2023 GW Epilepsy Board Review & Best Practices

Epidemiology

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DISCLOSURES

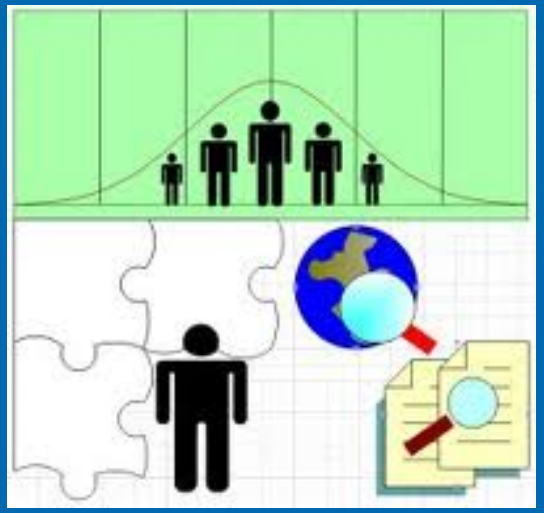
- **Disclosure of Financial Relationships**
  - **None**

- **Off-Label Usage**
  - **None**

** *Some of the tables/slides from Dr. Leeman-Markowski, MD previous lecture 2015.*

Epidemiology - Outline

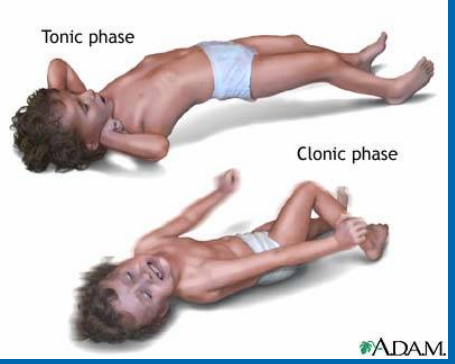
- Incidence and prevalence
- Natural history of epilepsy
  - recurrence after a single seizure
  - intractability
  - remission
  - relapse after medication withdrawal
  - mortality (SUDEP)



Statistics

- Epilepsy is the 4th most common neurological condition
- Approximately 2.2 million people in the US have epilepsy
- Epilepsy affects more than 65 million people worldwide (0.5-1%)
- These numbers are increasing (better diagnostic tools, aging), but may still be underestimates.

(IOM 2012)



The first seizure

- Acute symptomatic – 29-39/100,000 per year
- Single unprovoked – 23-61/100,000 per year.

- Lifetime risk of developing epilepsy by 80 years old = 1.4 - 3.3%.

Hauser WA. 2008 Epilepsia.

The first seizure

- 2 year recurrence risk – 25% to 66%

- Risk of recurrence: increases
  1. neurologic deficit
  2. focal seizures +/- Todd palsy
  3. abnormal EEG
  4. status epilepticus
  5. multiple seizures
  6. prior acute symptomatic seizures

Shinnar S et al 1990 Pediatrics; Lindsten H et al 2001 Acta Neurol Scand

The first seizure

- 20 people per 100,000
- 25,000 – 40,000 children per year in US

(Camfield et al Epilepsia 1996; Hauser et al Epilepsia1993; Jallon et al Epilepsia 1997)

- at **2 years**, recurrence risk:

  idiopathic first seizure: 32%

  remote symptomatic: 57%

The first seizure

- Prospective , population-based studies (Olafsson et al Neurol 2005; Loiseau P et al Epilepsia 2005)

  33 - 42% remote symptomatic

  21 – 53% cryptogenic**

  14 – 37% idiopathic**

* *Commission on Classification and Terminology of the ILAE (Berg 2010)*

Does treatment with AED after a first seizure change the long term prognosis for seizure remission?

- Class II (RCT, prospective, not placebo-controlled)

N=419, 114 (between 2-16 yold)

	1 or 2 year seizure remission
Pts treated after 1st sz	→ 68% , n= 215
Pts treated after 2nd sz	→ 60%, n = 204

risk of recurrence [RR]=1.04, 95% CI=1.3-0.82

Musicco et al. Treatment of first tonic clonic does not improve the prognosis of epilepsy. Neurology 1997;49:991-998.

Prediction of Risk of Seizure Recurrence after a single and early epilepsy: Further results from the MESS Trial

- Multicenter trial for Early Epilepsy and Single Seizures (MESS) Trial

  n=722

  Randomized to immediate and deferred tx

  ***Same conclusions obtained.

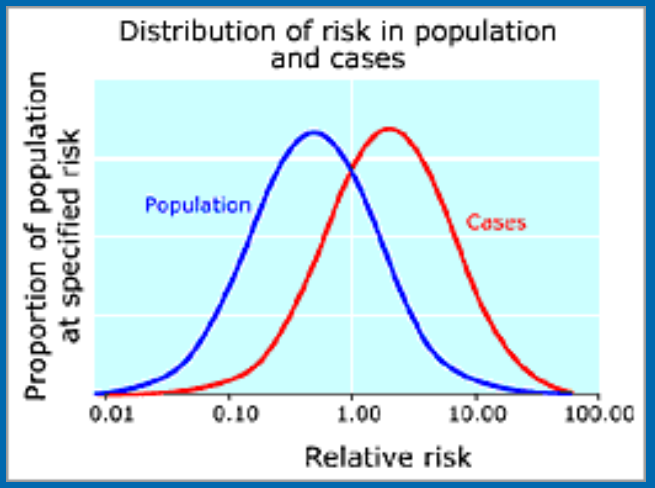
Kim LG et al Lancet Neurol 2006

Frequency Measures of Incidence and Prevalence

Incidence – number of new cases occurring in a given time. e.g. no. of cases per 100,000 population/year.

- **Epilepsy – 50 / 100,000 per year**
  higher in infants and older person
- About 40% develop epilepsy < 16 yold
  20% epilepsy > 65 yold

* Higher in low and middle income countries



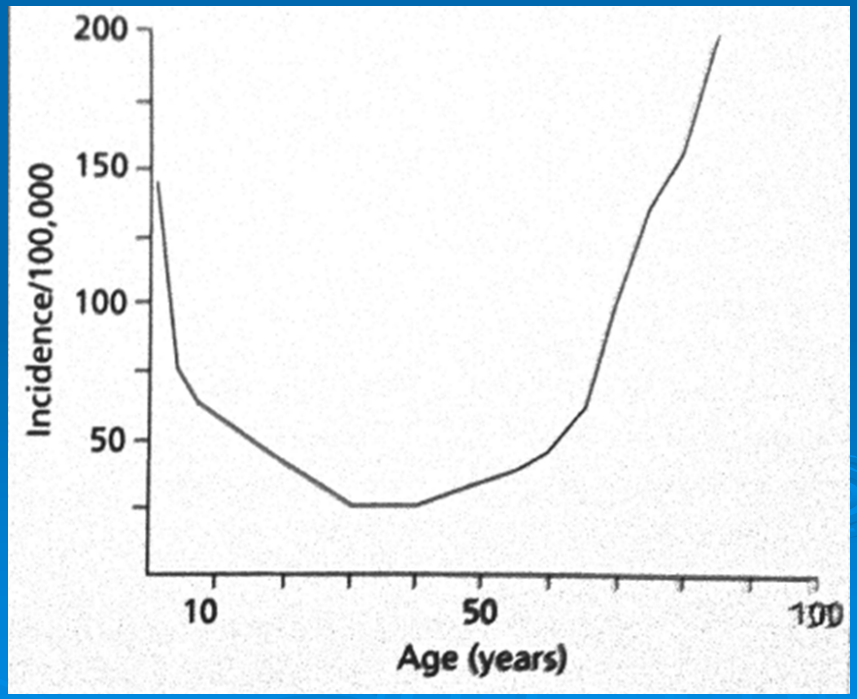
Hirtz et al 2007 Neurology 68:326-337

*

Age-specific incidence rate

Bimodal peaks in age-specific incidence (Forsgren 1996, Granieri 1983, Hauser 1996, Olafsson 2005, Sidenvall 1993)

- High in the first year of life
- Low throughout adult years
- Incidence increases > 55 years
- Over time, a trend for a decrease in childhood epilepsy, but an increase in older adults with epilepsy in developed countries.



Age-specific incidence rates based on combined results from studies in the USA, Iceland, and Sweden.

Frequency Measures of Incidence and Prevalence

- **Prevalence** – current number of active cases at a specific moment in time.

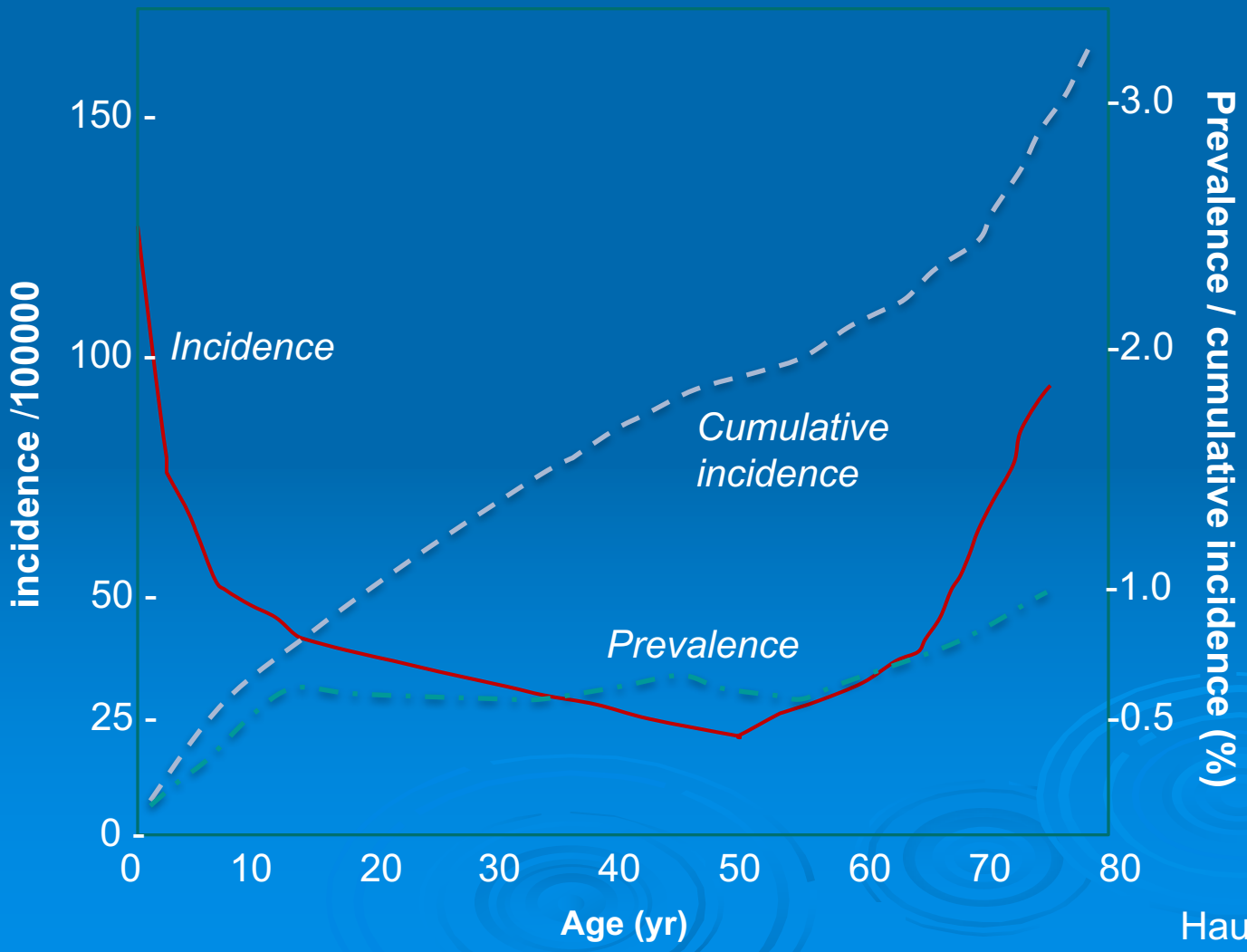
  - no. of persons with epilepsy /1000 population.

  - 4-10 cases /1000 population

  * Higher in developing countries

Incidence and Cumulative Incidence of Epilepsy

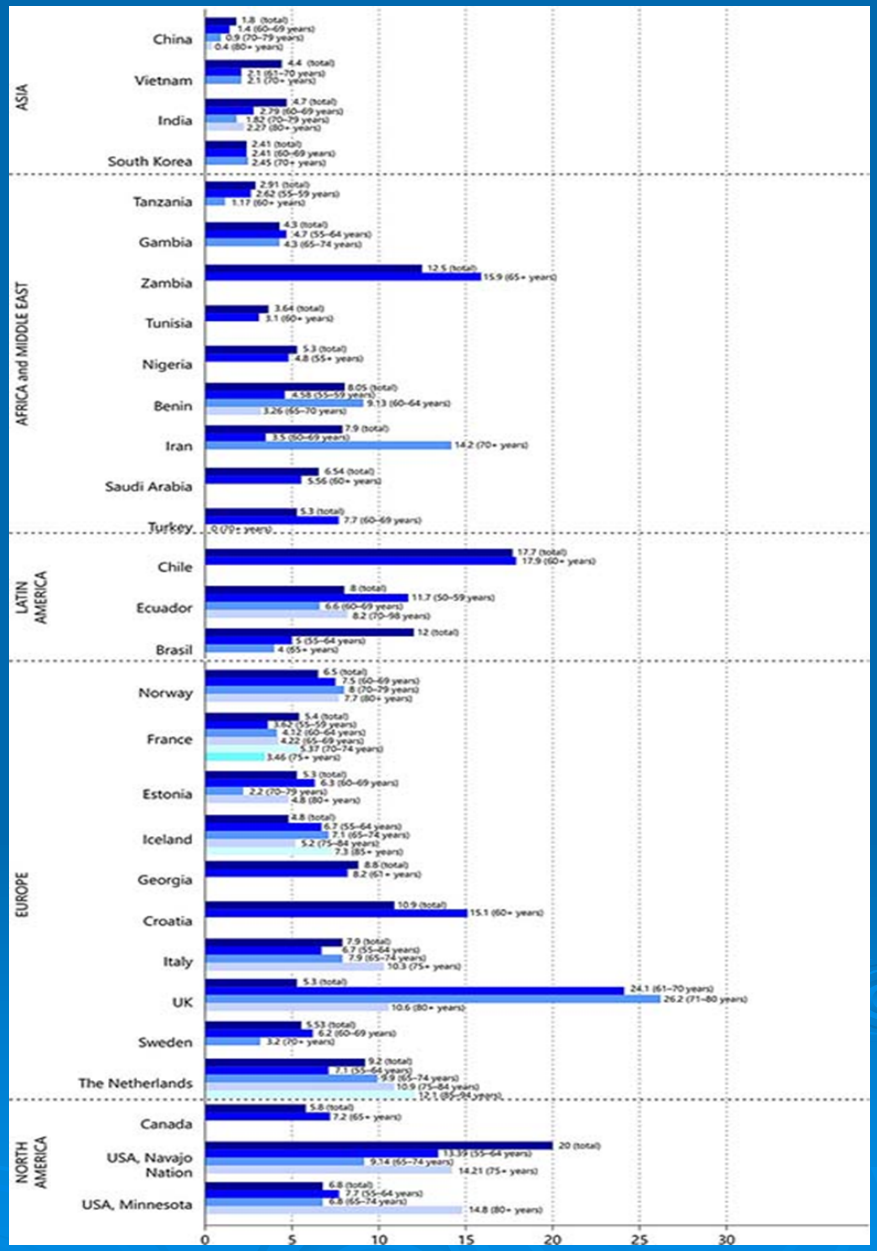
Age-specific incidence rate, cumulative incidence rate and prevalence rate of epilepsy in Rochester, Minnesota (1983-1974)



Hauser *et al*, 1983

Incidence of Epilepsy

- The incidence in high-income countries ranges from 24 to 71.0 per 100,000 per year.
- In low/middle-income countries, the incidence is higher and can be up to 190 per 100,000



Beghi, E and Giussani, G . Neuroepidemiology 2018;51:216–223

Distribution by Seizure Type and epilepsy syndrome

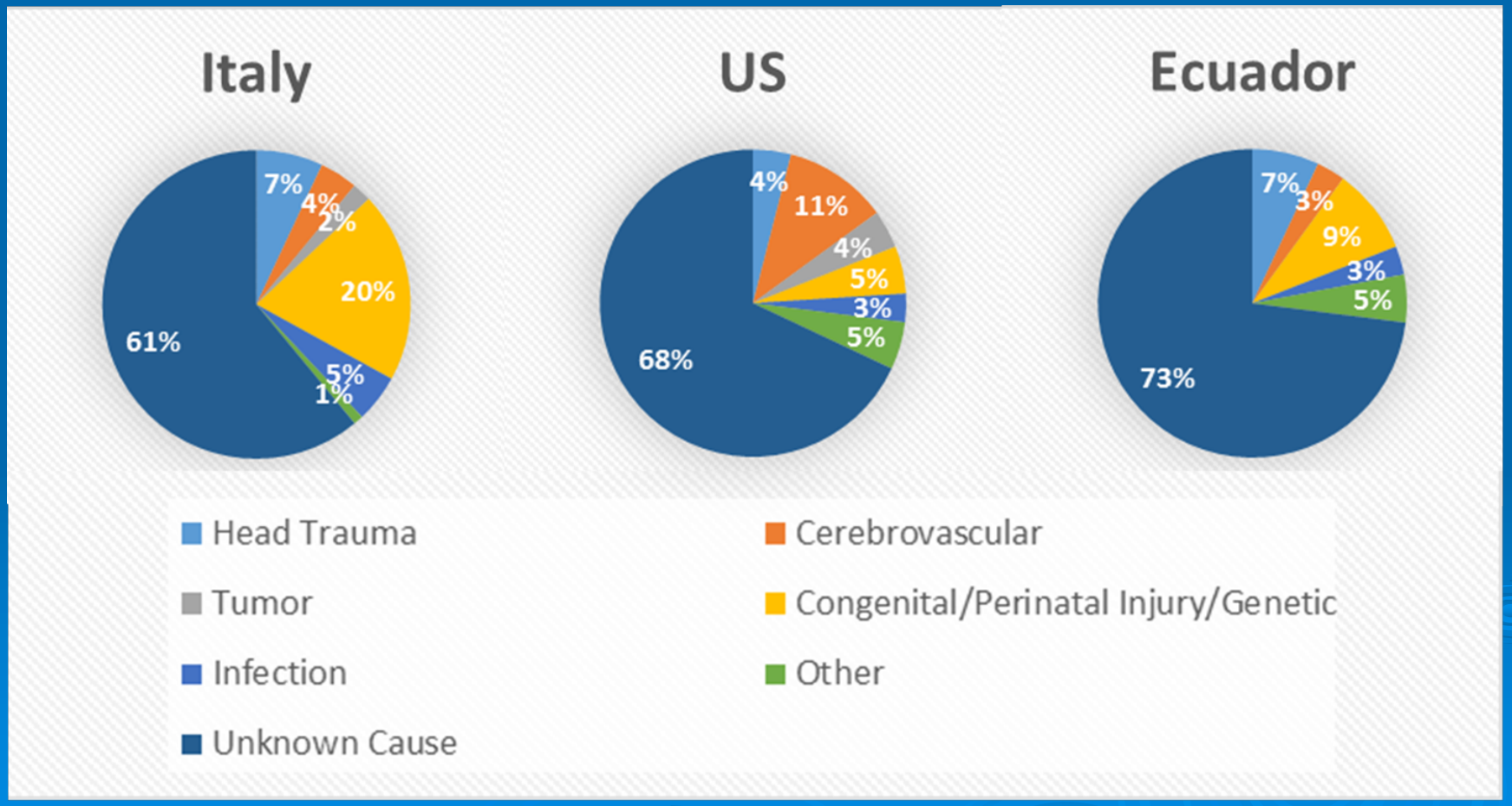
- Absence epilepsy
  incidence: 0.7 -8/ 100,000
  prevalence: 0.1 to 0.7/ 1000
- Juvenile myoclonic epilepsy
  incidence: 1 /100,000 persons
  prevalence: 0.1 – 0.2 /1000 (Jallon and Latour, 2005)
- Infantile spasms:
  incidence: 2-4.5/ 100,000 per year (Trevathan 1999)
- Lennox Gastaut :
  incidence: 1-2 / 100,000
  prevalence: 1.3 – 2.6 / 1000
  (Cowan, 2002)

Etiology by age

<15 years	15-34 years	35-64 years	≥65 years
• Congenital conditions	• CNS infection • Neoplasm • Head trauma • Birth injury/lesions	• **Cerebrovascular disease – 35%** • Neoplasm • Head trauma	• **Cerebrovascular disease – >60%** • Degenerative disease – 20%

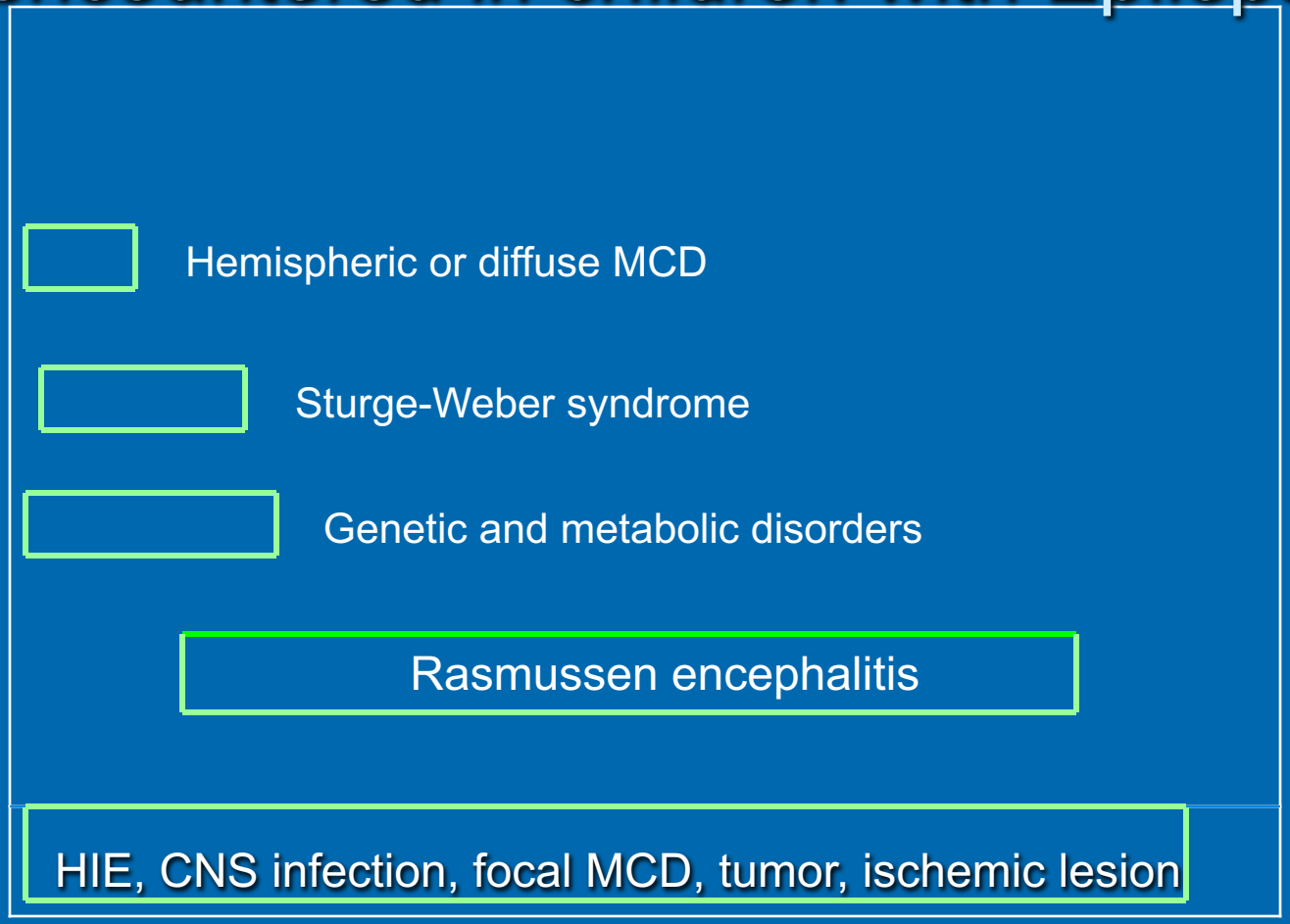
Hauser 1996

Etiology



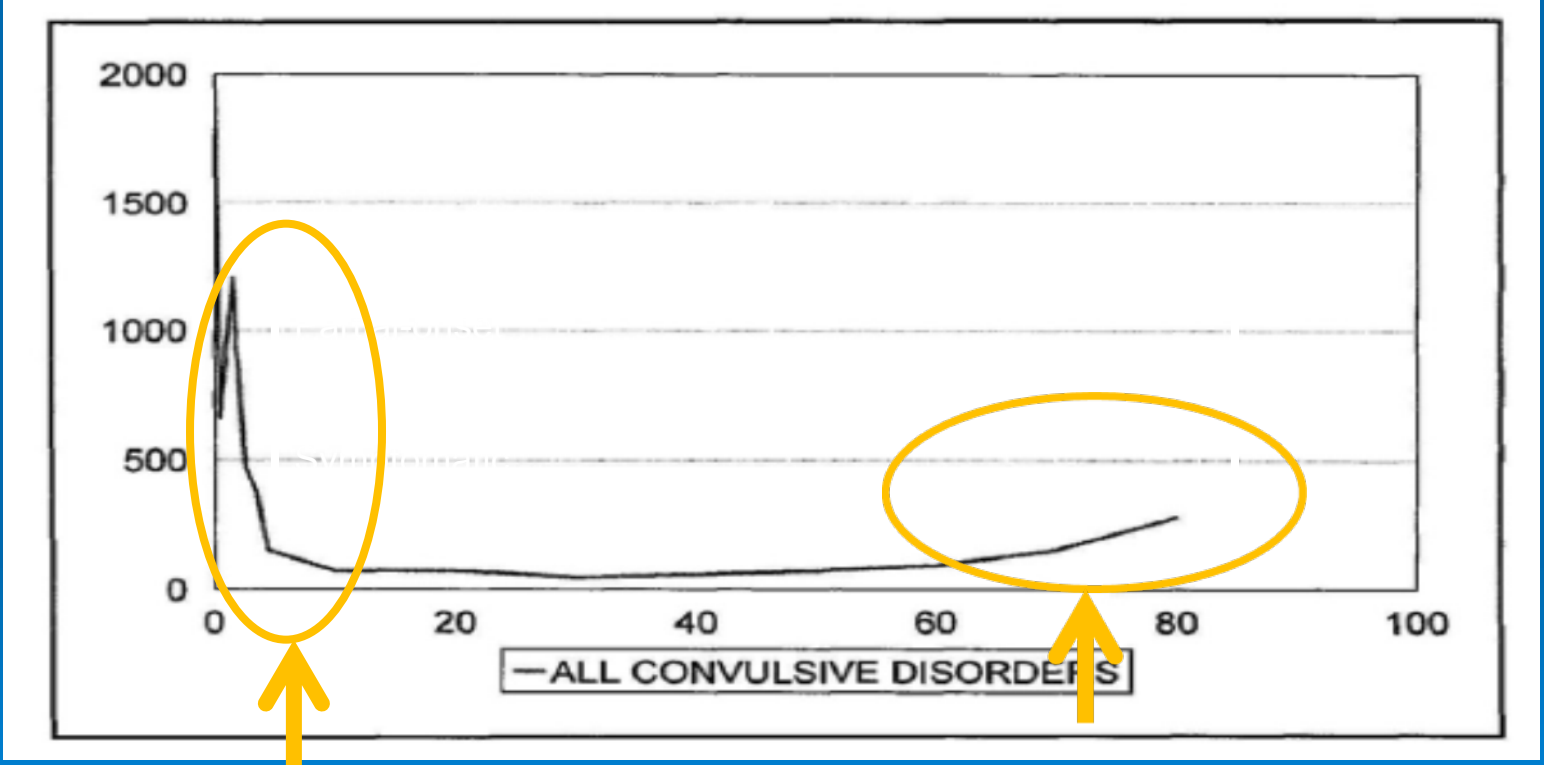
Hauser 1975, Placencia 1992, Granieri 1983

Usual age of onset and common etiologies/pathologic substrates often encountered in children with Epilepsy



Gupta A, Wylie E. Presurgical assessment of the Epilepsies with Clinical Neurophysiology and Functional Imaging. 2004

Common seizure type varies by age



Generalized-onset

- Greatest in first year
- Most common ages 0-5 years

Focal/Partial-onset

- At least 2-fold increase > 24 years
- 5-fold increase ≥ 75 years
- Symptomatic

Epilepsy risk in special populations

- 25.8% with mental retardation (MR)
- 13% with cerebral palsy (CP)
- 50% with both CP and MR
- 10% with Alzheimer
- 22% with stroke
- 33% with single unprovoked seizure

Definitions

- **Active epilepsy** – 1 seizure has occurred in the preceding period (2-5 years).

- **Remission** - no seizure has occurred in the preceding period (2-5 years).

Remission of Treated Epilepsy

- Community-based study Rochester, MN
  - 75% had 5 year remission

- The National General Practice Study of Epilepsy in United Kingdom (prospective study)
  - 60% had 5 year remission (9 years follow up)

**** Nearly 70% expected to enter remission.

Shafer SQ et al Epilepsia 1988; Cockerell OC et al Epilepsia 1997

Remission of Treated Epilepsy

Terminal remission data from selected studies

Reference	Study setting	Special study features	No. of patients	Median follow-up (years)	Years in remission	% in remission at median follow-up
Elwes et a. (32)	Hospital		106	5.5	2	79
Shafer et al. (29)	Community		432	17	5	66
Collaborative Group (33)	Hospital		280	4	1	70
Cockerell et al. (14)	Community	Definite epilepsy	564	7	5	68
Sillanpaa et al. (34)	Hospital	Children only	176	40	1	93
Lindsten et al. (35)	Community	≥1 baseline seizure ≥2 baseline seizures	107 89	9 9	5 5	64 58

From Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry. 2004; 75: 1376-1381.

Relapse

High risk of relapse:

- unrecognized minor seizure
- long history of seizure before remission
- structural brain lesion
- abnormal neurologic signs
- Learning disability
- past history of relapse
- more than one seizure type

MRC Antiepileptic drug withdrawal group. Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet 1991

Intractable Epilepsy

- 5-10% of epilepsy cases become refractory.
- 60% with focal seizures.

- etiology
- younger age at onset (<1 year old)
- high initial seizure frequency
- mental retardation

Intractable Epilepsy

- Prospective study: 613 children with newly diagnosed epilepsy

  10% met criteria for intractable epilepsy

  (failure of > 2 seizure meds, >1 seizure /month,
  over 18 month period)

- Increased risk of developing intractable epilepsy
  - cryptogenic/symptomatic generalized syndromes
  - high initial seizure frequency
  - focal slowing on EEG

Berg, AT et al. Early development of intractable epilepsy in children: a prospective study. Neurology 2001.

The New England Journal of Medicine

EARLY IDENTIFICATION OF REFRACTORY EPILEPSY

PATRICK KWAN, M.D., AND MARTIN J. BRODIE, M.D.

- 63% become seizure-free
- More likely if idiopathic and ≤ 20 seizures prior to treatment
  - AED #1: 47% seizure-free
  - AED #2: 13% seizure-free
  - AED #3: 1% seizure-free
- 3% seizure-free with two AEDs in combination
- Reason for failure is important predictor

Mortality

- **Standardized mortality rate (SMR)**

  observed no. of deaths in an epilepsy population to that expected based on the age and sex – specific mortality in a population

- SMR - 2-3 x higher in patients with epilepsy.

- Highest in children and >75 years old.
- Increased in remote symptomatic cases

Lhatoo et al Mortality in epilepsy Ann Neurol 2001

Mortality

- **Major causes**:

a. Epilepsy- related deaths

SUDEP, Status epilepticus, accidents and suicide

b. Deaths related to the underlying cause

c. Deaths unrelated to the underlying cause

Causes of Death in Epilepsy

Unrelated deaths

- Neoplasms outside the central nervous system
- Ischemic heart disease
- Pneumonia
- Others

Related to underlying disease

- Brain tumors
- Cerebrovascular disease
- Cerebral infection-abscesses and encephalitis
- Inherited disorders, e.g., Batten's disease

Nashef L, Shorvon SD. Mortality in epilepsy. Epilepsia. 1997; 38: 1059-1061.

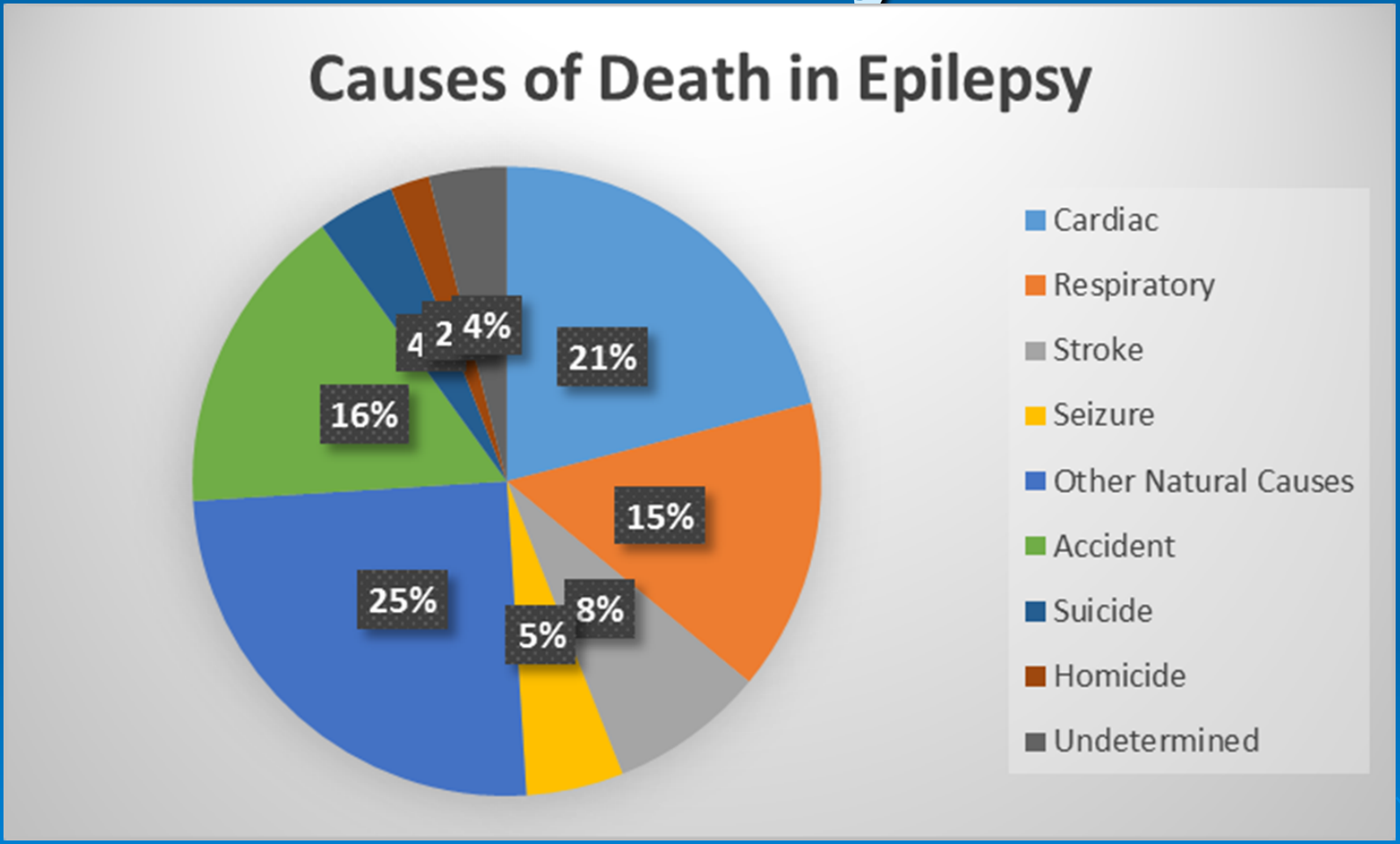
Causes of Death in Epilepsy

Epilepsy-related deaths

- Suicide
- Treatment-related deaths
- Idiosyncratic drug reactions
- Medication adverse effects
- Seizure-related deaths
- Status epilepticus
- Trauma, burns, drowning
- Asphyxiation, aspiration
- Aspiration pneumonia after a seizure
- Sudden unexpected death in epilepsy (SUDEP)

Nashef L, Shorvon SD. Mortality in epilepsy. Epilepsia. 1997; 38: 1059-1061.

Mortality



Barooni 2007

- SUDEP is the cause of death in 4-17% of unselected cases, 50% of refractory epilepsy
- SUDEP most common with recurrent generalized seizures, polypharmacy, coexisting neurologic disease

Mortality

- The true incidence of epilepsy- related deaths is unknown

  - U.S. national mortality records provide grossly incomplete data on epilepsy.

Mortality

Sudden unexpected death in epilepsy (SUDEP)

- occurs from a nontraumatic death with no obvious cause of death by postmortem examination.
- Mechanism not fully understood.

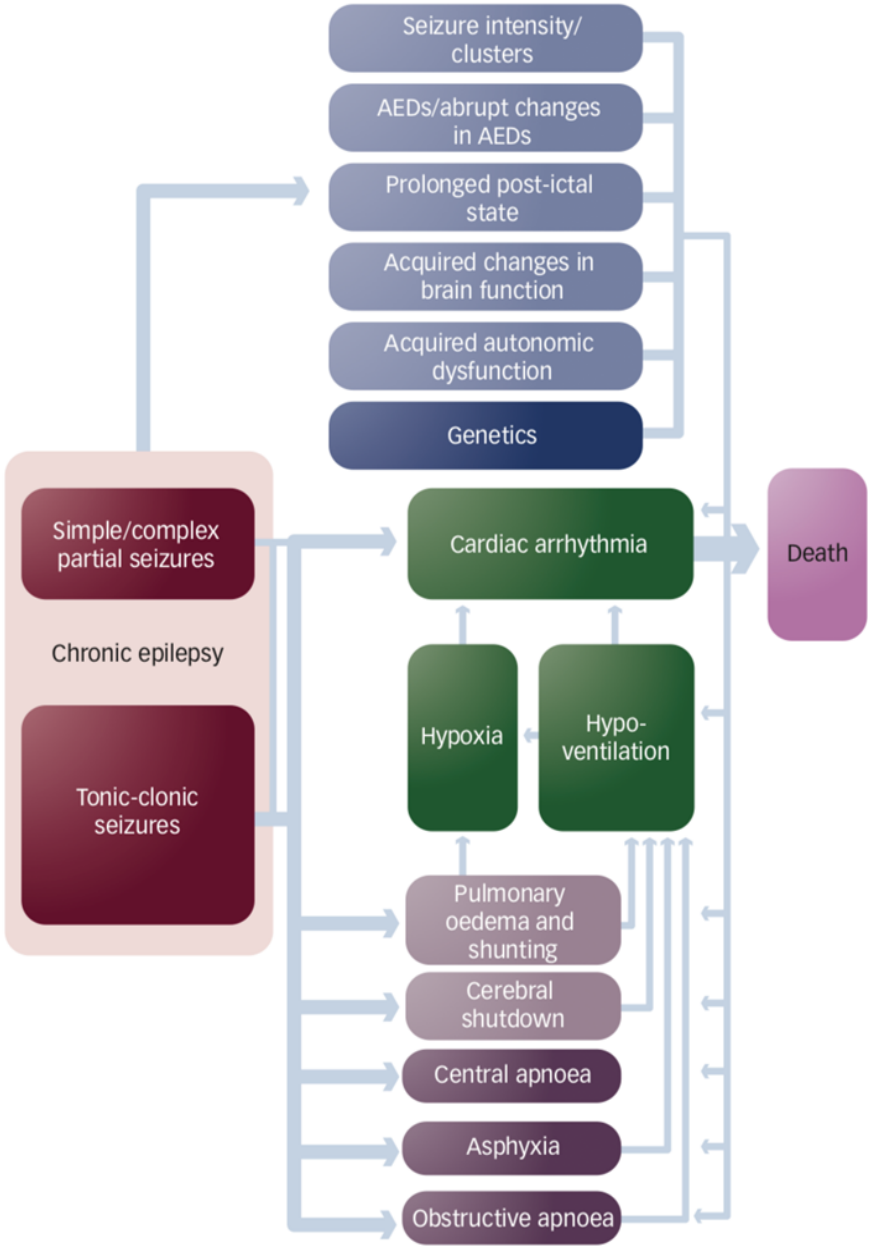
(proposed: cardiac arrhythmia, respiratory depression, cerebral autonomic dysfunction)

SUDEP - Mechanism

- **Mechanism not fully understood**

- Possibly multifactorial proposed:
  - cardiac arrhythmia,
  - respiratory depression
  - cerebral autonomic dysfunction
    (dysregulation of systemic or cerebral circulation)
  - seizure-induced hormonal and metabolic changes
    (during and after seizures)

Figure 2: Diagram of Possible Mechanisms of Sudden Unexpected Death in Epilepsy



Genes associated with sudden unexpected death in epilepsy (SUDEP).

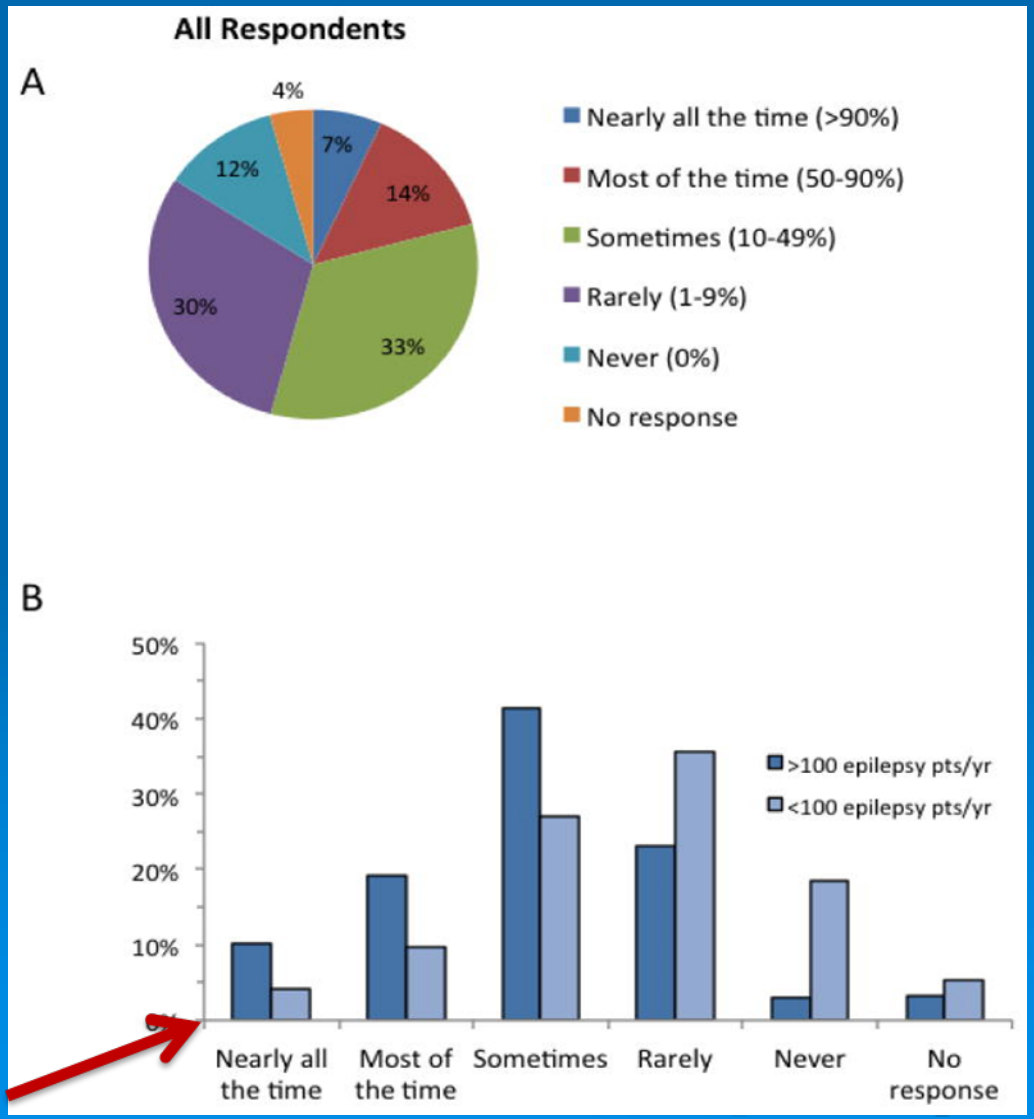
Gene	OMIM disease	Evidence for association with SUDEP
KCNA1	Episodic ataxia/myokymia syndrome	Animal model; variant found in SUDEP case
SCN1A	Dravet syndrome	Animal model; *de novo* variants found in SUDEP cases
SCN2A	Early-infantile epileptic encephalopathy 11	*De novo* variants found in SUDEP cases
SCN8A	Early-infantile epileptic encephalopathy 13	Animal model; *de novo* variants found in SUDEP cases
DEPDC5	Familial focal epilepsy with variable foci	*De novo* variants found in SUDEP cases
KCNQ1	Long QT syndrome type 1	Variants found in SUDEP cases
KCNH2	Long QT syndrome type 2	Variants found in SUDEP cases
SCN5A	Long QT syndrome type 3	*De novo* variant found in SUDEP case

Bagnall et al. Genetics Basis of Sudden Unexpected Death in Epilepsy. Neurology 2017

Epilepsy Behav. 2014 Jun;35:13-8. doi: 10.1016/j.yebeh.2014.03.022. Epub 2014 May 3.

Sudden unexpected death in epilepsy: knowledge and experience among U.S. and Canadian neurologists.

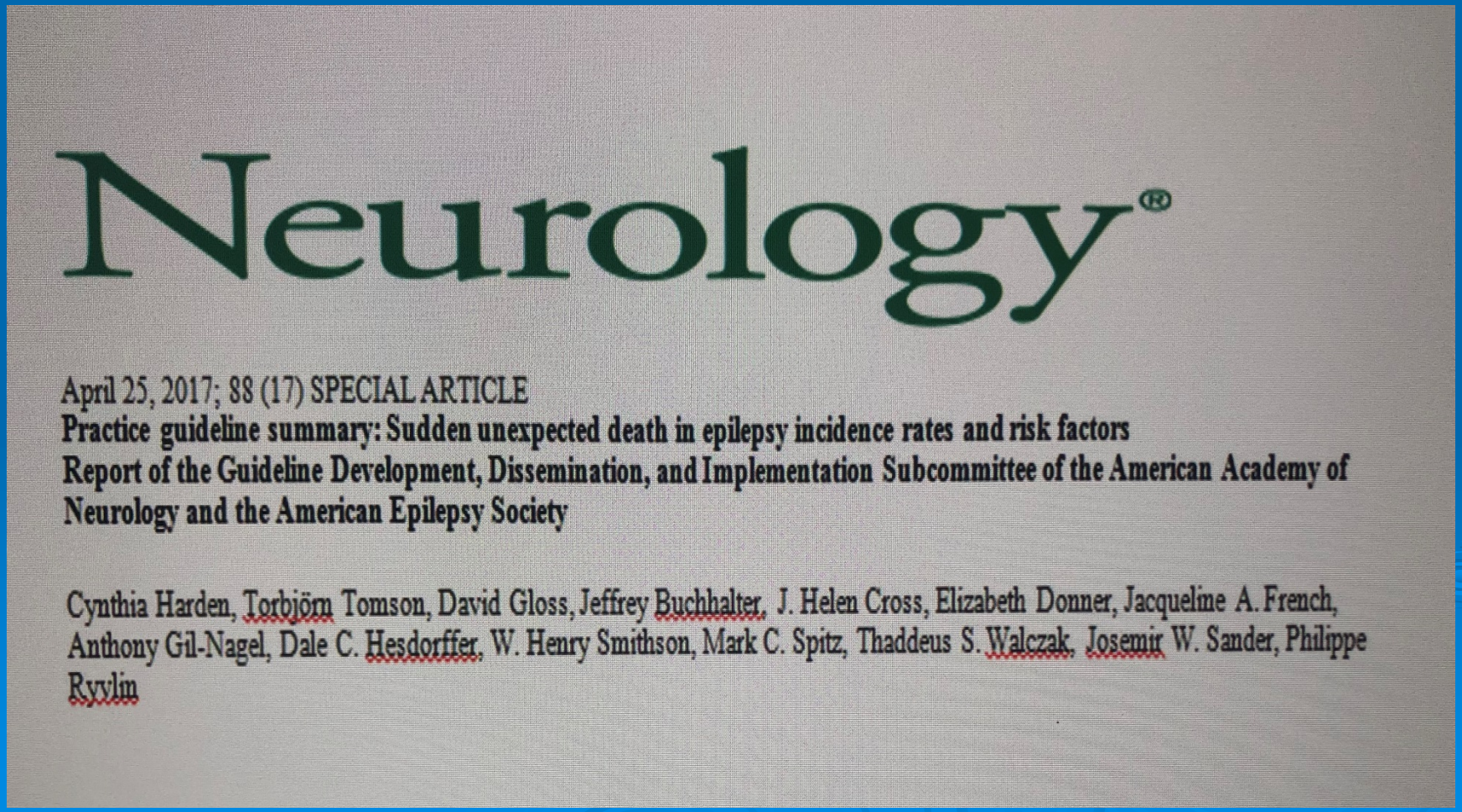
Friedman D[1], Donner EJ[2], Stephens D[3], Wright C[4], Devinsky O[5].



n= 1200 respondents

- U.S. and Canadian neurologists rarely discuss SUDEP with all patients with epilepsy/caregivers.
- Only 6.8 % discussed SUDEP nearly all the time.
- Nearly 60% of the respondents stated that rxn was negative.
- assessment of SUDEP risk factors revealed that most neurologists (82.8%) have limited knowledge about this subject.
- Surveys of physicians in the UK and Italy: most physicians do not discuss SUDEP

Practice guideline summary: Sudden expected death in epilepsy incidence rates and risk factors



Neurology®

April 25, 2017; 88 (17) SPECIAL ARTICLE

Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Cynthia Harden, Torbjörn Tomson, David Gloss, Jeffrey Buchhalter, J. Helen Cross, Elizabeth Donner, Jacqueline A. French, Anthony Gil-Nagel, Dale C. Hesdorffer, W. Henry Smithson, Mark C. Spitz, Thaddeus S. Walczak, Josemir W. Sander, Philippe Ryvlin

Harden C et al. Neurology April 2017

SUDEP -incidence

SUDEP risk in children with epilepsy:

0.22/1,000 patient-years

(95% CI 0.16-0.31)

SUDEP risk in adults with epilepsy:

1.2/1,000 patient-years

(95% CI 0.64-2.32)

Harden C et al. Neurology April 2017

SUDEP Incidence (Based on twelve Class 1 studies)

Population	SUDEP/1,000 patient-years (confidence interval)	Confidence
Overall	0.58 (0.31-1.08)	Low
Childhood	0.22 (0.16-0.31)	Moderate
Adulthood	1.2 (0.64-2.32)	Low

Harden C et al. Neurology April 2017

Incidence recommendation 1: SUDEP incidence in children

Level B

- There is a rare risk of SUDEP.
- In 1 year, SUDEP typically affects 1 in 4,500 children with epilepsy; in other words, annually, 4,499 of 4,500 children will not be affected by SUDEP.

Harden C et al. Neurology April 2017

Incidence recommendation 2: SUDEP incidence in adults

Level B

- There is a small risk of SUDEP.
- In 1 year, SUDEP typically affects 1 in 1,000 adults with epilepsy; in other words, annually, 999 of 1,000 adults will not be affected by SUDEP.

Harden C et al. Neurology April 2017

SUDEP Risk factors (Based on 6 Class I and 16 Class II articles

Factor	Odds Ratio (CI)	Confidence level
Presence of GTCs vs lack of GTCS	10 (17-14)	Moderate
Frequency of GTCS	OR 5.07 (2.94-8.76) for 1-2 GTCS per year and OR 15.46 (9.92-24.10) for >3 GTCS per year	High
Not being seizure-free for 1-5 y	4.7 (1.4-16)	Moderate
Not adding an AED when patients are medically refractory	6 (2-20)	Moderate
Nocturnal supervision (risk reduction)	0.4 (0.2-0.8)	Moderate
Use of nocturnal listening device (risk reduction)	0.1 (0.0.3)	Moderate

Harden C et al. Neurology April 2017

SUDEP Risk factors (Based on 6 Class I and 16 Class II articles)

- Major risk factor:

  Presence and frequency of GTCS.

  - if with >3 GTCS per year, with 15-fold increased risk of SUDEP.
  - moderate confidence in the evidence from 2 Class II studies.

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is low that the following factors are associated with altering SUDEP risk:

- Nocturnal seizures (associated with increased risk)
- Any specific AED (none associated specifically with increased risk)
- LTG use in women (associated with increased risk)
- Never having been treated with an AED (associated with increased risk)
- Number of AEDs used overall (associated with increased risk)
- Heart rate variability (not associated with increased risk)
- Extratemporal epilepsy (associated with increased risk)
- Intellectual disability (associated with increased risk)
- Male gender (associated with increased risk)
- Anxiolytic drug use (associated with increased risk)

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is very low that the following factors are associated with altering SUDEP risk:

- Overall seizure frequency when evaluated by using all seizure types
- Medically refractory epilepsy vs not having well-controlled seizures defined as no seizures for the past year
- Monotherapy vs polytherapy
- CBZ, PHT, or VPA levels that are above, below, or within the reference range
- Psychotropic drug use
- Mental health disorders, lung disorders, or alcohol use

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:

- LTG use in people with highly refractory epilepsy
- Frequent changes in AEDs
- Therapeutic drug monitoring
- Undergoing a resective epilepsy surgical procedure**
- Engel outcome of epilepsy surgery**
- VNS use for more than 2 years**

**Although current research does not rule out the possibility of a beneficial effect or, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing SUDEP risk.

AAN/AES: Practice Guideline: SUDEP Incidence Rates and Risk factors

The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:

- Epilepsy etiology - idiopathic or localization related
- Structural lesion on MRI
- Duration of epilepsy
- Age at epilepsy onset
- Postictal EEG suppression

SUDEP – Practice Guidelines Recommendations (AAN, AES)

- Level B: Epilepsy with GTCS – physicians should actively manage epilepsy therapies to reduce seizures.
- Level C: with frequent GTCS and nocturnal seizures, physicians should advise (if permitted) to use nocturnal supervision or nocturnal precautions.
- Level B: Clinicians should tell patients that seizure freedom particularly from GTCS, strongly associated with decreased risk of SUDEP.

Mortality

- **Status Epilepticus fatalities**

  estimates vary widely

  median estimate: 0.94/100,000 annually

  (Rosenow F et al, Epilepsia 2007)

- **Accidental deaths**

  drowning, traffic accidents, trauma, falls, burns, aspiration

  1.2% - 6.5 % in community based studies.

Mortality

Suicides

- Suicides per 100,000 population in US is 12.4*

- Suicide increased risk with:
  1. mental illness
  2. drug addiction
  3. Temporal lobe epilepsy
  4. personality disorder
  5. early onset epilepsy (adolescence)

* Calculated from data from U.S. Centers for Disease Control and Prevention.

Conclusion: Epidemiology

- Incidence and prevalence
- Natural history of epilepsy
  - recurrence after a single seizure
  - intractability
  - remission
  - relapse after medication withdrawal
  - mortality

Board Questions

Question 1

The incidence of epilepsy is the number of new cases occurring in a given time. What is the incidence of epilepsy?

a. 4-10 cases/1000 population

b. 50 cases/100,000 per year

c. 250 cases/100,000 per year

d. 200,000 cases

Question 2

Which one of the following is not an epilepsy related death:

a. Cerebrovascular accident

b. Sudden unexpected death in epilepsy

c. Suicides

d. Drowning

e. Adverse drug effects

Question 3

The risk for SUDEP is higher in which of the following patient with epilepsy?

a. A 24 year old female with history of GTCs on 3 seizure medications with no seizures for a year.
b. A 17 year old male with depression with 4-6 focal seizures per month.
c. A 6 year old girl with once a month GTCs on Valproic acid.
d. A 10 year old boy with a right frontal focal cortical dysplasia on Lamotrigine, Oxcarbazepine with 2 focal seizures per month being worked up for epilepsy surgery.

Question 4

Risk of suicide is highest in association with the following except:

a. Substance abuse

b. Temporal lobe epilepsy

c. Frontal lobe epilepsy

d. Mental illness

e. Adolescence

Question 5

5. Which of the following statement is correct:

a. In 1 year, SUDEP typically affects 1 in 4,500 children with epilepsy.

b. In the practice guidelines for SUDEP, clinicians should tell patients that seizure freedom particularly from focal seizures are strongly associated with decreased risk of SUDEP.

c. The number of AEDs used overall is a major risk factor for SUDEP.

d. The age of epilepsy onset is a major risk factor for SUDEP.