SUDDEN UNEXPECTED DEATH IN EPILEPSY

What is it, what happens, what causes it, how to prevent it, why not to panic

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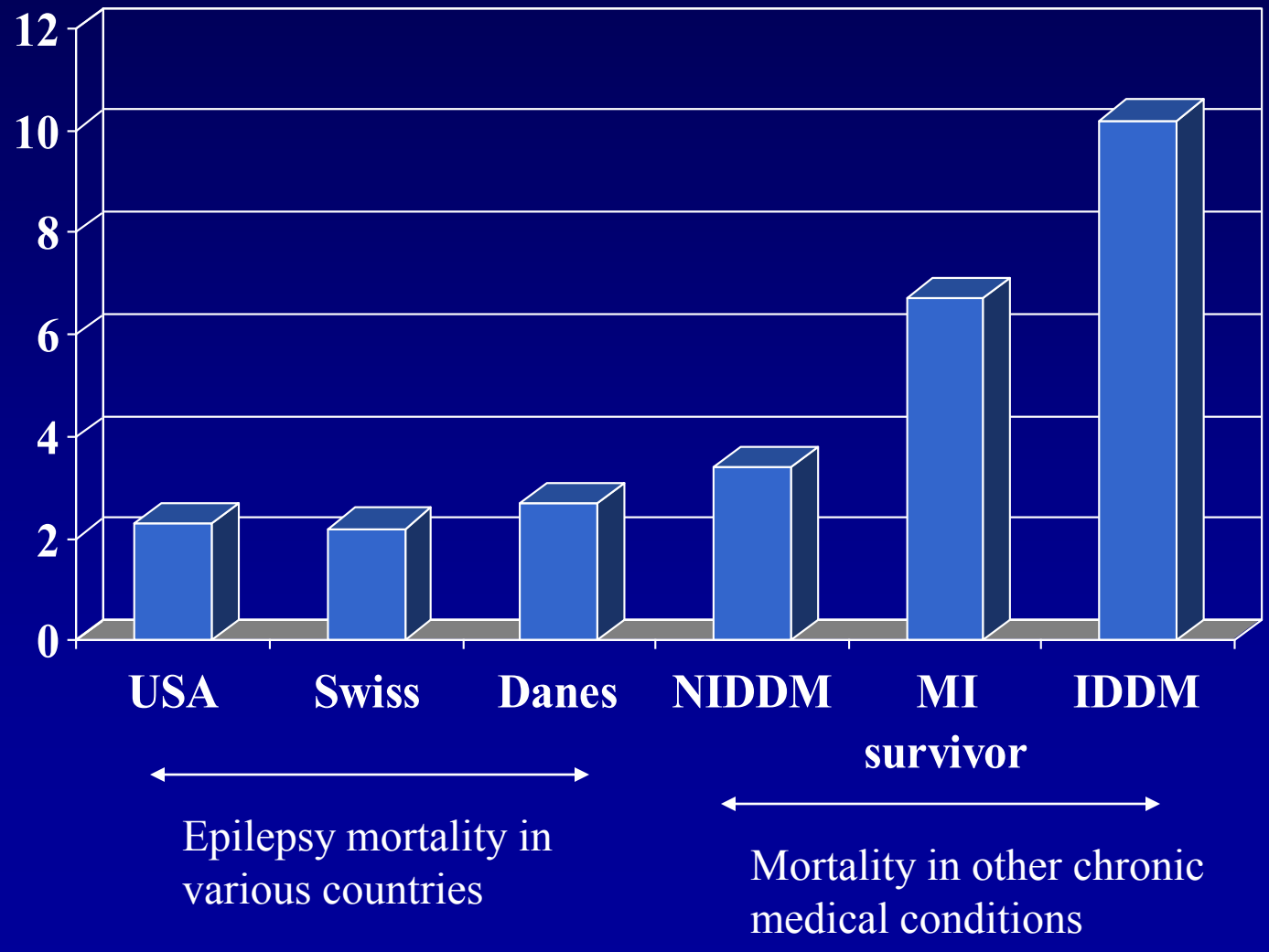
MINCEP Epilepsy Care

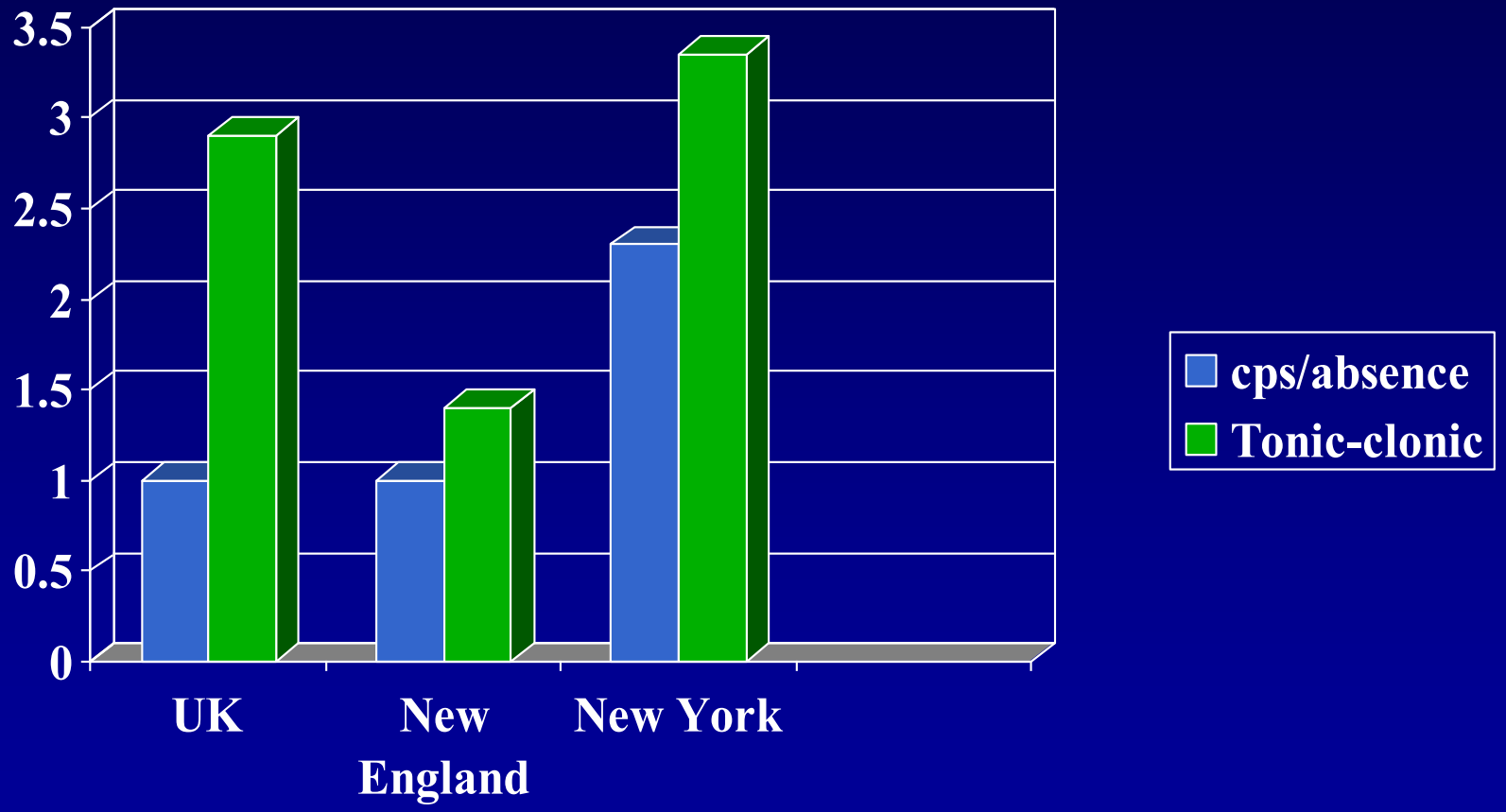
Mortality in epilepsy some facts

- Everyone dies sooner or later. But we all want it to be later.
- In any given year somewhat more people with epilepsy will die than people without epilepsy. (Mortality is increased in epilepsy). This is not out of line compared to other chronic diseases.
- People with rare or no tonic-clonic seizures seem to have normal mortality.

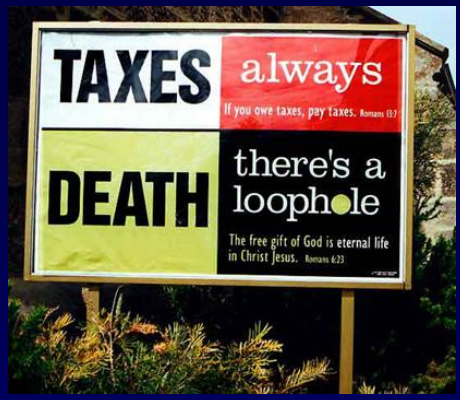
Standardized mortality ratio is somewhat increased in people with epilepsy



Increased mortality in people with epilepsy is related to tonic-clonic seizures



Mortality in epilepsy
Some more facts



- People with epilepsy usually die from the disease causing the epilepsy or from natural causes rather than an epileptic seizure.
- Suicide and accidents appear to be more common in people with epilepsy but don’t by themselves account for much of epilepsy related deaths
- Sudden unexpected death in epilepsy (SUDEP) accounts for about 20% of deaths in epilepsy

Causes of death not directly related to seizures (4,001 deaths in Swedish PWE)

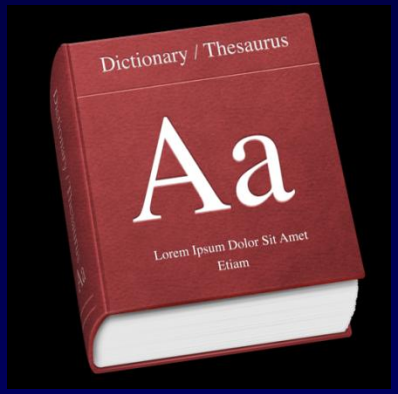
Cause of death	Percent of death	SMR
Heart disease	16%	2.5 (2.3-2.7)
Stroke	14%	5.3 (4.9-5.8)
Brain Tumors	4%	29.9 (25.3-35.1)
Pneumonia	5.5%	4.2 (3.6-4.8)
Alcohol abuse	4.7%	24.6 (21.0-28.6)
Suicide	1.3%	3.5 (2.6-4.6)

The increased mortality in epilepsy is largely due to the causes of epilepsy rather than to the seizures.

Causes of death potentially related to seizures (4,001 deaths in Swedish PWE)

Causes	Percent of deaths	SMR
Transport accident	0.3%	1.8 (0.9-3.4)
Accidental falls	1.7%	4.6 (3.5-5.8)
Accdents (fire/flame)	0.4%	10.3 (5.8-17.0)
Accidents (drowning, suffocation, foreign body)	0.6%	8.2 (5.2-12.1)
Other injuries	1.6%	11.1 (8.5-14.1)
SUDEP	**8.6%**	**20.3**

SUDEP: What is it?
The scientific definition



- Person diagnosed with epilepsy
- Death occurs unexpectedly while person in reasonable state of health
- Death occurs over minutes
- Death occurs in benign circumstances while patient engaged in normal activities
- No obvious cause of death
  - Definite: sufficient description, autopsy, toxicology
  - Probable: no obvious cause but no autopsy, toxicology
  - Possible: information re circumstances of death insufficient

SUDEP: how often does it happen?
Incidence related to seizure severity

- Geographically based (Olmsted county) 0.35/1000
- Large epilepsy cohorts
  - Minnesota 1.0/1000
  - Stockholm 1.3/1000
  - Saskatchewan 0.8/1000
- Drug development program
  - gabapentin 3.8/1000
  - Lamotrigine 3.5/1000
  - VNS 4.1/1000
- Epilepsy surgery program
  - Philadelphia (Graduate Hospital) 4.0/1000

SUDEP appears very rare in children (0.2 – 0.43/1000)
Possible exception: severe myoclonic epilepsy of childhood (Dravet syndrome)

What happens during SUDEP? (1)
Tonic-clonic seizures often shortly precede SUDEP

- Leestma, Walczak et al, 1989. 58 cases presenting to Cook County coroner (prospective collection) over 1 year.

- Found dead, no witnessed sz
  - In bed……..20
  - On floor……..…14
  - In bathtub……...2
- Death after seizure
  - Witnessed……..22 (50%)
  - Indirect signs……...7

- Langan, Nashef et al, 2005.
  154 cases from a variety of sources in UK collected over 9 years.

- Death after seizure
  - Witnessed…… 21 (42%)
  - Indirect signs……44

What happens during SUDEP? (2)

Position at death suggests respiratory compromise
Death occurs shortly but not immediately after GTC

- Nashef et al 1998: 11/26 (42%) found face down or in position in which respiration may have been compromised. Kloster et al 1999: 17/24 (71%) found prone.
- Leestma, Walczak et al. 1989. Results of resuscitative efforts in the field & hospital in 12 cases
  - 7 initially alive but resuscitative efforts failed in the field
  - 1 died in ER after inability to convert pulseless junctional rhythm
  - 1 reverted to NSR in ER but was deeply comatose with fixed and dilated pupils and succumbed to caridac arrest 7 hours later
  - 3 appeared deeply postictal but otherwise stable and transferred to normal floor. Found pulseless 2 to 4 hours later. Therapeutic AED levels found in 2 of 3 at autopsy (all had received ER loads). Though not under constant observation no further sz observed.

What happens during SUDEP? (3)

- 33% - 63% found dead in bed, presumably asleep at time of death
- 50% - 67% die after a witnessed tonic-clonic seizure. Seizure preceding death does not appear any different from person's usual tonic-clonic seizure
- 42% - 81% found in prone position when position reported

SOURCES: Leestma, Walczak et al 1989, Earnest et al 1992, Coyle et al 1994, Nashef et al 1998, Kloster & Engelskjon 1999, Walczak, Leppik et al 2001)

SUDEP: risk factors

- Frequent generalized tonic-clonic seizures
  - By far strongest, most consistent risk factor
- Treatment with more than two antiseizure medications
  - Much weaker risk than occurrence of seizures
- Younger age at onset
- Symptomatic cause of epilepsy
- Lack of well defined plan of care during and following tonic-clonic seizures
  - Strong risk in British studies, not evaluated in most studies, didn't pan out in the metanalysis

Hesdorrfer et al, Epilepsia June 2011

WHY ?

Mechanisms must be consistent with observed epidemiology & pathology

- SUDEP often occurs during sleep
- SUDEP closely related to the occurrence and frequency of generalized tonic-clonic seizures
- Death appears to occur shortly after the tonic-clonic seizure but not necessarily immediately
- Treatment with multiple AEDs appears to increase risk independently from seizure severity

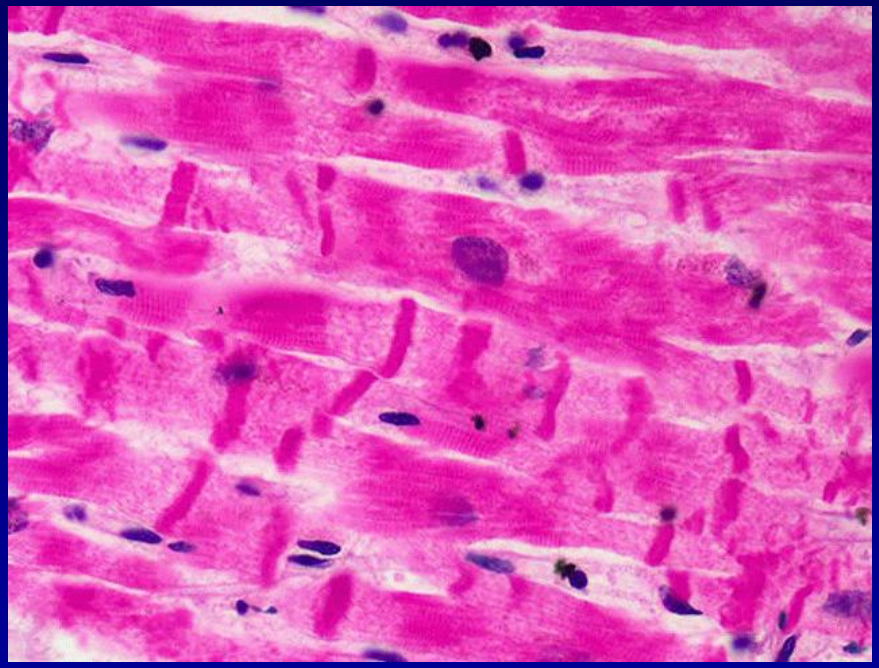
Potential Mechanisms for SUDEP

- CARDIAC: arrhythmia causes SUDEP
- RESPIRATORY: persistent postictal apnea causes SUDEP, arrhythmia occurs later.

How often do arrhythmias occur during seizures?

- In large series of ambulatory EEG monitoring of interictal and ictal EKG, tachyarrythmia is common but potentially fatal arrhythmia is rare.
- Asystole most common severe ictal arrythmia occuring in 0/56, 1/281, 1/87, 0/102 seizures in 4 recent studies of patients undergoing videomonitoring totalling 190 patients (Kielson 1987, Zijlmans 2002, Nei 2004, Opherk 2002).
- Our own experience: 5 patients with asystole in approx 400 patients with epilepsy undergoing video monitoring (1%).
- Arrythmia occurs during both complex partial and tonic-clonic seizures. Side and lobe of seizure onset are not consistently associated with occurrence of arrythmia.

Do chronic GTCs cause contraction band necrosis or “myocardial disorganization”?

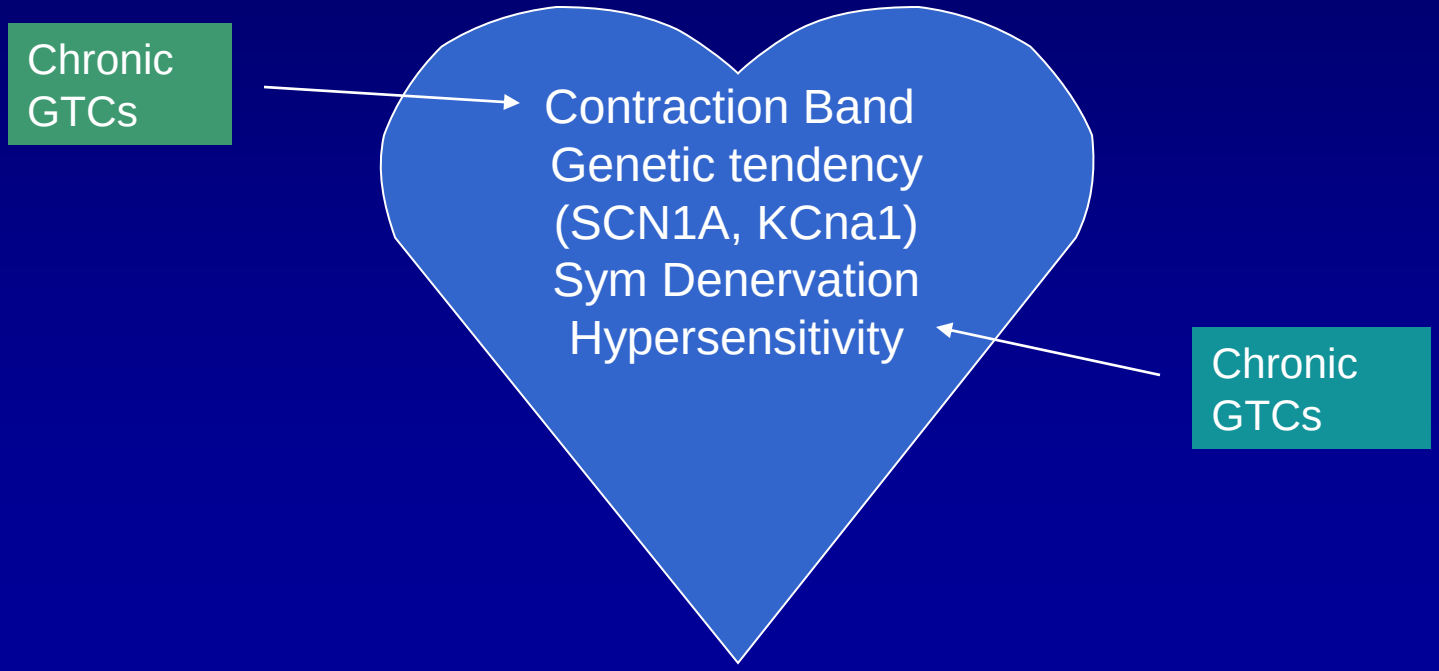


Oac.med.jhmi.edu/…/heart/ischemic.058A.html

- Contraction bands and other evidence of myocardial disorganization more common in high sympathetic output states (both neurogenic and other etiologies)
- Contraction bands more common in death related to status epilepticus than in controls (Manno 2005)
- Sporadic reports of contraction bands in other epileptic hearts. Are they more common in chronic epilepsy than in controls? In SUDEP?

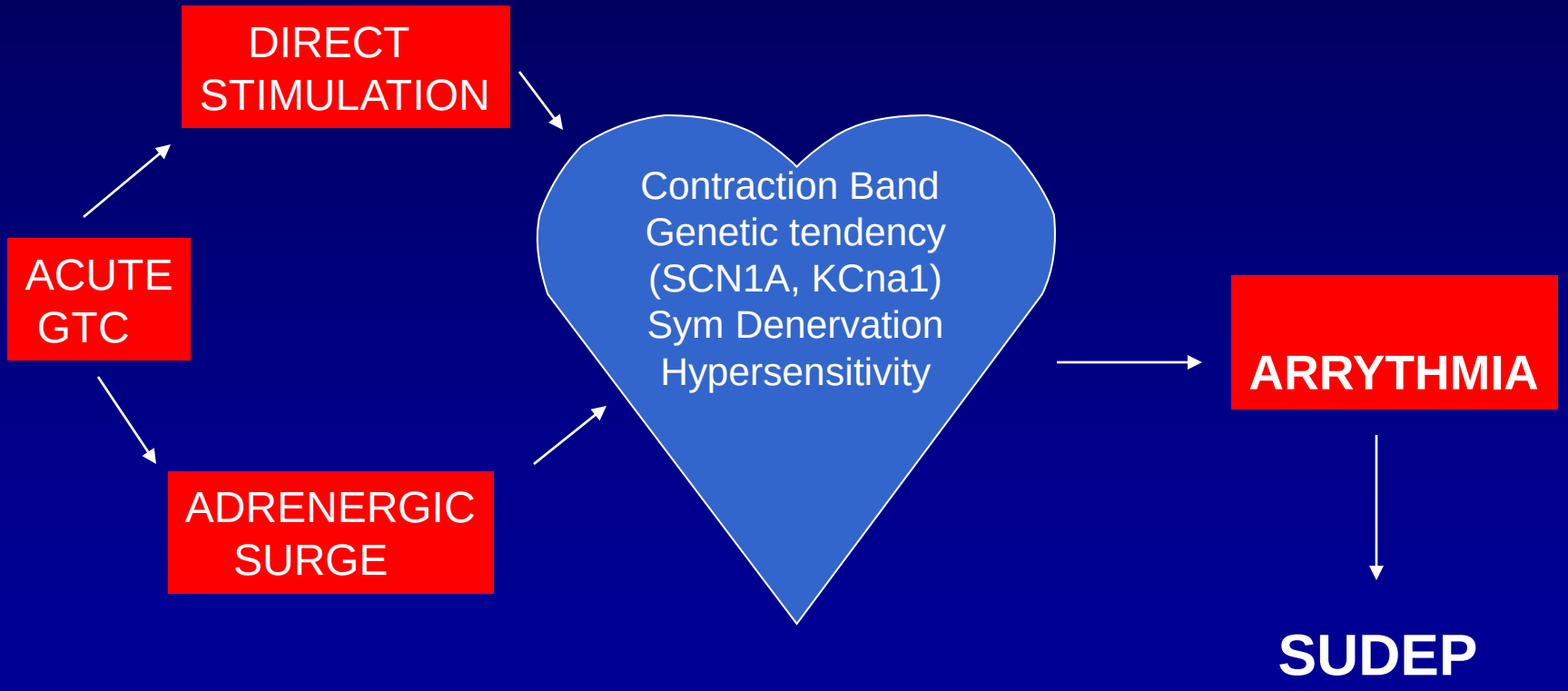
Does cardiac arrhythmia cause SUDEP?

1. Chronic GTCs set up substrate for fatal arrhythmia



Does cardiac arrhythmia cause SUDEP?

2. Acute GTC causes fatal arrhythmia



Does cardiac arrhythmia cause SUDEP?
Maybe

YES

- Severe arrhythmias documented during seizures; may be common enough over a lifetime of frequent seizures.
- Reasonable amount of evidence supports proposed mechanisms

NO

- Animal models favor another mechanism
- Rare recorded cases of SUDEP-near SUDEP favor another mechanism

Apnea common after seizures

- Walker & Fish 1997. 79 seizures in 37 patients on a videomonitoring unit. Nine generalized seizures: central apnea in all. 70 complex partial seizures: apnea occurred in 27/70. 81% central, 11% mixed, 8% obstructive.
- Duration 10-75 sec, mean 29 sec. O2 sats varied from no change to 61%. Mean and median O2 sat following seizure was 80%.
- Bateman et al 2010 304 partial seizures, 51 with secondary generalization. Central apnea occurred in 50%, obstructive apnea in 85. Mean desaturation following seizure 75%.

SUDEP less common in supervised settings.

- British case control study of SUDEP (n=154)
  - No supervision OR 1.0
  - Adult same room OR 0.4 (0.2-0.8)
  - Special precautions OR 0.1 (0.0-0.3)

- British study of SUDEP in school for pts with chronic epilepsy and mental retardation
  - All deaths occurred outside institutional setting.
  - No deaths occurred in institutional setting with consistent monitoring and organized protocol for first aid following seizures.

Langan et al 2005, Nashef et al 1995

5 video-EEG monitored SUDEP cases

Tao et al 2010, Bateman et al 2010 (2), personal review (2)

- Video, EKG and EEG in all cases.
- Patient prone in 4/5 cases with video.
- In all cases GTC; not unusually severe or intense but intense EEG suppression following seizures.
- Normal cardiac rhythm for 2 to 30 minutes following EEG cessation of seizure; then progressive bradycardia, asystole. Cessation of respirations preceded cessation of EKG in all 4/5 cases. In ictal asystole cases, asystole occurs during or at termination of seizure.

THESE CASES SUGGEST THAT CENTRAL APNEA, POSSIBLY DUE TO INTENSE POSTICTAL INHIBITION IS THE ETIOLOGY OF SUDEP

Sheep SE model of SUDEP
Johnson et al, 1995, 1997

- Bicuculline induced status epilepticus. Sheep dieing < 5 min compared to survivors. 4/13 sheep died: “SUDEP equivalent”.
- **Respiratory failure preceded arrhythmia in all.**
- Catecholamine levels massively elevated,didn’t differ in SUDEP sheep and survivors.
- Pulmonary edema more extensive, pulmonary artery pressures higher in dieing sheep but insufficient by themselves to account for observed respiratory failure.
- Followup study in 8 tracheotomized sheep. **Significant central apnea occurred in all.** Again, no arrhythmia. But only 1 died in < 5 min. 3 died total, one related to myocardial infarction, one to persistent apnea, 1 to apnea and arrhythmia, unclear which worse.

DBA/2 mouse AGS model of SUDEP

Venit et al 2004, Tupal et al 2006

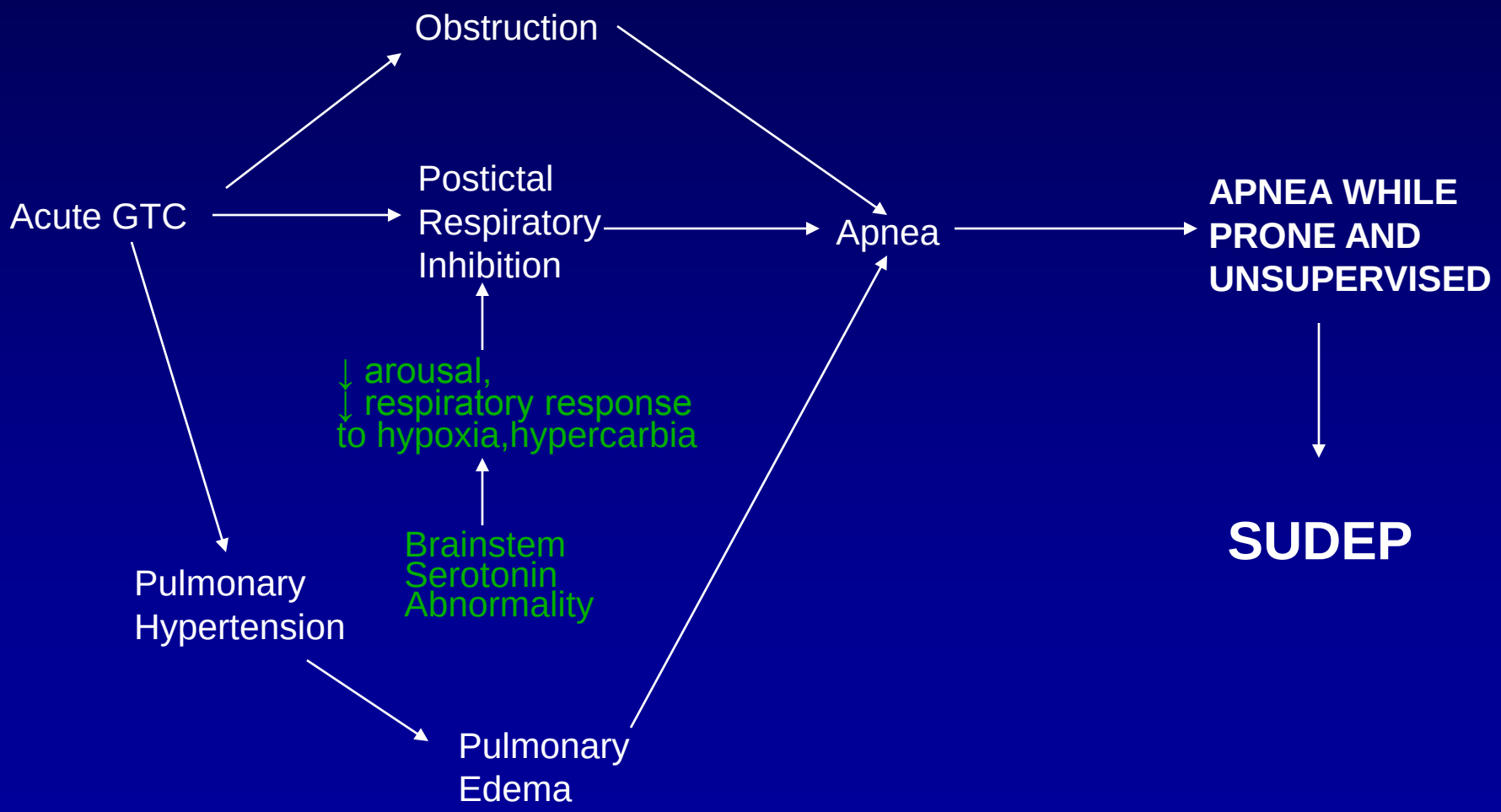
- Respiratory arrest follows 70% audiogenic seizures in several susceptible strains. Death if not resuscitated.
- Deficiency in serotonergic brainstem activation in DBA/2 mice may be responsible for both seizures and respiratory arrest.
- Ventilation for 10 seconds terminates respiratory arrest.
- Audiogenic stimulus in oxygen rich environment triggers usual seizure but no respiratory arrest. Fluoxetine prevents RA, cyproheptadine potentiates RA.

ANIMAL MODELS SUGGEST CENTRAL APNEA IS CRITICAL IN PATHOGENESIS OF SUDEP AND
SUGGEST SEROTONIN PLAYS AN IMPORTANT ROLE.

More data implicating serotonin in SUDEP

- Brainstem serotonin neurons important in maintaining arousal and respiratory response to hypoxia, hypercarbia
- MDMA (Ecstasy) damages brainstem serotonergic neurons and appears to cause sleep apnea.
- SIDS (sudden infant death syndrome) has many similarities to SUDEP. Much evidence of defect in serotonin system in infants that die of SIDS.
  - Decreased serotonin receptor binding
  - Decreased extracellular serotonin levels
  - Increased number of immature serotonin neurons
- Postictal hypoxia following GTC less severe if subject treated with SSRI which increases serotonin levels.

Persistent postictal apnea causes SUDEP



Does persistent central apnea and obstructive apnea cause SUDEP?

Probably Yes

YES

- Apnea almost invariable following GTCs.
- Evidence of upper airway obstruction common in SUDEP.
- SUDEP cases less common when people are continuously monitored and perhaps attended to and stimulated consistently
- Recorded human cases and animal models support this mechanism.

NO

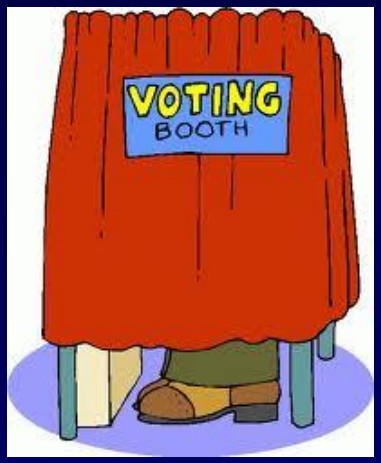
- Monitored cases are few. Animal models may not be relevant.

DIFFERENT OR MULTIPLE MECHANISMS MAY BE RELEVANT IN DIFFERENT CASES.

Preventing SUDEP
Health professional

- Aggressive treatment to minimize occurrence of generalized tonic-clonic seizures, using enough but not escessive antiseizure medications.
- Discuss SUDEP with those at higher risk. Discuss in all patients with tonic-clonic seizures?
- Education re first aid for GTCs
  - Rescue position, open airway
  - Respiratory assessment, Stimulation if hypoventilation (this may terminate attenuation of electrocerebral activity and start normal respiration), attend until some recovery

Time to express your opinion



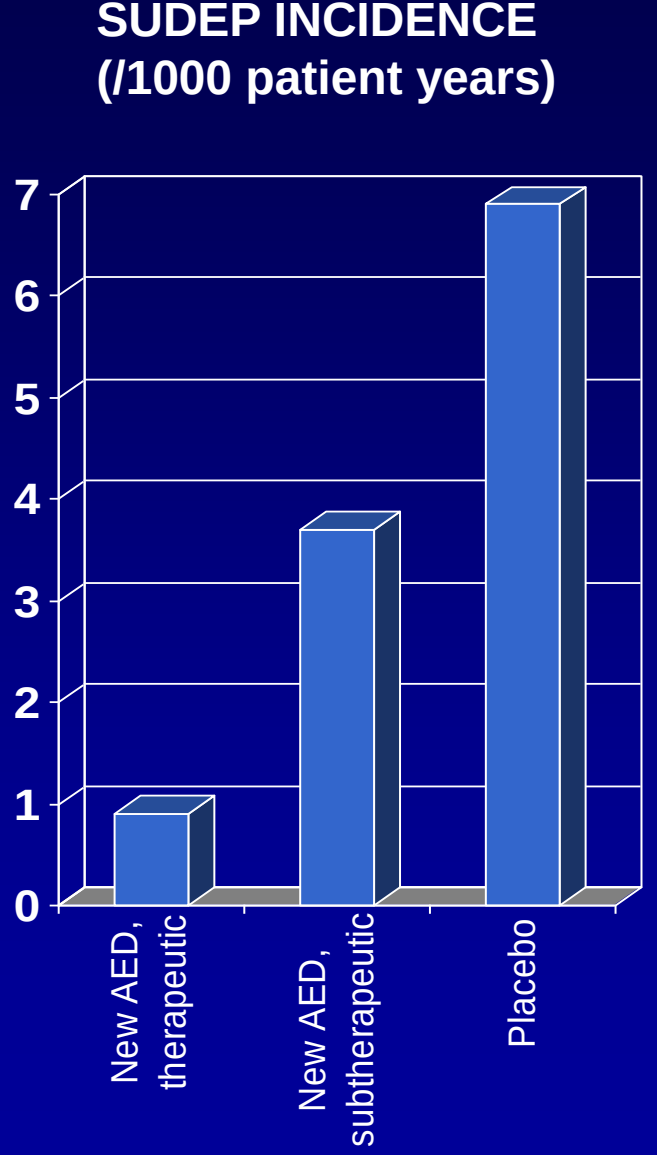
- Do you think doctors should discuss SUDEP with patients at all?
- Do you think doctors should discuss SUDEP with patients after their first seizure?
- Do you think doctors should discuss SUDEP with patients only after several tonic-clonic seizures?

British treatment standards require discussion of SUDEP in all cases of epilepsy. American standards are being developed.

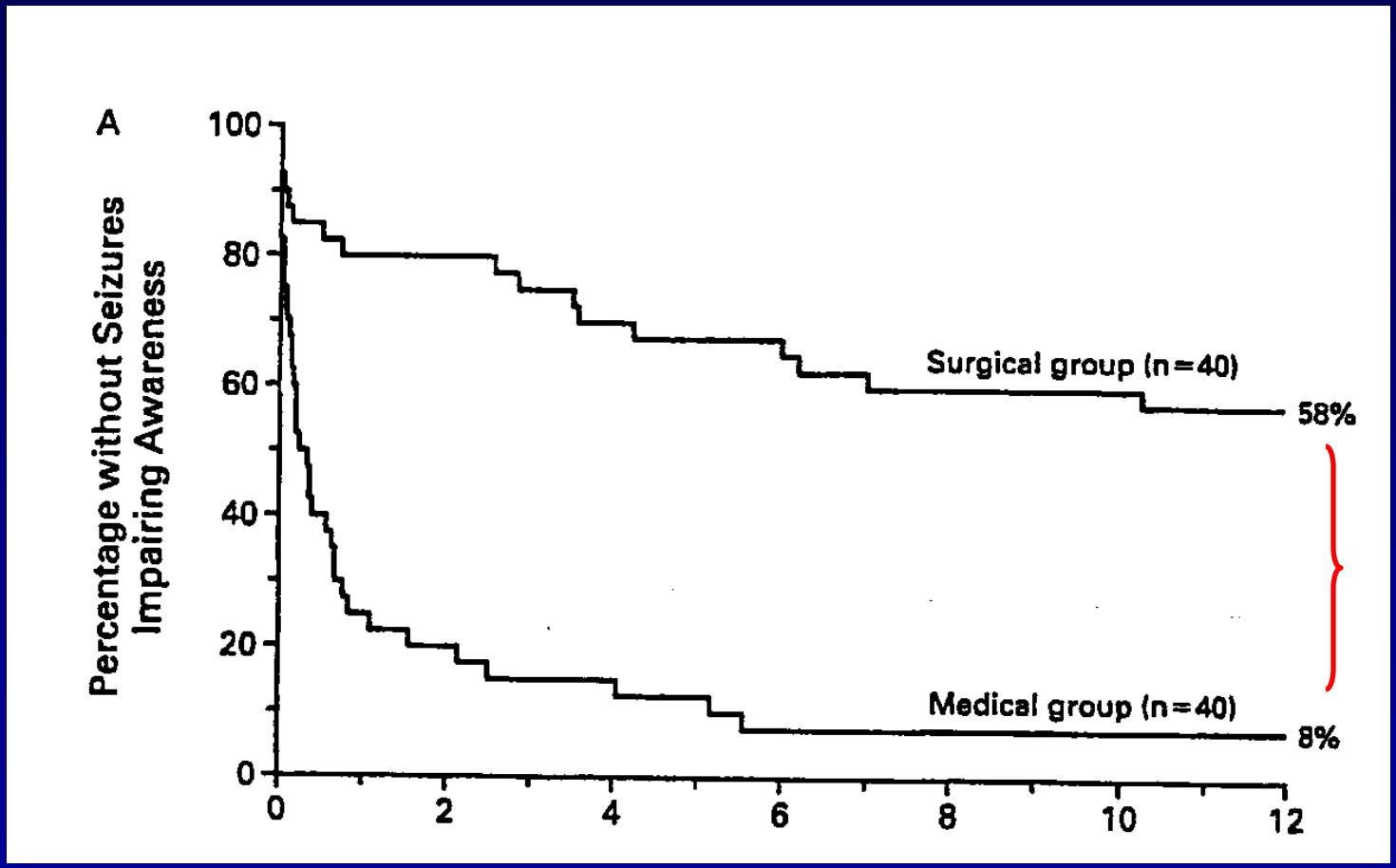
Adding a new AED decreases SUDEP

Ryvlin et al, Lancet Neurology Sept 2011

- Meta-analysis of 21,224 patients followed for 5,589 patient years in 112 drug trials.
- All had failed multiple AEDs and most treated with >1 AED at time new drug added.
- SUDEP accounted for 20/33 deaths.
- 3 SUDEPs in subjects treated with therapeutic doses of new drug, 3 SUDEPs in subjects treated with subtherapeutic doses of new drug, 14 SUDEP in subjects treated with placebo. Statistically significant!
- BOTTOM LINE: KEEP TRYING!



Randomized controlled trial
Seizure control



Wiebe et al., *N. Engl. J. Med*., 2001

Epilepsy surgery in the proper setting may help decrease mortality

Results from the multicenter epilepsy surgery trial

- 532 people with epilepsy unresponsive to medications being evaluated for epilepsy surgery. Enrolled at 7 centers and followed prospectively for up to 7.7 years.
- 144 ended up having medical treatment only, 388 ended up having epilepsy surgery.

- In medically treated group 11/144 (7.6%) died during followup.
  20 deaths per 1000 patient years.

- In surgically treated group 11/388 (2.8%) died during followup.
  6 deaths per 1000 patient years.

- Almost all those who died had persistent seizures. Causes of death included SUDEP (37%), seizure related accidents (30%), suicide (23%), others

Preventing SUDEP
Patient & caregiver

- Compliance with AED treatment
- Sleep on back not on belly?
  - Hard to enforce this
  - May increase sleep apnea, shoulder dislocation
- Proper postictal first aid.
- Should patients at high risk be attended at night or fitted with apnea monitors?
  - Some data supports this but not conclusive.
  - Implications regarding patient independence, emotional well-being of caregivers, and false positives. Finding the balance may be difficult and has to be assessed on individual basis.

Preventing SUDEP
Research Efforts

- Reliable seizure alarm devices
- Omega three supplement trial
- Genetic risk factors for SUDEP
  - Sodium channel dysfunction
  - Serotonin respiratory dysfunction
- SUDEP brain, heart tissue bank
- Will serotonin cure SUDEP?

How to live a long life with epilepsy 1

- Treat underlying causes of epilepsy aggressively, especially heart disease and stroke.
- Aggressive treatment to control seizures, especially generalized tonic-clonic seizures
- Be on the lookout for depression and get it treated
- Minimize drug-related unsteadiness
- Never swim alone. Shower rather than tub bath
- Use common sense, ask for advice before engaging in other situations that may be risky
- MAINTAIN GOOD GENERAL HEALTH HABITS!

How to live a long life with epilepsy 2
(people with epilepsy at higher risk)

- Avoid unsupervised bathing
- Minimize burn risks
  - Antiscalding devices
  - Avoid curling irons, clothing irons, exposed heaters
  - Kitchen precautions
- Helmets for selected patients
- Avoid high places without protection
- Minimizing SUDEP risks
- Epilepsy surgery, continuing aggressive care if indicated, especially to control tonic-clonic sz

DON’T WORRY! BE HAPPY!

- A positive, level-headed approach to the issues associated with chronic disease is as important as any number of medical interventions.
- ***The odds are on your side.*** The worst outcomes probably won’t happen to you. So don’t live your life anticipating that they will.