

Steven L. Thornton, M.D.
Southern Illinois University School of Medicine
Department of Psychiatry
Division of Developmental Disabilities

Epilepsy and SUDEP: An Underrecognized Complication of Epilepsy

Vignettes

1. Panic Disorder?
2. "The patient is eloping"
3. The slow mode
4. "It's just one of his behaviors"
5. Third day post-op

Staff Observations of Seizure Related Behaviors

- Irritability
- Quietness
- Yelling
- Chanting
- Eloping
- Affectionate (hugging)
- Silliness (giggling)
- Spinning in circles
- Lying on the floor and sliding
- Running into walls
- Touching genitals
- Picking at old abdominal wound
- Belching

Facts

- I/DD is seen in ~3% of population
- Epilepsy is seen in 1 – 2% of the population
- Epilepsy is seen in 10 - 20% of I/DD patients
- Epilepsy is seen in 45 – 59% of severe I/DD pts
- 40% of institutionalized patients have epilepsy
- Psychiatric comorbidity is high
- Seizure diagnosis is difficult due use of sedatives and behaviors

Facts

- Observer reporting is often inaccurate, underreporting non T/C seizures, and over reporting stereotypical behaviors as seizures
- AED treatment is life-long
- Polypharmacy is common
- The I/DD population has increased vulnerability to the effects of the seizures and the AEDs

Facts

- Seizures *are not* benign
- Seizures cause blunt trauma, lacerations, fractures, burns, concussion, subdural hematoma, and intracerebral hemorrhage
- Risk factor for aspiration
- Mortality rate shows a 2 – 3 fold increase compared to the general population
- SUDEP – accounts for 2 – 17% of all deaths in epilepsy patients

SUDEP Risk Factors

1. Occurrence of T/C seizure type
2. Use of greater than 2 AEDs
3. IQ less than 70

SUDEP is the 5th leading cause of death in epilepsy patients, behind neoplasm, heart disease, CVA, and accidents/suicide

What Will be Covered:

- Seizure Overview
- Behaviors/Manifestations of Epileptic Syndromes
- I/DD Syndromes and Epilepsy
- Complications of Seizure Disorders
- SUDEP



Overview of Seizures - History

Epilepsy has been observed since antiquity. The first known writings were recorded on stone tablets between 500 – 700 BC. It was described in the Bible and written about by Hippocrates. He recognized that the symptoms originated in the brain. Many historical figures have been known to suffer from epilepsy.

Overview of Seizures - History

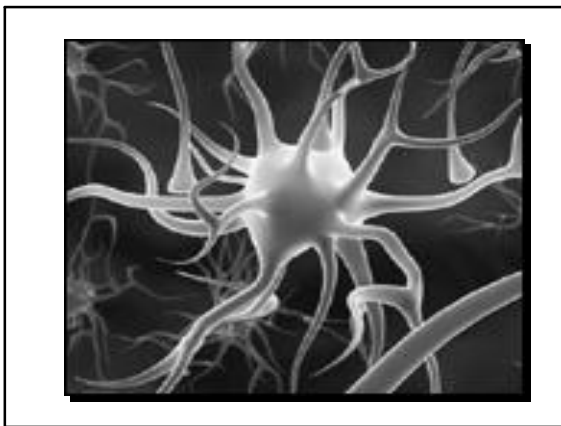
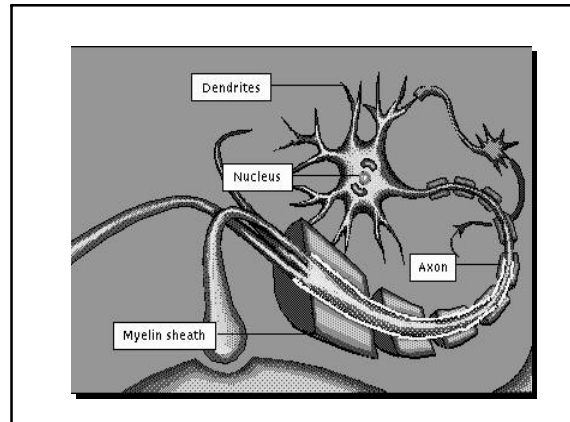
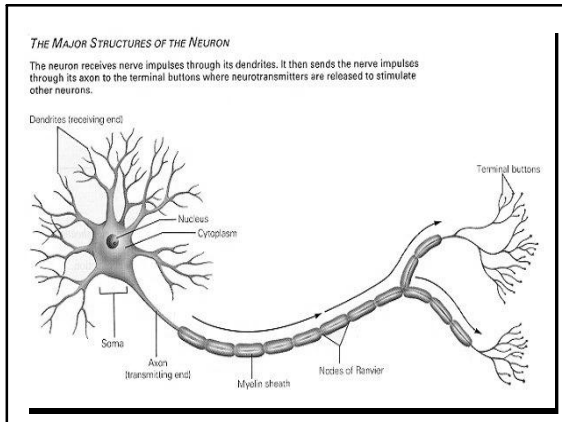
Alexander the Great, Julius Caesar, Napoleon Bonaparte, Dickens, and Van Gogh are just a few of the leaders and artists who have been affected by epilepsy.

Epilepsy has been depicted in art and at one time was felt to be "the sacred disease" in which the person was possessed by an evil spirit. This stigma is only slowly being dispelled today through better understanding and education.



Overview of Seizures

- An epileptic seizure is sudden synchronous discharge of a network of neurons. Which results in changes of consciousness, behavior, emotion, motor function or sensation.



Overview of Seizures

- Epilepsy is a condition in which seizures recur, usually spontaneously.
- Nonepileptic seizures occur singularly or in a discrete cluster commonly caused by an acute condition.

Nonepileptic Seizures

- The differential diagnosis of nonepileptic seizures includes:
 - Infection
 - Trauma
 - Tumors
 - Toxins
 - Metabolic derangements

Seizure Classification - Partial

- Simple Partial
- Complex Partial
- Secondarily Generalized

Seizure Classification - Generalized

- Nonconvulsive
 - Absence
 - Atonic
- Convulsive
 - Tonic
 - Clonic
 - Myoclonic
 - Tonic/Clonic

Seizure Type vs. Epileptic Syndrome

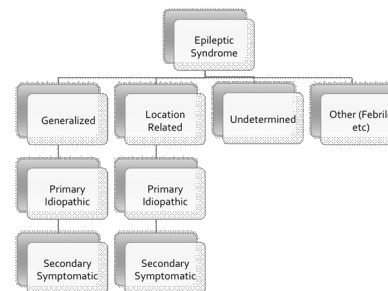
- Seizure type is determined by the patient's behavior and the EEG pattern during the event



Seizure Type vs. Epileptic Syndrome

- A syndrome is defined by:
 - Seizure type(s)
 - Natural history
 - EEG (ictal and interictal)
 - Response to AED treatment
 - Etiology

ILAE Classification of Epilepsies



Epidemiology

Epilepsy Prevalence:

- General Population 1-2%
- Mild to Moderated I/DD 14-24%
- Severe I/DD 45-67%
- Profound I/DD 50-82%

Diagnostic Difficulties

- Recognition of a seizure event
- Accurate and timely reporting
- Assessment by physician
- Difficulty obtaining tests
 - Usually need general anesthesia to obtain an MRI
 - EEG is also difficult to obtain, as may require sedation

Diagnostic Difficulties

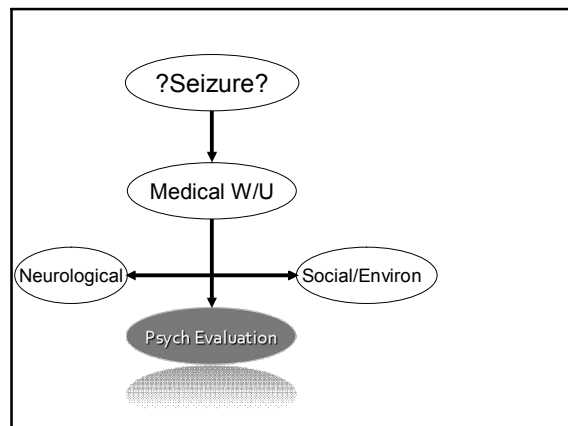
- Nonepileptic myoclonus
- Movement disorders or tonic posturing with GERD and other painful disorders
- Sleep disorders
 - Restless leg syndrome
 - Obstructive sleep apnea
- Stereotyped behavior (SIB)

Diagnostic Difficulties

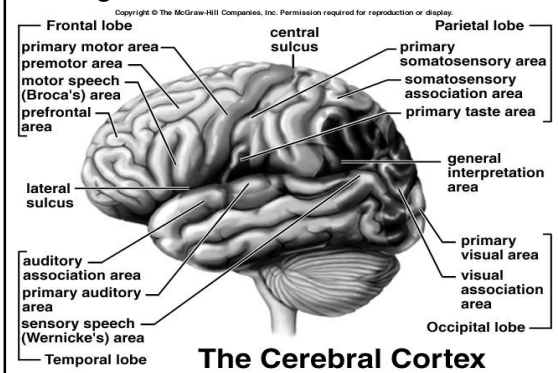
- ADRs of psychotropic meds
- Manifestations of primary psychiatric disorders
 - Prevalence in I/DD is high
- Pseudoseizures
 - Frequently seen in patients with I/DD evaluated for seizures
- Several seizure types in same person

Diagnostic Approach

- Use the Biopsychosocial approach
- First consider trauma, pain or serious medical problems that could present with a seizure event or as a seizure look-a-like
- Next consider psychiatric disorders or acting out behaviors related to social or environmental factors



Regional Brain Function



Regional Brain Function

- *Basic Frontal Lobe Functions*
 - Consciousness
 - Judgments we make about what occurs daily
 - Controls our emotional response
 - Controls our expressive language
 - Assigns meanings to the words we choose
 - Memory for habits and motor activities

Regional Brain Function

- *Basic Parietal Lobe Functions*
 - Location for visual attention
 - Location for touch perception
 - Goal directed voluntary movements
 - Manipulation of objects
 - Integration of different senses that allows for understanding a single concept

Regional Brain Function

- *Basic Temporal Lobe Functions*
 - Hearing ability
 - Memory acquisition
 - Some visual perceptions
 - Categorization of objects
- *Basic Occipital Lobe Function*
 - Vision

Behaviors/Manifestations of Epileptic Syndromes

- *Temporal Lobe Epilepsy*
 - Aura
 - Abnormal sensations
 - Epigastric sensations (stomach rising, smells, tastes)
 - Sensation of déjà vu (recalled emotion / memory)
 - Sudden, intense emotion

Behaviors/Manifestations

- *Temporal Lobe Epilepsy*
 - Abnormal mouth behaviors
 - Lip smacking
 - Chewing or swallowing without cause
 - Profuse salivation
 - Abnormal head movements
 - Forced turning of the head or eyes, usually opposite the seizure focus

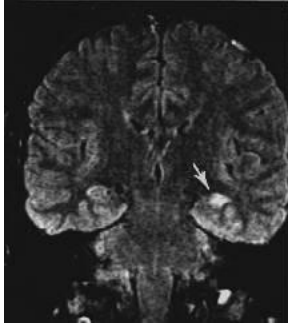
Behaviors/Manifestations

- *Temporal Lobe Epilepsy*
 - Abnormal movements
 - Automatisms – repetitive movements such as picking at clothing
 - Abnormal sensations
 - Numbness, tingling, or crawling sensations
 - Sensory hallucinations (visual, hearing, touch)

Behaviors/Manifestations

- *Temporal Lobe Epilepsy*
 - Autonomic symptoms
 - Abdominal pain
 - Nausea
 - Sweating
 - Flushed face
 - Dilated pupils
 - Rapid heart rate

Mesial Temporal Sclerosis



Behaviors/Manifestations

- *Frontal Lobe Epilepsy*
 - Generalized motor activity
 - Sexual automatisms
 - Vocalizations
 - Focal, tonic, and clonic activity

Behaviors/Manifestations

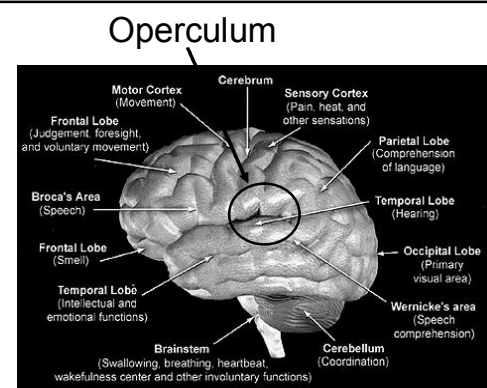
- *Orbitofrontal and Cingulate gyrus origin*
 - Automatisms
 - Staring
 - Autonomic disturbances
 - Affective manifestations

Behaviors/Manifestations

- *Supplementary Motor Epilepsy*
 - Nocturnal seizures (brief)
 - Asymmetrical tonic posturing
 - Vocalizations
 - Preserved consciousness

Behaviors/Manifestations

- *Opercular Area Seizures*
 - Salivation
 - Mastication
 - Speech arrest
 - Laryngeal symptoms
 - Autonomic signs
 - Gustatory and epigastric disturbances



Behaviors/Manifestations

- *Dorsolateral Frontal Convexity Seizures*
 - Version
 - Speech arrest
- *Perirolandic Region Seizures*
 - Repetitive focal motor sz
 - Myoclonus
 - Focal motor status

Behaviors/Manifestations

- *Parietal Lobe Epilepsy*
 - Auras of lateralized somatosensory symptoms
 - Vertigo
 - Epigastric sensations
 - Cephalic sensations
 - Automatism
 - Asymmetrical tonic posturing
 - Ictal spread to temporal or frontal lobes

Behaviors/Manifestations

- *Occipital Lobe Epilepsy*
 - Elementary visual hallucinations
 - Sensations of eye movement
 - Nausea and vomiting
 - Eye blinking
 - Ictal blindness

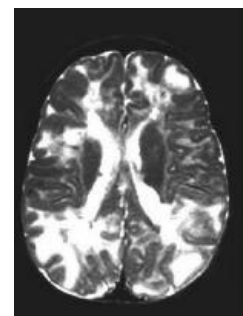
Behaviors/Manifestations

- *Generalized Tonic/Clonic Seizures*
 - Vague Prodrome (hours to days)
 - Headache
 - Mood changes – anxiety, irritability
 - Change in appetite
 - Dizziness or lightheadedness
 - Postictal State
 - Confusion, Lethargy, Myalgia, Headache

I/DD Syndromes and Epilepsy

- Neurocutaneous Syndromes – Tuberous Sclerosis
 - 80% have seizures, 60% have I/DD
 - Childhood – infantile spasms are the most common
 - Older Children – evolves into Lennox-Gastaut
 - Young adults – complex partial seizures – most common
- *Very difficult seizures to manage*

Tuberous Sclerosis



I/DD Syndromes and Epilepsy

- Neurocutaneous Syndromes – Sturge-Weber-Dimitri syndrome
- Note – the facial and meningeal angiomas are usually on the same side
 - I/DD – 50 - 60%, Hemiparesis – 30%
 - Focal motor seizures +/- secondary generalization are the most common
- Often seizure remits or is well controlled with AEDs

I/DD Syndromes and Epilepsy

- Neurocutaneous Syndromes – Neurofibromatosis I
- Only 3-5% have seizures
- Due to the intracranial tumors, this requires close follow up when seizures are not controlled

I/DD Syndromes and Epilepsy



Neurofibromas

I/DD Syndromes and Epilepsy

- Cerebral Palsy
 - Epileptic seizures – up to 70% (hemiplegic)
 - Seizures may start at any age, most start in infancy
- Most intractable seizures seen in adults with I/DD are seen in patients with CP

I/DD Syndromes and Epilepsy

- Cerebral Palsy
 - Most common epileptic seizures in CP
 - Generalized tonic and tonic/clonic
 - Partial complex seizures with and without secondary generalization
 - Myoclonic
 - Atonic
 - Lennox-Gaustaut Syndrome
 - Least common – Typical absence

I/DD Syndromes and Epilepsy

- Malformations of Cortical Development
 - (This is a group of disorders featuring congenital deficiency in neuronal proliferation, migration, or organization)
 - It is estimated that 20 – 25% of children with intractable seizures have these malformations
 - Found in 4.3% of patients with epilepsy, in a retrospective MRI study
 - Among patients with I/DD, incidence was 13%

I/DD Syndromes and Epilepsy

- Autism
 - Incidence of epileptic seizures is 20 – 30% in children and adolescents
 - Seizures are seen more frequently if I/DD is severe
- *Note – in a small group of children with language regression and autism, the regression was associated with onset of seizures. AED or steroid treatment helped improve the regression in some of these patients.*

I/DD Syndromes and Epilepsy

- Fragile X Syndrome (one of the most common chromosomal abnormalities in males with MR)
 - Associated with focal rolandic seizures in children, is not seen in adults
 - These seizures respond well to AEDs
 - Adult patients have these focal seizure transformed into generalized seizures

I/DD Syndromes and Epilepsy

- Rett's syndrome (the most common condition associated with I/DD in girls)
 - Epileptic seizures are seen in 25 – 30 % of cases
 - Most seizures – generalized and complex partial
 - Small number have infantile spasms or myoclonic epilepsy

I/DD Syndromes and Epilepsy

- Angelman syndrome
 - (usually from deletion of chromosome arm 15q 11-13 inherited from the mother, of interest Prader-Willi syndrome involves the same area but involves the chromosome from the father)*
 - There are 4 subclasses of Angelman syndrome depending on the specific chromosome abnormality

I/DD Syndromes and Epilepsy

- Angelman syndrome
 - Although the phenotype is similar, the seizure severity varies among the classes
 - Class I – severe intractable epilepsy (myoclonic and atypical absences) are most common
 - Abnormal movements seen in this syndrome often do not correlate with EEG epileptiform activity

I/DD Syndromes and Epilepsy

- Angelman syndrome
 - Other epileptic seizures seen include – atonic, generalized extensor tonic, flexor spasms, and secondarily generalized tonic/clonic seizures
 - In adults, the epilepsy may be very resistant to treatment with AEDs.

I/DD Syndromes and Epilepsy

- Down syndrome
 - Epileptic seizures often manifest in adults in their late 40's as another expression of Alzheimer disease
 - Myoclonus is seen the most
 - Generalized T/C and status can also occur
 - In advanced cases, myoclonus is nearly constant and difficult to control
 - The myoclonus is elicited by external stimuli, photomyoclonus frequently develops

Complications of Seizure Disorders

- Increased mortality rate
 - 2-3 fold increase over general population
 - Life expectancy shortened by up to 20 years

Remember: Prevalence of epilepsy is 1-2%

Complications of Seizure Disorders

- Direct physical injuries
 - Fractures
 - Lacerations
 - Bruises
 - Burns

Complications of Seizure Disorders

- Accidental Death
 - Drowning – most common
- Head trauma
 - Common, but rarely causes death

Complications of Seizure Disorders

- Neufeld et al found the following
 - 30% of patients reported trauma
- Most common injuries reported:
 - Blunt trauma 40%
 - Lacerations 28%
 - Fracture/dislocation 17%

Complications of Seizure Disorders

- Most common injuries reported:
 - Burns 6%
 - Concussion 6%
 - Subdural hematoma 3%
 - Intracerebral bleed 1%

Complications of Seizure Disorders

- Aspiration pneumonia
 - Monitor patient's vital signs (including oxygen saturation) frequently over next few days
 - Have a low threshold for obtaining lab tests
 - Have an even lower threshold for using antibiotics

Complications of Seizure Disorders

- Aspiration pneumonia
 - Early, frequent use of nebulizers to help keep airways clean and open
 - Be preemptive – do not wait for signs and symptoms to present if aspiration is suspected

Complications of Seizure Disorders

- In a study, by Gastaut, of 400 drivers with epilepsy
 - 133 had a seizure while driving
 - 73 of these patients had an accident caused by a seizure while driving
 - A seizure-free period of >12 months reduced this risk, as did a predictable aura

Injury Prevention Guidelines

- Treat epilepsy aggressively
- Minimize drug-related ataxia
- Use recovery position during seizure
- Never swim alone
- Driving restrictions until > 12 months seizure-free
- No unattended bathing

Injury Prevention Guidelines

- Microwave cooking
- Wear a helmet
- Use of a high-low bed and floor mat
- Avoid heights
- Avoid known seizure precipitants

Injury Prevention Guidelines

- Most importantly identify:
 - Predisposing factors
 - Precipitating factors
 - Perpetuating factors
- Institute an effective intervention plan when any of the above factors are identified

Complications of Treatment

- Adverse reactions to AEDs
 - Cerebellar toxicity (ataxia)
 - Including residual toxicity
 - Decline in intellectual function
 - Personality change

Complications of Treatment

- Adverse reactions to AEDs
 - Involuntary movements
 - Sensory neuropathy
 - From demyelination
 - All AEDs can cause depression of cortical function

Complications of Treatment

- Special concerns using AEDs in the I/DD population
 - Increased sensitivity to cognitive and behavioral side effects
 - Increased sensitivity to drug interactions
 - Patients are often on others meds which lower the seizure threshold

Complications of Treatment

- Special concerns using AEDs in the I/DD population
 - ADRs are difficult to assess, may present as a generic behavioral change seen anytime the person experiences discomfort
 - CNS side effects are more pronounced due to the underlying static encephalopathy

Complications of Treatment

- Another management challenge in the I/DD population:
 - Accurate reporting of seizures
 - Recognition
 - Frequency
 - Description

Minimize Complications

- Strive for monotherapy with AEDs
 - Reduction in polypharmacy results in decreased seizure frequency and improvement in patient's behavior
- Use lowest effective doses
- Assure compliance

Minimize Complications

- Monitor therapeutic drug levels
- Examine patients routinely for signs of toxicity
- Be aware of AED interactions and use caution when considering other medications

Neurobiological Complications

- Neurobiological Consequences
 - Ionic Fluxes (begins immediately)
 - Robust changes of intracellular calcium after seizure mediated depolarization
 - Kinase activation (within 1 hour of sz)
 - Represents stimulation of secondary messenger systems
 - Immediate early gene activation
 - (5 minutes - 6 hours)

Neurobiological Complications

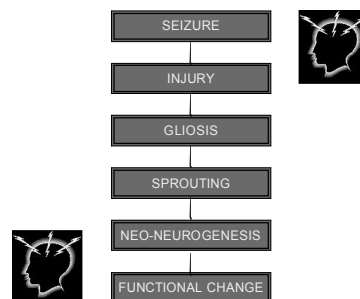
- Neurobiological Consequences
 - Late gene expression
 - Encoding:
 - Peptides
 - Receptors
 - Cytokines
 - Glial fibrillary acid proteins
 - Cytoskeletal proteins
 - Protein expression and modification
 - (2 hrs to 3 days)

Neurobiological Complications

- Neurobiological Consequences
 - Mossy fiber sprouting and synaptic reorganization
 - Neuronal cell loss
 - (6 hours – 14 days)
 - Gliosis
 - Glial cells – multiple roles including transmitter reuptake, glucose transport, and trophic support
 - (6 hours – 5 days)

Neurobiological Complications

- Neurobiological Consequences
 - Neo-neurogenesis (days to weeks)
 - Behavioral deficits (6 hours – months)
 - Memory
 - Learning
 - Increased susceptibility to future seizures



Neurobiological Complications

- Epilepsy-related psychiatric issues
 - Psychosis
 - 2-9% of patients with epilepsy
 - Half of these patients have schizophrenia

Neurobiological Complications

- Epilepsy-related psychiatric issues
 - Mood Disorders
 - Up to 55%
 - Suicide
 - 13%
 - 5-10 times higher than the general population

Neurobiological Complications

- Epilepsy-related psychiatric issues
 - Anxiety Disorders
 - Interictal anxiety – 66%
 - Pseudoseizures
 - 30 – 40 %

Neurobiological Complications

- Psychosocial Issues
 - Driving/transportation
 - Loss of independence
 - Insurance
 - Employment
 - Decreased leisure time physical activity
 - Low self-esteem
 - Interpersonal relationships

Causes of Death

- | | |
|---------------------------|-------|
| ▪ Neoplasm | 20% |
| ▪ Heart Disease | 19% |
| ▪ Cerebrovascular Disease | 14% |
| ▪ Accidents and Suicide | 6% |
| ▪ SUDEP | 2-18% |

Sudden Unexpected Death in Epilepsy

- Sudden unexplained death in epilepsy is **24 times** greater than that of the general population
- Risk factors:
 - Increased seizure frequency
 - Multiple number of AEDs
 - Early onset epilepsy
 - Frequent changes of AEDs

Sudden Unexpected Death in Epilepsy

- I/DD patients have a 4.6 fold increased risk of SUDEP
- Risk factors
 - Nonambulatory status
 - Poorly controlled epilepsy
 - Increased seizure frequency
 - Increased number of AEDs

Sudden Unexpected Death in Epilepsy

- Pathophysiology of SUDEP
 - Cardiac arrhythmia
 - Central apnea
 - Autopsy findings:
 - Pulmonary edema
 - Increased lung, heart, and liver weight

Sudden Unexpected Death in Epilepsy

- Pathophysiology of SUDEP
- Faingold's studies on a rat model have noted that serotonin plays a role in respiratory arrest (RA), and he has used fluoxetine to show a decrease in RA.

Sudden Unexpected Death in Epilepsy

- SUDEP prevention strategies
 - Night supervision or monitoring device, avoid prone sleeping
 - Optimized seizure management

Sudden Unexpected Death in Epilepsy

- SUDEP prevention strategies
 - Avoid precipitants
 - Avoid sedating medications
 - Caregivers need to be proficient in CPR and first aid
 - Consider use of other treatments

CONCLUDING REMARKS

- Be wary of information stating that 'this is just one of his behaviors'
- Evaluate a new or unusual behavior using the biopsychosocial approach
- Recognize the spectrum of behaviors associated with epileptic seizures

- Be aware of seizure types associated with developmental syndromes
- Treat appropriately, limiting the number of AEDs used and targeting low seizure frequency
- Identify people with SUDEP risk factors and take precautions as deemed necessary



Until he extends the circle of his compassion to all living things, man will not himself find peace.

--- *Albert Schweitzer*

