models of epilepsy. These deaths should be viewed as a research opportunity to learn more about their relevance to SUDEP. When possible, simultaneously monitor cardiac, respiratory (including for central and obstructive components), cortical (EEG), brainstem, and autonomic function in these models.
- c) Consider adding monitoring of the phrenic nerve in animal models of SUDEP.

- d) Expand research regarding effects of commonly used antiepileptic drugs and their withdrawal on peri-ictal cardiac and pulmonary function, and on cardiac ion channels important in human arrhythmia syndromes.
- e) Study preventative drugs in animal models of sudden death, including beta blockers (to block the hyperadrenergic state), selective serotonin reuptake inhibitors (SSRIs; to enhance respiratory drive and reverse possible serotonergic dysfunction), adenosine blockers, opiate blockers, statins, alpha blockers (to block the hyperadrenergic drive and neurogenic pulmonary edema), fish oil, exercise and other specific agents with potential for rapid translation to clinical investigation.
- f) Use experimental models to evaluate whether there is an animal equivalent to the post-ictal ‘cerebral shutdown’ that seems to occur in some humans with SUDEP.
- g) Study the effect of tactile stimulation on resumption of breathing and oxygenation in the post-ictal setting in animal models.
- h) Devise animal studies based on single or multiple cage occupancy to evaluate the role of nocturnal supervision or room sharing in SUDEP prevention.
- h) Explore the effect of stress on SUDEP.
- i) Investigate the neurophysiology and record activity from respiratory neurons during seizures in serotonin neuron knockout animal models to assess possible roles of other non-serotonin mechanisms involved in the ascending arousal system including norepinephrine, acetylcholine and histamine.
- j) Use central microdialysis in rats to evaluate neuronal release of different neurotransmitters before, during and after seizures; correlate these with cardiac, respiratory and autonomic effects of the seizures.

- k) Consider studying an animal model of epilepsy in a low oxygen environment.
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- ii) Clinical investigations
 - a) Retrospectively explore environmental factors such as cigarette smoke exposure and room sharing, family history of sudden death including SIDS, and possibly genetics, including utilizing existing large databases that include SUDEP deaths.
 - b) Prospectively evaluate respiratory markers, arousability measures, infectious and inflammatory markers, and additional autonomic studies including baroreflex sensitivity (not just heart rate variability) in patients at risk for SUDEP, and perform specialized neuropathological studies of SUDEP cases to determine if there is evidence of abnormalities of neurons involved in autonomic and respiratory control, including serotonin neurons.
 - c) Study the effect of stimulation on resumption of breathing and oxygenation in the post-ictal period in patients in epilepsy monitoring units.
 - d) Study ictal and post-ictal apnea and desaturation and their relation to SUDEP. Consider routine oxygenation and respiratory monitoring in all video/EEG monitoring units. Study the role of soft pillows in peri-ictal respiration and SUDEP—could pillows that prevent obstruction and re-breathing help?
 - e) Support and contribute to existing SUDEP research projects, such as Mortemus in Europe (see <http://mortemus.org>).
 - f) Evaluate for the presence and history of comorbid cardiac disease in epilepsy patients, or the misdiagnosis of epilepsy in cardiac patients.

- g) Obtain sentinel EKG in all patients with epilepsy, particularly refractory epilepsy, to identify conditions associated with potentially lethal cardiac arrhythmias, including long or short QT syndrome, Wolff-Parkinson-White, and Brugada syndrome.
- h) Screen existing cardiac arrhythmia or implanted defibrillator databases for patients with epilepsy.
- i) Perform additional prospective studies on long-term cardiac monitoring, such as with implantable loop recorders, in high risk patients.
- j) Obtain a cardiac evaluation in patients with exercise-induced “seizures” to exclude cardiac events.
- k) Standardize post-mortem cardiac evaluations for patients with SUDEP.
- l) Evaluate which feature of nocturnal supervision or room sharing may be protective for SUDEP.
- m) Evaluate the role of medications known to be preventative in other conditions of sudden death, including beta blockers, selective serotonin receptor inhibitors (SSRIs), statins, alpha blockers, fish oil, and exercise. Examine existing large databases of medication use, including those from clinical drug trials, for possible protective or adverse effects (to then be studied prospectively). Consider using surrogate markers of outcome initially, such as post-ictal central apnea when studying SSRIs.
- n) Study mood disorders, especially depression, and their treatment as risk factors for SUDEP. For example, is post-ictal dysphoria/depression a marker for seizure-related serotonin deficit that might predispose to central apnea?
- o) Study the effect of antiepileptic drugs (chronic use, withdrawal, combinations) and stimulation devices being used to treat epilepsy more thoroughly in regard to their

potential effect on SUDEP. Can vagus nerve, thalamic, or other stimulation via implanted devices used for epilepsy decrease post-ictal apnea or central shutdown?

p) Study sudden death in epilepsy patients even when it does not qualify as definite SUDEP. For example, study seizure-related myocardial infarction or arrhythmia in adults with epilepsy and known cardiac disease, addressing whether or not epilepsy increases the chance of sudden death in these patients. Would beta blockers be preventative? This is an expanding group as the population ages. Similarly, death during status epilepticus warrants further study (many of the mechanisms are likely to be similar to SUDEP), and near-SUDEP should be included in any SUDEP registries or studies.

q) Study the ability to detect cardiac injury from seizures via cardiac imaging or post-ictal biomarkers (such as troponin or brain natriuretic peptide), and its potential relation to SUDEP.

r) Consider using electroconvulsive therapy for depression as a model for studying the acute effects of seizures, especially the brain activity itself, on cardiopulmonary and autonomic function.

iii) Genetics

a) Obtain a detailed family history of sudden death, including SIDS, and arrhythmias, in all patients with epilepsy. When positive, refer to cardiology for evaluation and genetic testing.

b) Organize an international study of families with both epilepsy (or even SUDEP) and at least one family member with unexplained sudden death for genetic studies.

Consider cardiac MRI and other advanced cardiac studies to detect subtle abnormalities including arrhythmogenic right ventricular cardiomyopathy for these patients.

c) Consider an international study of Dravet syndrome to determine the rate of SUDEP in this condition, its mechanism and potential preventative measures.

d) Bank DNA in large studies of SUDEP and study the genetic risk factors known today and those recognized in the future.

e) Study the same genetic risk factors in animal models of SUDEP.

f) Bank tissue of SUDEP victims and controls for genetic studies.

iv) Devices

a) Develop an implanted device that can perform long term monitoring of EKG, oxygenation, chest wall movements, and preferably EEG as well, with alarm capabilities. The device experts present felt that this was not difficult technically, but might require tapping into a larger market for financial reasons, such as sleep apnea, SIDS or sudden cardiac death. This type of device could ultimately be combined with the appropriate treatment modality, such as cardiac defibrillation, cardiac pacing, phrenic nerve or diaphragm pacing, an alerting stimulus, or even direct or indirect brainstem stimulation for central apnea. This type of device could then be used in the highest risk patients for both prevention and research into the mechanism of SUDEP.

b) Improve existing oxygenation monitors for routine home and epilepsy monitoring unit use during sleep.

- c) Study devices for seizure detection/notification for home use, including those being advertised now (most or all without scientific data supporting their use). These could be easily and quickly studied in epilepsy monitoring units, and could utilize various combinations of information obtained from EMG (muscle), EKG, EEG, oximetry, and sudden change in body position via accelerometers. Consider pursuing restrictions in false marketing claims of these device manufacturers without data, and encouraging them to perform proper studies first.

- v) Case-identification
 - a) Collaborate with the National Association of Medical Examiners to increase awareness of SUDEP, to maximize the quantity and quality of postmortem examinations, to make sure the term SUDEP appears on death certificates, and to obtain referrals to a central registry/tissue bank.
 - b) Develop a standardized post-mortem evaluation for SUDEP cases, include cardiac and pulmonary exams.
 - c) Consider establishing SUDEP as a reportable condition, requiring autopsy and DNA banking, as has been done for sudden death in children in some states.
 - d) The presence of a gene mutation, serotonin deficit, cardiac fibrosis or other possible explanation of the mechanism of death in an individual with epilepsy who dies suddenly and unexpectedly does not change the diagnosis of SUDEP. The term “unexplained” may not be ideal as we learn more about SUDEP and are able to explain death in some cases; hence the word “unexpected” is preferred, though also not ideal.

- e) Consider the use of “verbal autopsies”, or standardized questions about the circumstances surrounding death.

- vi) Collaboration/Consortium
Consider a multicenter study of high risk patients (e.g., those with refractory convulsions, especially in sleep), enroll and study them while in the epilepsy monitoring unit, then follow them closely including providing a medical alert piece of jewelry with an emergency phone number to be called in the event of hospital admission or death, and study the following in these patients while in the epilepsy monitoring unit:
 - i) 12-lead EKG
 - ii) Blood/DNA for banking. Blood for DNA can be banked via blood-spot cards that are easy to store and can be kept at room temperature.
 - iii) Baseline echocardiogram; cardiac monitoring, including ictal and post-ictal.
 - iv) Autonomic evaluation, including heart rate variability, baroreceptor sensitivity and response to Valsalva.
 - v) Respiratory evaluation, including oxygen saturation in the interictal, ictal and post-ictal states; nasal airflow, chest and abdominal wall movement; sighs/yawns/arousability measures (as in SIDS studies); possibly full polysomnography.
 - vi) Standardized history including family history of sudden death, in-utero and postnatal smoke exposure, sleep habits/environment, alcohol and drug use
 - vii) Check CRP, post-ictal troponin and post-ictal brain natriuretic peptide

- viii) Consider including a volunteer, high-risk subgroup of patients in whom a device would be implanted to record O2, EKG, EEG, and respiratory effort
- ix) Annual phone follow-up and repeat questionnaire, including information about medications, illicit drugs, alcohol, compliance, sleep habits, SUDEP awareness, etc
- x) In the event of near-SUDEP or SUDEP, provide readily accessible information to first responders, emergency room staff, or medical examiner office on how to contact the study center (i.e., prior educational programs, medical alert ID or bracelet).
- xi) If probable or possible SUDEP occurs:
- Perform a standardized autopsy, preferably with select tissues analyzed at a central or regional site. Of note, one should not rely on formalin-fixed, paraffin embedded tissue for genetic studies but rather blood-spot cards, blood in EDTA, or frozen tissue.
 - detailed cardiopulmonary exam
 - specialized brainstem neuropathology, including serotonin evaluation
 - further genetic studies on tissue
- xii) Create SUDEP registry and central tissue bank, possibly managed by a SUDEP consortium or coalition (see section V: Future directions, below). It was estimated that there are about 2000 SUDEP deaths per year in the U.S., and perhaps 400-500 per year in the U.K. Include cases with and without known seizures at the time of death, and possibly include prolonged seizures/status epilepticus if no obvious cause of death.

II. EDUCATING PEOPLE WITH EPILEPSY AND THEIR FAMILIES ABOUT SUDEP

A. Ethics: The right to know versus the right not to know

To address the issue of specific benefits and harms of discussing SUDEP with people with epilepsy and their families, the primary principles of bioethics were considered: respect for autonomy, non-maleficence, beneficence and justice. This discussion was guided by the framework in the text *Clinical Ethics: A Practical Approach to Ethical Decisions in Clinical Medicine* by Jonsen et al (Jonsen et al, 2006).

The potential benefits of health care providers discussing SUDEP with people with epilepsy and their families include:

- i) Helps health care providers and people with epilepsy share in treatment goals
- ii) Helps to establish a "truth telling" relationship
- iii) Avoids a false sense of security and resulting complacency regarding epilepsy and its treatment
- iv) Allows for expression of the natural anxiety regarding epilepsy and encourages it to be dealt with in a constructive fashion
- v) Allows people with epilepsy to organize their lives with reasonable expectations
- vi)

Allows people with epilepsy and their families to help reduce possible risk factors for SUDEP, e.g., by ensuring medical compliance and minimizing behavior that can exacerbate seizures.

- vii) Significantly reduces the fear of SUDEP in low risk populations, especially in those who fear dying due to seizures but have been afraid to inquire (the “unasked question”).
- viii) If SUDEP does occur, the family’s pain, grief and blame may be lessened by having been fully informed, knowing the patient was fully informed, and knowing how to get information and grief counseling, including discussing with other affected individuals’ families.

It was also pointed out that the physician’s primary obligation should remain to help the patients themselves (for adults with capacity), rather than their families or caregivers.

The potential risks of health care providers discussing SUDEP with people with epilepsy and their families include:

- i) Precipitating anxiety, depression or post-traumatic stress disorder in individuals with a predisposed psychological makeup.
- ii) In certain cultures, the discussion could be interpreted as predisposing the individual to the event.
- iii) Misunderstanding of ‘low risk’ as ‘no risk’.

B. When & How to Provide Information to people with epilepsy and their families

At the time of the workshop, two published studies addressed the issue of practitioners’ communication with their patients about SUDEP. Lewis et al (Lewis et al, 2008) conducted a survey of members of the UK Clinical Nurse Epilepsy Specialists association and other nurses with an interest in epilepsy. Fifty percent of surveyed nurses discuss SUDEP with most or all patients, done so by the request of the physician. When discussing specific risks,

48% of nurses raised the issue of SUDEP. When discussing general risks, 71% of nurses raised the issues of SUDEP. With regard to timing of the discussion, 45% of nurses discussed SUDEP at the time of diagnosis, and 17% when therapy was started. The nurses reported responses of anxiety (49%), depressed mood (13%), anger (10%), disbelief (23%) and objection to being told (16%); however, improved adherence to treatment was reported in 62% of cases.

Morton et al (Morton et al, 2006) conducted a survey of UK neurologists to determine compliance with the National Institute of Clinical Excellence (NICE) guidelines, which recommend that SUDEP be discussed with people with epilepsy. Twenty-six percent of physicians surveyed reported that they discussed SUDEP with the majority of their patients, 61% discussed SUDEP with some of their patients, 7.5% with none, and 5% all. Doctors who discussed SUDEP with all or a majority of their patients were significantly less likely to report negative reactions from their patients, and noted most patients received the information with equanimity or positively compared to those doctors who did not discuss SUDEP frequently. A wide variety of reasons for discussing SUDEP and the perceived reactions of patients were reported.

In a qualitative study of 35 patients with epilepsy (Prinjha et al, 2005), all wanted to know more about their epilepsy. SUDEP was one of the concerns raised by some.

There is no specific existing literature to guide the health care provider in assessing the readiness of a person with epilepsy or their family to learn about SUDEP, the timing and content of these discussions, or the necessary cultural and social considerations.

C. Recommendations (see Table 2 for summary):

- i) Except for the rare, specific patient with a cultural or psychological context in which the physician is convinced that the discussion will be harmful, it was the consensus of the discussants that the benefits of disclosing the risk of SUDEP to patients outweigh the harms. This is particularly (but not only) true in patients with generalized tonic-clonic seizures. Further research is needed in this area.
- ii) The increased risk of sudden death, including SUDEP, associated with epilepsy should be disclosed as part of the overall education and counseling to patients about their condition and prognosis of living with epilepsy.
- iii) A brief clinical tool should be designed to assess readiness to learn about SUDEP, then tested. This could be used to determine how and when people with epilepsy and their families should receive information about SUDEP.
- iv) Focus groups should be held for people recently diagnosed with epilepsy, people with medically intractable epilepsy, and families who have been affected by SUDEP to determine when and how much information should be presented.
- v) Research studies should be performed to determine the best methods of educating people with epilepsy and their families, to assess the effects of discussing SUDEP on the patient and family (both immediate and long-term), and to assess the effectiveness of discussion on reducing identified risk factors and the incidence of SUDEP.

vi) Learning materials should be developed that include consistent, appropriate information for the public to ensure that SUDEP education is accurate and communicated appropriately. This information should exist on the major portals available for the public including: the Epilepsy Foundation, Center for Disease Control, Citizens United for Research in Epilepsy (CURE), and epilepsy.com. Information should be available in multiple levels of description to accommodate the different education levels, and in multiple languages. Materials should be available in a variety of formats, including print, web-based, podcast, and other.

III EDUCATING HEALTH CARE PROVIDERS ABOUT SUDEP

There is a paucity of data regarding health care provider knowledge of and attitudes towards discussing SUDEP.

A. Recommendations

- i) Develop a survey aimed at identifying:
 - Health professionals' knowledge of SUDEP
 - Health professionals' expectations of patients' and families' reactions to information on SUDEP
 - Health professionals' timing of discussion of SUDEP with patients and families
 - Health professionals' comfort in discussing SUDEP with patients and families
 - Health professionals' perceptions of the utility of educational tools for educating their patients

ii) Develop and disseminate consistent (if not identical) information regarding SUDEP to professionals. The information should be based on the highest level of evidence available especially with regard to risk factors. Communication should be via society websites: AES, AAN, ANA, CNS, CDC, EF, epilepsy.com, and well-known family medicine, and pediatric society websites. Educational materials must consider the heterogeneity of individuals affected by epilepsy and how this may affect the information they may receive about SUDEP. Different versions should be developed for neurologists, primary care providers, pathologists, coroners, etc.

iii) Guidelines should be developed that provide recommendations for the why, when and how of discussing SUDEP. Guidelines should be based on evidence, rather than opinion and consensus and developed by organizations with credibility in the medical community (e.g. the American Academy of Neurology, American Epilepsy Society). The process should build upon the experience of those who have developed SUDEP guidelines in other countries. In specific, health care providers should be part of the guideline development process and not feel coerced by professional or legal recourse regarding the need to adapt a guideline to the specific needs of individual people with epilepsy. The intended and un-intended consequences of guidelines should be considered based upon the experience of countries in which guidelines are in place. The important role of the bereaved community with regard to advocacy and production of educational materials was acknowledged. Specific consideration should be given to meeting the needs of the broad spectrum of individuals affected by epilepsy (as determined by future research) as well as the social and legal implications of proposed guidelines.

IV. PREVENTION OF SUDEP WITH CURRENT KNOWLEDGE AND DATA

Based on current knowledge, the most effective means of prevention is to *reduce the frequency of seizures, especially but not only generalized tonic-clonic seizures, through maximal epilepsy care*, including maximizing compliance with medications, avoiding seizure triggers such as sleep deprivation and heavy ethanol use, and consideration of epilepsy surgery in appropriate candidates in a timely fashion, as recommended in the prior AES/EF SUDEP Task Force report (So et al, 2009); unnecessary polytherapy should be avoided, as this may represent an independent risk factor for SUDEP (though it may also be a marker of epilepsy severity, despite attempts to control for this in multiple studies). To this end, the measures discussed above regarding patient, family and care provider education were endorsed. It was emphasized that research is essential for prevention and the recommendations made to develop a research agenda in SUDEP above will aid with prevention in the long term. Preliminary evidence suggests that nocturnal supervision or monitoring devices may be protective for SUDEP, but this requires further study.

Additional recommendations to aid in SUDEP prevention include:

- A) Educate patients about research promotion and participation,
- B) Increase awareness of what constitutes good seizure management, both in care providers and patients
- C) Increase awareness of SUDEP in the public domain, including through the use of lay media

- D) Establish collaborations between support groups, funding sources, health care professionals and others, both nationally and internationally, to advance the public discussion of SUDEP.
- E) Consider the experience of other organizations in advancing SUDEP discussion and strategies, including international epilepsy organizations such as Epilepsy Bereaved UK and Epilepsy Australia as well as non-epilepsy programs such as those involved with SIDS prevention..
- F) Consider developing a SUDEP practice guideline via the American Academy of Neurology (AAN)
- G) For future clinical studies, consider using social science study designs to compare SUDEP rates before and after interventions in various regions, and following trends over time. Consider randomizing communities to “aggressive educational campaign” or standard care and following SUDEP rates; this would require accurate registry information and high case ascertainment.
- H) Concentrate research on *modifiable* risk factors, both at the animal and human level.

V. FUTURE DIRECTIONS

- A) Present the workshop recommendations at the American Epilepsy Society meeting in December 2008. This was done, and feedback was encouraged and received.
- B) Create an ongoing SUDEP workgroup. This has already begun. *The SUDEP Coalition* has been formed jointly by the American Epilepsy Society (AES), The Epilepsy Foundation, Citizens United for Research in Epilepsy (CURE), and NINDS. Its main

purpose will be to help promote and organize SUDEP research and other SUDEP related activities, including the creation of the recommended SUDEP registry and tissue banks.

The Coalition will fall under the umbrella of the American Epilepsy Society for administrative and practical purposes, and information about it will be kept on the AES website at www.aesnet.org/SUDEP.

C) Encourage funding sources to solicit and fund proposals on SUDEP.

VI. CONCLUSIONS

SUDEP is not rare, and is a devastating complication of epilepsy. Except in extenuating circumstances, all people with epilepsy should be educated about SUDEP as part of their general education on the potential harms of seizures. Increasing awareness may facilitate improved seizure control, possibly decreasing the incidence of SUDEP. In addition, education and increased awareness will lead to increased funding for research into the causes and prevention of SUDEP. In the past few years, there has been significant advance in our understanding of the clinical and physiologic features of SUDEP in both people and animals. With this expansion of clinical, genetic, and basic science research and newly established multidisciplinary collaborations, there is significant hope of advancing our understanding of SUDEP and ultimately our ability to prevent it.

VII. APPENDIX: Participants

Scientific session co-chairs: Elson So and Jeff Noebels

Sub-section moderators:

Clinical Factors: Elizabeth Donner, Anne Berg

Cardiorespiratory and Autonomic Mechanisms: Lawrence Hirsch, Martin Samuels

Genetics: Alica Goldman, Michael Ackerman
Case Identification: Nancy Temkin, Paul Schraeder
Prevention: Nina Graves, Lina Nashef

Education session co-chairs: Jeffrey Buchhalter and Tess Sierzant
Subsection moderators:

Ethics: Nancy Collins; Jane Hanna
Educating Patients and Families: Joan Austin, Fran London
Educating Professionals: Andres Kanner, Jackie Bainbridge
Guidelines: Cynthia Harden, Susan Duncan
Prevention: Rosemary Panelli, David Thurman

Other Participants: see attached Excel spreadsheet

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TABLE 1: Avenues of scientific research related to SUDEP and its prevention.
(See text, plus full report online for details)

| System | Avenue of research | Potential impact on SUDEP prevention |
|--------------------|--|--|
| Cardiac | Investigate the utility of obtaining an EKG in all patients with epilepsy | Identification of high risk patient or group; development of medical or device-mediated prevention of arrhythmias. |
| | Investigate the role of drugs known to prevent sudden cardiac death (unrelated to epilepsy), including use of existing large databases of epilepsy patients. | Prevention of cardiac-related causes of SUDEP by using medications currently available. |
| | Study peri-ictal changes in EKG, and effects of AEDs | Identification of high risk patients, or specific cause in a given patient; medical or device-mediated prevention of arrhythmias |
| | Assess peri-ictal cardiac function, including looking for apical ballooning on echocardiography, and postictal cardiac injury markers such as troponin and brain natriuretic peptide | Use of beta-blockers; identification and prevention of seizure-related cardiac injury |
| | Conduct prolonged EKG monitoring (months-years) | Identification of near-SUDEP and prevention of arrhythmia-related SUDEP |
| | Perform cardiac MRI in high-risk patients | Prevention of arrhythmias, including ones associated with arrhythmogenic right ventricular cardiomyopathy |
| | | |
| Autonomic | Examine measures of static and dynamic autonomic function, including in the peri-ictal setting | Identification of high risk patients; intervention that is more specific to defined deficit. |
| | | |
| Respiratory | Study the role of prone sleep position, rebreathing and partial obstruction | Avoidance of prone position (possibly with help of a device); use of safer pillows or bedding. |
| | Investigate arousability and the rate of sighs and gasps at baseline while awake and asleep as risk factors for SUDEP | Identification of high risk patients |
| | Evaluate postictal respiratory function, including role of tactile or other alerting stimuli in aborting central apnea | Identification of high risk patients; postictal stimulation to abort apnea, possibly via a device |
| | Study role of serotonin and SSRIs and peri-ictal respiration (including retrospective study of epilepsy patients in existing large databases that have SUDEP information) | Use of SSRIs for prevention; identification of high-risk patients. |
| | Assess relationship of sleep apnea and other nocturnal respiratory measures to SUDEP | Identification of high-risk patients; use of CPAP and nocturnal oxygen |
| | Consider role of oxygen in prevention of SUDEP | Administration of oxygen peri-ictally |
| | Define physiology of postictal apnea, including role of “cerebral shutdown”, brainstem spreading depression, neurotransmitters | Prevention of postictal apnea via medication, device or stimulation |

| | | |
|--|---|--|
| | (including serotonin, opiates, adenosine, acetylcholine, histamine, norepinephrine), and triggers to resume breathing | |
| | Evaluate peri-ictal pulmonary edema | Prevention by using medications such as alpha blockers; identification of high risk patients |
| | Study the postictal hypoxic state, its pathophysiology including ventilation/perfusion mismatch, and its relationship to SUDEP | Use of oxygenation to prevent complications of hypoxia or reverse cardiorespiratory compromise; identification of high risk patients |
| | Assess role of aspiration and laryngospasm | Prevention of asphyxia |
| | Monitor phrenic nerve in SUDEP models | Use of phrenic nerve or diaphragmatic pacing |
| | | |
| Genetic | Investigate genes known to be involved in sudden cardiac death or SIDS, and genes known to be involved in epilepsy but that are also expressed in the cardiac, autonomic or respiratory systems. | Identification of high risk patients; prevention of arrhythmias via medication or devices. |
| | Identify family history of sudden cardiac death | Identification of high risk patients. |
| | Bank tissues/DNA of large cohort of high risk individuals and SUDEP persons | Identification of genes, and therefore high risk patients, and determine possible mechanisms |
| | | |
| Medical devices | Develop better home monitors, including an oxygen saturation monitor | Early identification of potential SUDEP, allowing earlier intervention |
| | Develop implanted device that can record and store EEG, EKG, oxygenation, respiratory effort, and body position or movement; include alarms and ability to activate treatment devices such as cardiac pacemakers, defibrillators, alerting stimuli, phrenic/diaphragmatic pacemakers, or even brainstem stimulators for cerebral shutdown with central apnea. | Individualized prevention of SUDEP according to underlying mechanisms specific to the individual. |
| | Study existing home “seizure monitors”, preferably prior to commercial marketing and use | Early identification of potential SUDEP allowing intervention |
| | Investigate the role of pacemakers once specific arrhythmias are found | Prevention of arrhythmia-related SUDEP |
| | | |
| Postmortem, including case identification | Education of, and collaboration with, medical examiners to increase recognition and documentation of SUDEP, and referral to central study sites | Early identification of SUDEP individuals for prompt initiation of study measures or protocol |
| | Develop and distribute a standardized SUDEP protocol for autopsy and clinical data collection at time of death | Collection of sufficient clinical and autopsy data for confident determination of definite SUDEP cases; obtain research material |
| | Establish SUDEP as a reportable condition with requirements for autopsy and tissue banking | Collection of tissue specimens for research investigations into risk factors and pathologic mechanisms underlying SUDEP |
| | Study brainstem respiratory centers, including serotonergic system as in SIDS | Determination of specific mechanisms for potential pharmacologic, genetic or device-mediated intervention |
| | Detailed investigation and banking of DNA and tissues for genetic | Determination of genes that contribute to SUDEP occurrence, for |

| | | |
|--------------|---|--|
| | studies | future research into methods of therapeutic intervention. |
| | Initiate detailed cardiac studies, including thin slices for subtle fibrosis or other injury | |
| | Perform postmortem examinations with specific protocol, including investigation of brain, heart, lungs, and autonomic system , preferably at centralized site(s) | |
| | Obtain controls without epilepsy for all of the above | |
| | | |
| Other | Study the effect of room sharing or special monitoring devices such as “baby monitors.” | Reduction of SUDEP risk |
| | Assess the effect of prenatal and post-natal tobacco smoke exposure, recent infection, fever, and inflammatory markers | Identification of high-risk factors and their avoidance |
| | Determine the rate of SUDEP in specific epilepsy syndromes, such as Dravet syndrome, and role of SCN1A mutations | Identification of specific high-risk groups, warranting more intensive monitoring and investigation |
| | Investigate the effect of implanted deep brain and responsive brain stimulators on the rate of SUDEP and on peri-ictal respiration | |
| | Study the effect of AEDs on all of the above measures, including interictal and peri-ictal cardiac, respiratory and autonomic measures. Also consider effect of withdrawal of AEDs. | Avoidance of specific AEDs in specific circumstances |
| | Review in detail all near-SUDEP cases and implement aggressive individualized monitoring and prevention measures | Prevention of recurrence in given individual |
| | Investigate status-epilepticus-related death | Prevention of this other form of seizure-related death |
| | Assess the role of seizure-related myocardial infarction | Prevention of this form of seizure-related sudden death , which may be under-recognized |
| | Maintain an ongoing multidisciplinary research consortium | |
| | Conduct large collaborative studies of high risk patients | |
| | Increase education and awareness of the public, patients and health care professionals | Improvement of compliance and better avoidance of seizure triggers such as sleep deprivation and ethanol |
| | Advocate early referral to tertiary centers for refractory seizures | Maximize seizure control, including via epilepsy surgery |
| | Study the benefit of decreasing polytherapy, possibly via a randomized trial of reduction in number of AEDs | |
| | | |

Abbreviations: AED: antiepileptic drug; CPAP: continuous positive airway pressure; EKG: electrocardiogram; EEG: electroencephalogram; MRI: magnetic resonance imaging; SIDS: Sudden infant death syndrome; SSRI’s: Selective serotonin reuptake inhibitors. SUDEP: Sudden unexpected death in epilepsy patients

Table 2:
Avenues of research related to SUDEP education and awareness

- Determine if patients at low risk of SUDEP want to be educated
- Determine how patients/families learn best about SUDEP
- Determine ‘readiness’ to learn so that information can be presented at the optimal time
- Determine the barriers providers have to discussing SUDEP
- Determine the best format for presenting information in the office and out
- Determine barriers to providers following guidelines for presentation of information regarding SUDEP
- Determine the effect of education on patients’ anxiety, quality of life, compliance, avoidance of high-risk behaviors, and the incidence of SUDEP