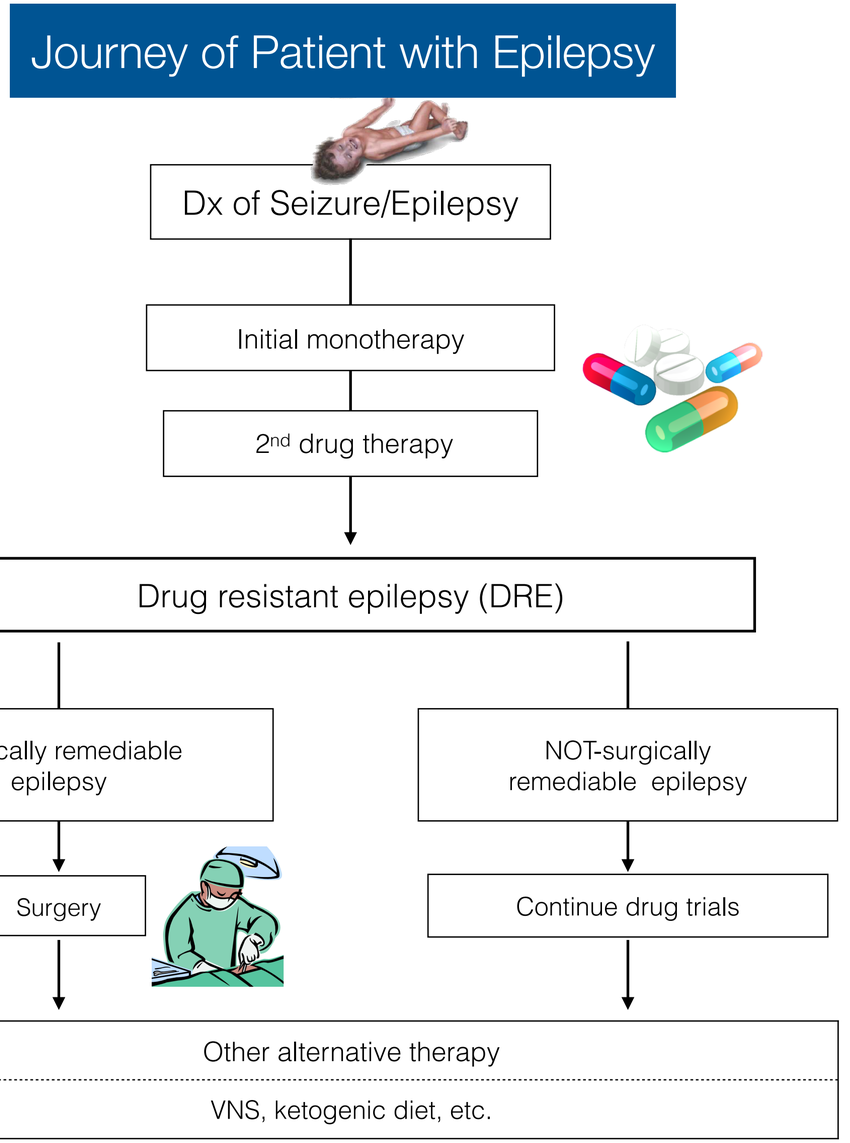
Natural History and Prognosis of Epilepsy

Atiwat Soontornpun, M.D.

Assistant Professor
Department of Internal Medicine, Faculty of Medicine,
Chiang Mai University and
Northern Neuroscience Center, Chiang Mai, Thailand

Outlines

- Prognosis after a first unprovoked seizure
- Prognosis of treated epilepsy & intractable epilepsy
- Prognosis of epilepsy after treatment withdrawal
- Prognosis of untreated epilepsy
- Mortality



Epilepsia, 50(5):1102–1108, 2009
doi: 10.1111/j.1528-1167.2008.01945.x

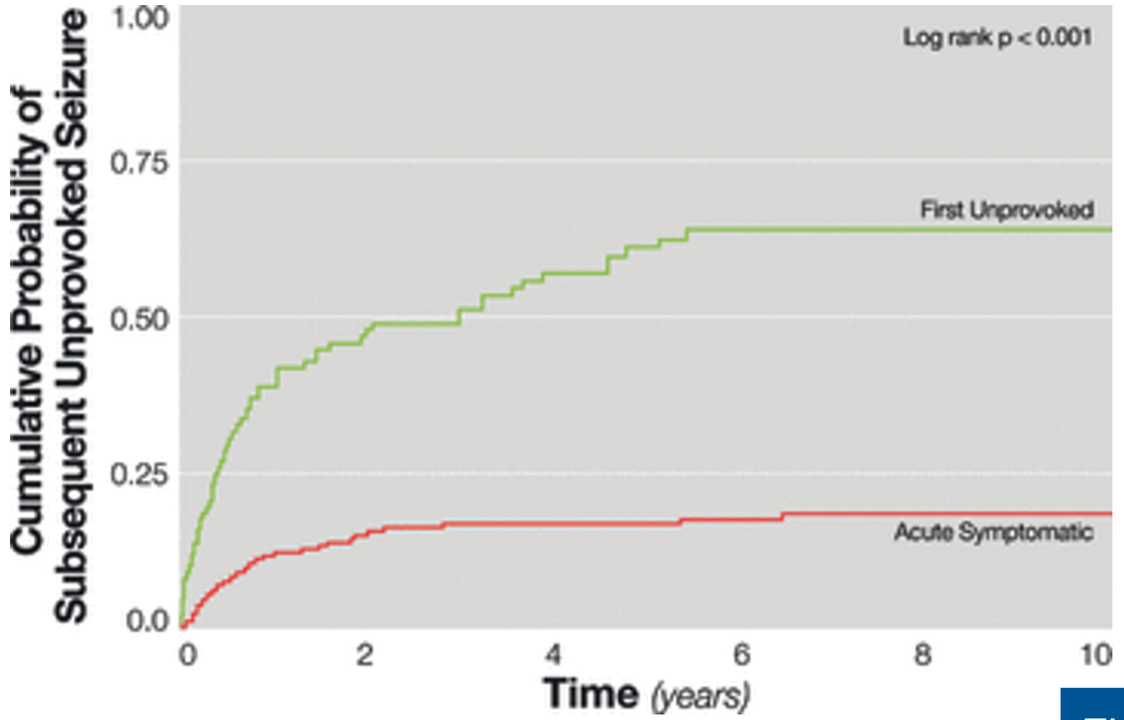
FULL-LENGTH ORIGINAL RESEARCH

Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure

*Dale C. Hesdorffer, †Emma K. T. Benn, ‡Gregory D. Cascino, and §¶W. Allen Hauser

Prognosis of a first seizure

To compare subsequent unprovoked seizure risk
Rochester Epidemiology Project's records-linkage system
1955 to 1984
First acute symptomatic (n=262) vs.
First unprovoked seizure (CNS infection, stroke, TBI) (n=148)
O: Subsequent unprovoked seizure over next 10y



64.8%

18.7%

First unprovoked seizure
- Stroke 71.5%
- TBI 46.6%
- CNS injection 63.5%

First unprovoked seizures have higher risk for subsequent seizure

Febrile Seizure (FS)

- Occurring between 3mo and 5y, associated with fever, without intracranial infection of defined cause[1] (1mo[2], 6mo)
- 2-5% of children <5y, peak incidence in second year of life
- Two categories:
    1. simple FS (solitary events, <15min, lacking focal feature, neurologically normal children)
    2. complex FS (>15min, focal feature, recurrence w/n 24h, abnormal neurologic status)
- recurrence 30-35%, risk[3]: young age (<1YO), FS in relative, low degree of fever, brief duration between onset of fever and initial seizure
- ***<u>↑ risk fo epilepsy</u>***, 2-4% of FS[4], risk: neurodevelopmental abnormality, complex FS, fm Hx of epilepsy, duration of fever

1. NIH. *Epilepsia* 1981; 2. ILAE *Epilepsia* 1993; 3. Berg AT et al. *Arch Pediatr Adolesc Med* 1997; 4. Verity et al. 1985

First Unprovoked Seizure

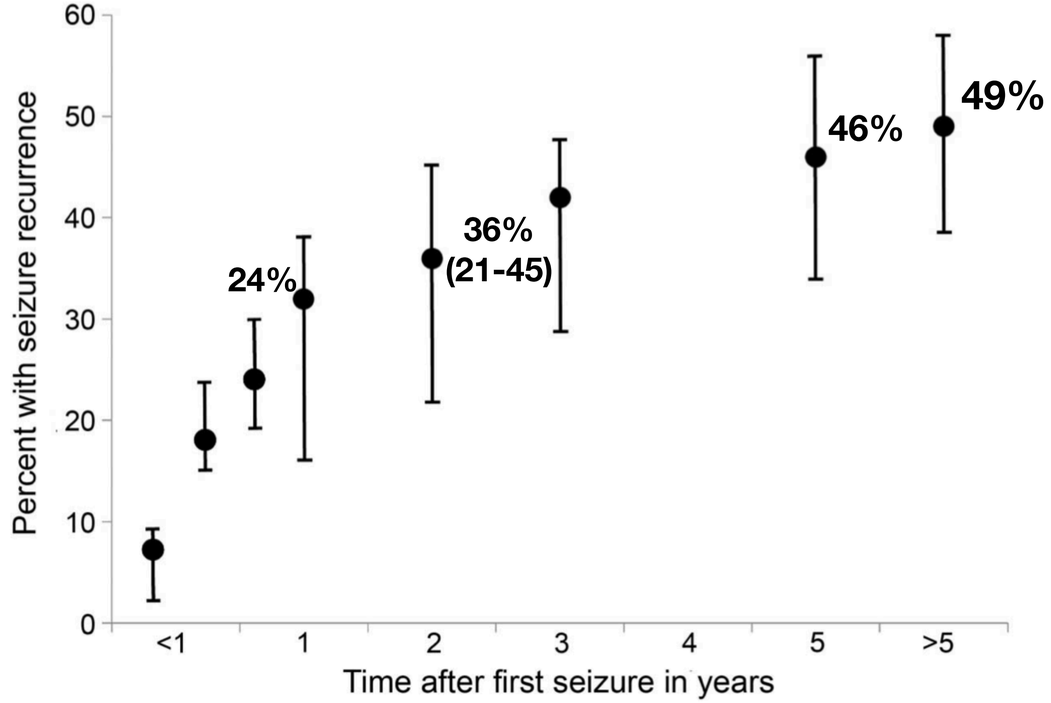
SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Evidence-based guideline: Management of an unprovoked first seizure in adults

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

Figure 1 Percentages of patients with first seizure experiencing a recurrent seizure over time



To provide recommendations for unprovoked first seizure
Systematic review: 47 articles

- Individual risk can vary
- ~50% within 6mo, greatest risk within first 2y
- Risk decrease with time

Krumholz A et al. *Neurology* 2015

Predictors of Recurrence

	2y-risk
idiopathic + normal EEGs	24%
idiopathic + abnormal EEGs	48%
remote symptomatic + normal EEGs	48%
remote symptomatic + abnormal EEGs	65%

Other factors

- neurologic deficit
- developmental delay
- nocturnal seizure (OR 2.1)
- abnormal imaging (HR 2.44)

Berg AT & Shinnar S. *Neurology* 1991; Kim LG et al. *Lancet Neurol* 2006; Krumholz A et al. *Neurology* 2015

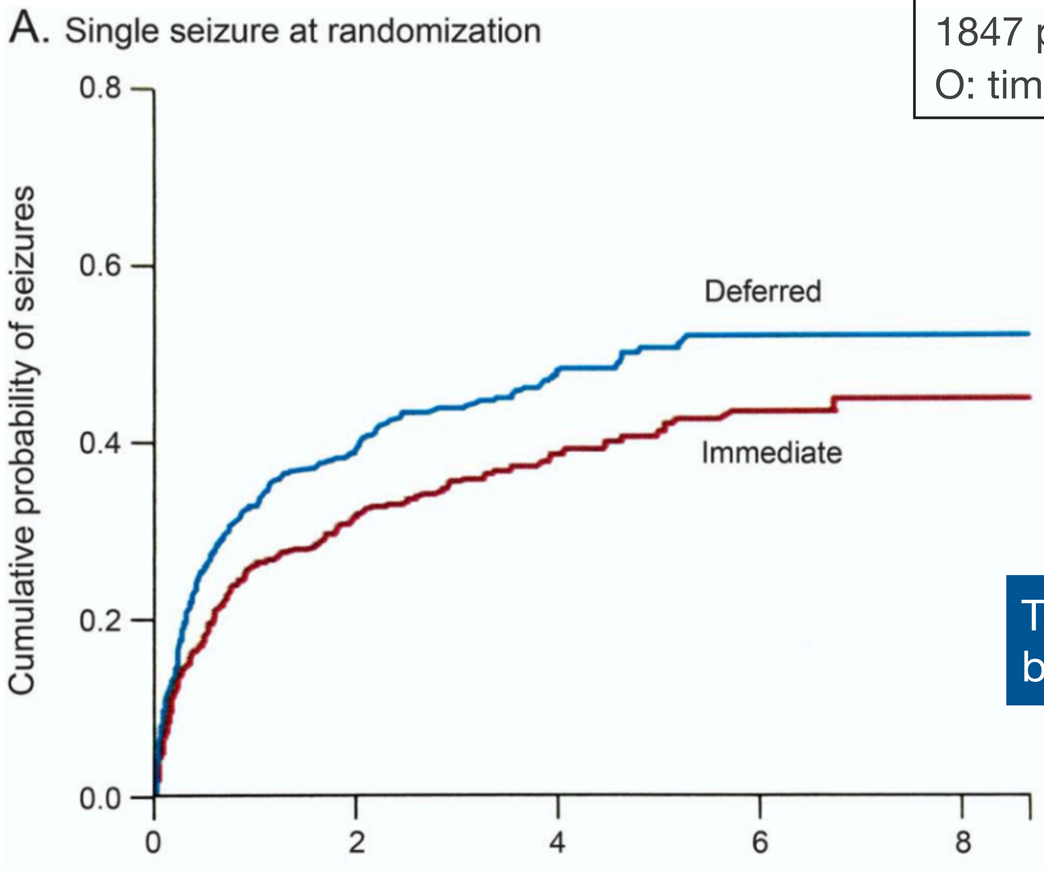
Treatment of First Seizure

Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial

*A Marson, A Jacoby, A Johnson, L Kim, C Gamble, D Chadwick, on behalf of the Medical Research Council MESS Study Group**

MESS: MRC Multicentre trial for Early Epilepsy and Single Seizures

To assess effect of immediate vs. deferred treatment on outcomes
1847 pt with single and early epilepsy
O: time to first seizure, time to 2y remission, seizures between 1-3y and 3-5y



Treatment of first seizure reduce the risk of short-term relapse(1-2y), but does not affect long-term remission

Marson A et al. *Lancet* 2005; Kim LG et al. *Lancet Neurol* 2006; Krumholz A et al. *Neurology* 2015

Epilepsia, 20:729–737, 1979.
Raven Press, New York

Remission of Seizures and Relapse in Patients with Epilepsy

*John F. Annegers, †W. Allen Hauser, and *Lila R. Elveback

*Department of Medical Statistics and Epidemiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901; and †Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York 10032

Treated Epilepsy

Medical records linkage system of the Mayo Clinic Epilepsy in population of Rochester, Minnesota
457 patients
O: seizure-free period of 5 years
f/u: ≥5y (328 followed ≥10y, 141 ≥20y)

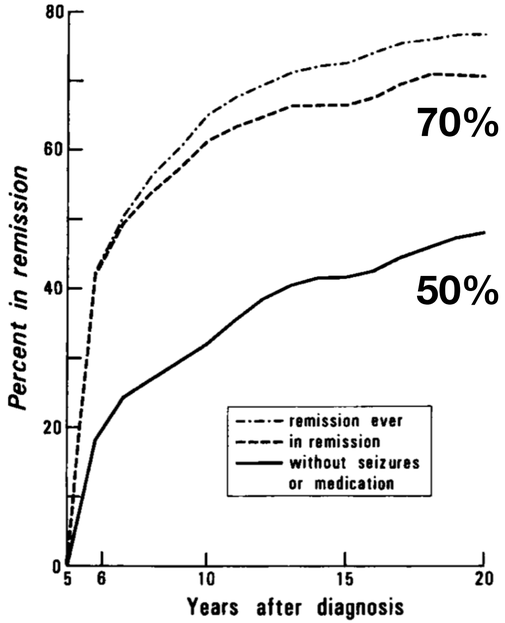


FIG. 1. Remissions among all 457 cases. Remission ever: percentage of patients who achieved remission status. In remission: percentage who have been seizure-free during last 5 years or more. Without seizures or medication: percentage during last 5 years or more.

Poorer in …

- *neurologic deficit at birth or mental retardation*
- *symptomatic epilepsy* lower chance than idiopathic

Remission highest in generalized seizures before 10YO

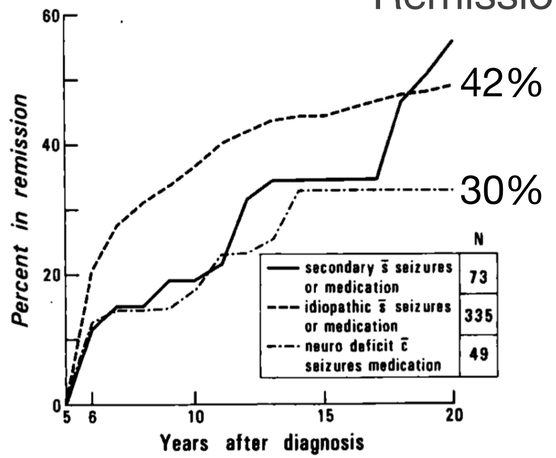


FIG. 3. Percentage in remission, by etiology and medication status.

The overall prognosis of epilepsy is favourable for majority

Delayed time to first remission identifies poor long-term drug response of childhood-onset epilepsy: A prospective population-based study

Matti Sillanpää [a,b], Dieter Schmidt [c,*]

[a] Department of Public Health, University of Turku, Turku, Finland
[b] Department of Child Neurology, University of Turku, Turku, Finland
[c] Epilepsy Research Group, Berlin, Germany

Long-term seizure freedom is highly depend on length of time to first remission

catchment area of University of Turku Central Hospital, Turku, Finland

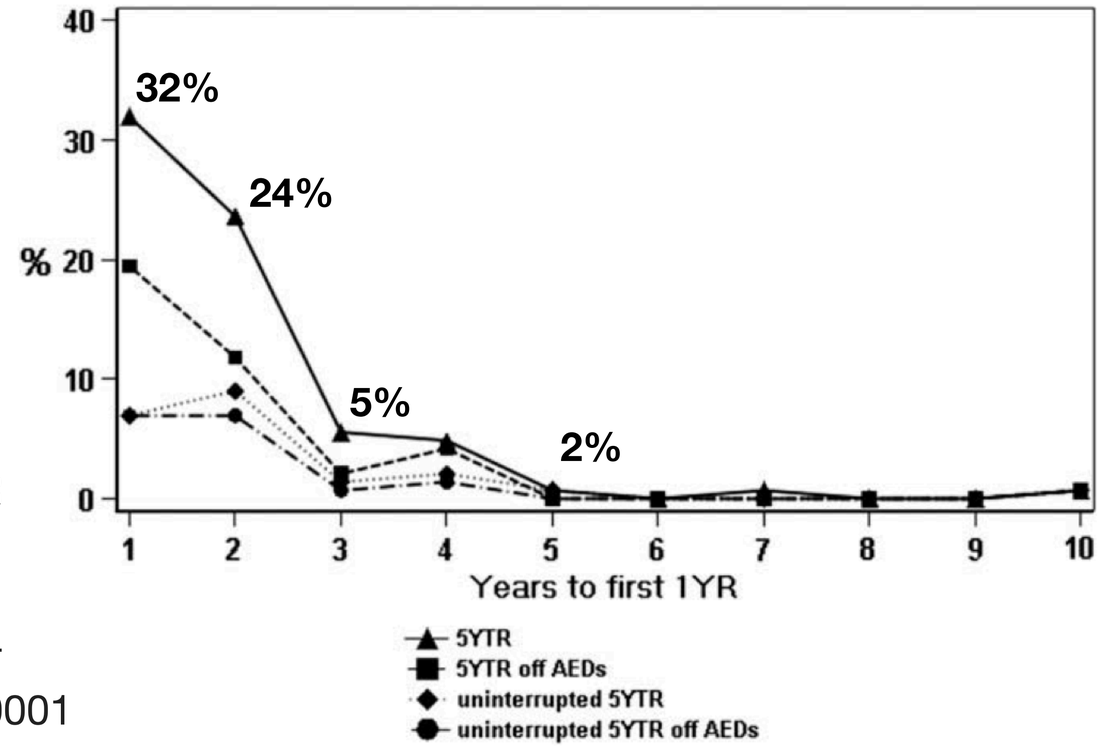
To assess time to 1-year remission as determinant of entering 5YTR

childhood-onset epilepsy, <16 y

144 patients, ≤6y 70%, female 48%

O: five-year terminal remission (5YTR), **68%**

f/u: 40y



1YR within first 5y had 11x better chance to enter 5YTR

Idiopathic vs symptomatic: OR 6.1; p<0.0001

Less than weekly *pretreatment* seizure frequency: OR 4.7; p=0.0004

Less than weekly seizure frequency *during treatment*: OR 5.5; p<0.0001

Sillanpaa M & Schmidt D. *Epilepsy Behav* 2009

Prognostic Predictors

Prognostic Predictor	Author, year
Symptomatic aetiology	Bonnett *et al.*, 2014; Wirrell *et al.*, 2012; Sillanpää *et al.*, 2012; Sillanpää and Schmidt, 2009a; Jallon *et al.*, 2003; Berg *et al.*, 2001; Ko and Holmes, 1999; Aikiä *et al.*, 1999; Sillanpää *et al.*, 1998; Annegers *et al.*, 1979
Abnormal intelligence	Sillanpää *et al.*, 2012; Wirrell *et al.*, 2012; Aikiä *et al.*, 1999; Sillanpää, 1993; Camfield *et al.*, 1993; Brorson and Wranne, 1987
Tonic or simple focal seizures	Bonnett *et al.*, 2014; Su *et al.*, 2013; Jonsson and Eeg-Olofsson, 2011; Del Felice *et al.*, 2010; Ko and Holmes, 1999; Shafer *et al.*, 1988
Complex focal or atonic seizures	Aikiä *et al.*, 1999; Sillanpää, 1993
Early childhood age at onset	Wirrell *et al.*, 2012; Sillanpää *et al.*, 2012; Ko and Holmes, 1999; Sillanpää, 1993; Camfield *et al.*, 1993
Prior neonatal seizures	Sillanpää, 1993; Camfield *et al.*, 1993
High seizure frequency prior to treatment	Su *et al.*, 2013; Berg *et al.*, 2001; Camfield *et al.*, 1993
High seizure frequency during early treatment	MacDonald *et al.*, 2000; Arts *et al.*, 1999; Cockerell *et al.*, 1997
Poor early effects of treatment	Bonnett *et al.*, 2014; Sillanpää *et al.*, 2012; Arts *et al.*, 1999; Sillanpää *et al.*, 1998; Annegers *et al.*, 1979
Neurological dysfunction	Annegers *et al.*, 1979
Abnormal interictal EEG	Berg *et al.*, 2014; Su *et al.*, 2013; Wirrell *et al.*, 2012; Berg *et al.*, 2001; Shafer *et al.*, 1988
Time to first remission	Sillanpää *et al.*, 2012; Sillanpää and Schmidt, 2009b

Predictor

- Symptomatic etiology
- Neurologic deficit/MR
- Early seizure frequency
- Longer time to first remission
- Age: <1y, older age
- Focal seizure, multiple types
- Abnormal EEG

Neghi E et al. *Epileptic Disord* 2015

Prognosis of Epilepsy Syndromes

	characteristics	frequency	examples
Excellent prognosis	hight probability of spontaneous remission, few seizures occur	20-30%	benign neonatal seizures, rolandic epilepsy, benign myoclonic epilepsy of infancy
Good prognosis	easy ASM control, possibility of spontaneous remission	30-40%	CAE, GTC on awakening, some focal epilepsy
Drug-dependent prognosis	may respond to ASM, but repalpse after withdrawal	10-20%	JME, most focal epilepsy
Poor	continuous seizures despite intensive ASMs	20%	congenital neurological defects, PME, West syndrome, LGS, some focal epilepsy

Sander JW. *Epilepsia* 1993

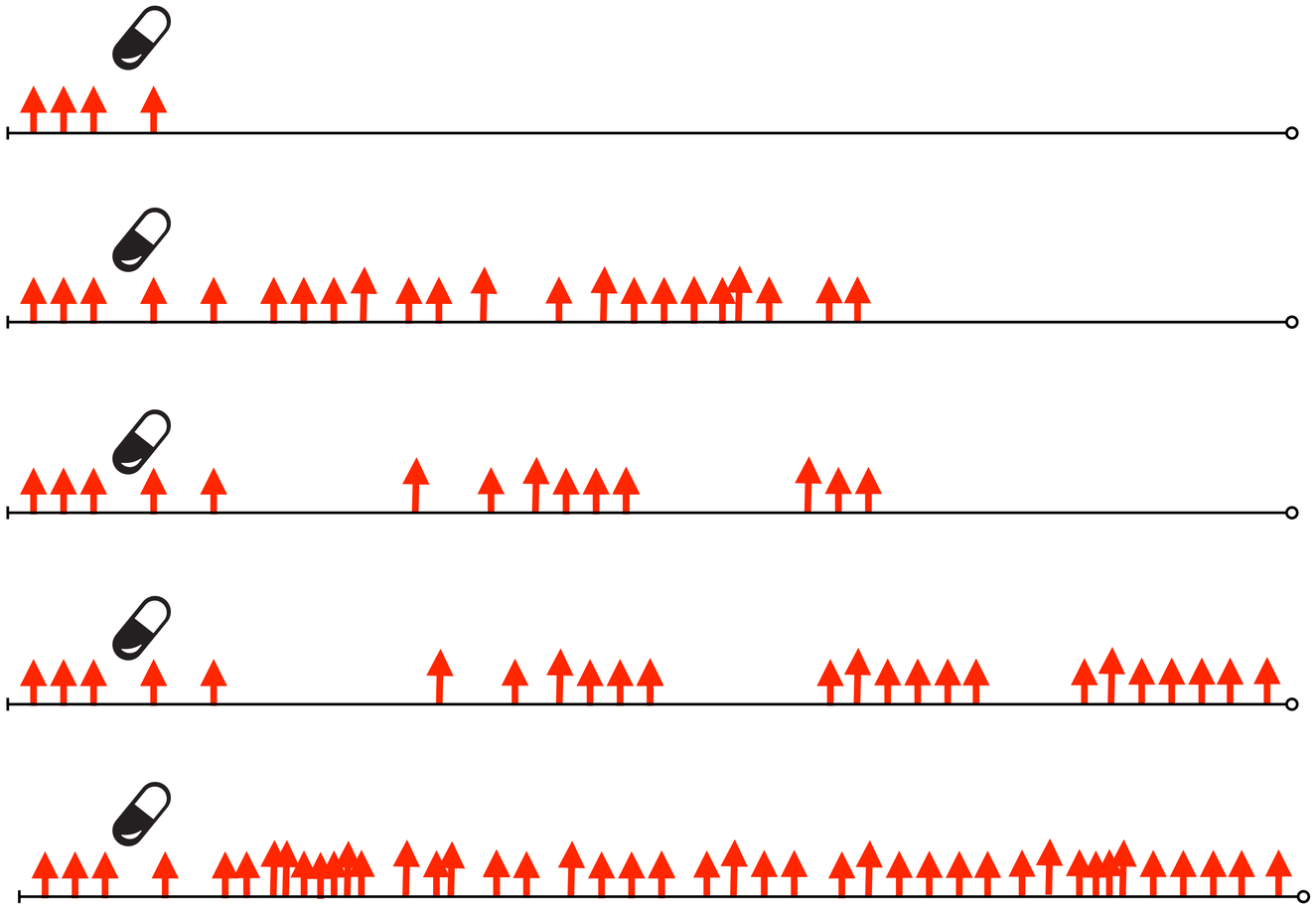
Prognosis of Epilepsy Syndromes

Syndrome	Study design	Cases	Follow-up (years)	Sz-free %	Author, year
BECTS	Retrospective cohort	29	12-17	**89**	Callenbach *et al.*, 2010
Panayiotopoulos	Retrospective cohort	93	1-14	**41**	Specchio *et al.*, 2010
CAE	Retrospective cohort	47	12-17	**93**	Callenbach *et al.*, 2009
CAE/JAE	Retrospective cohort	163	3-69	**56 (CAE)** **62 (JAE)**	Trinka *et al.*, 2004
JME	Retrospective cohort	186	1-41	**58**	Martínez et al., 2006
West	Retrospective cohort	214	20-35	**33**	Riikonen, 2001
LGS	Retrospective cohort	107	>3 in 74	**3**	Goldsmith *et al.*, 2000
Dravet	Retrospective cohort & review	24	Up to age 50	**8**	Genton *et al.*, 2011
Landau-Kleffner	Retrospective cohort	9	6-25	**0**	Cockerell *et al.*, 2011
ESES	Prospective cohort	32	>3	**43 (>90% reduction)**	Liukkonen *et al.*, 2010
EGMA	Retrospective cohort	42	40	**62**	Holtkamp et al., 2014

BECTS: benign childhood epilepsy with centrotemporal spikes; CAE: childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; LGS: Lennox-Gastaut syndrome; ESES: encephalopathy with status epilepticus during sleep; EGMA: epilepsy with grand mal on awakening.

Beghi E et al. *Epileptic Disord* 2015

Patterns of Treatment Response



A. **Early remission**, sustained without relapsed
(smooth-sailing epilepsy)

B. **Early pharmaco-resistance,**
achieved sustained remission without relapsed

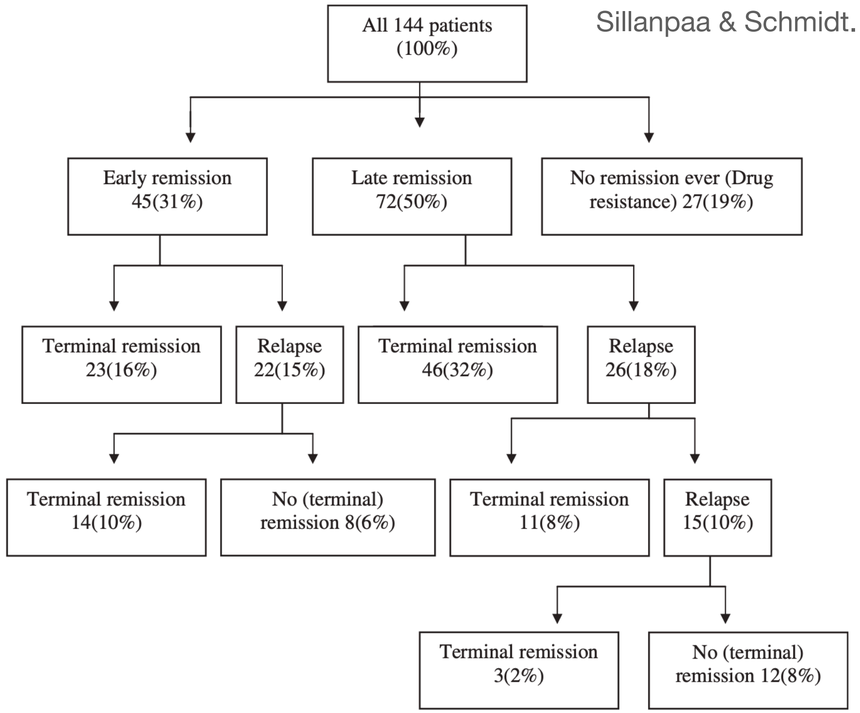
C. **Remitting-relapsing course**
C1: terminal remission
C2: no terminal remission

D. No remission period ever

Active Epilepsy is a Dynamic Process

University of Turku Central Hospital, Finland
≤15y (childhood-onset epilepsy)
follow-up 37y (11-42)
remission: seizure-free period of ≥5 consecutive years

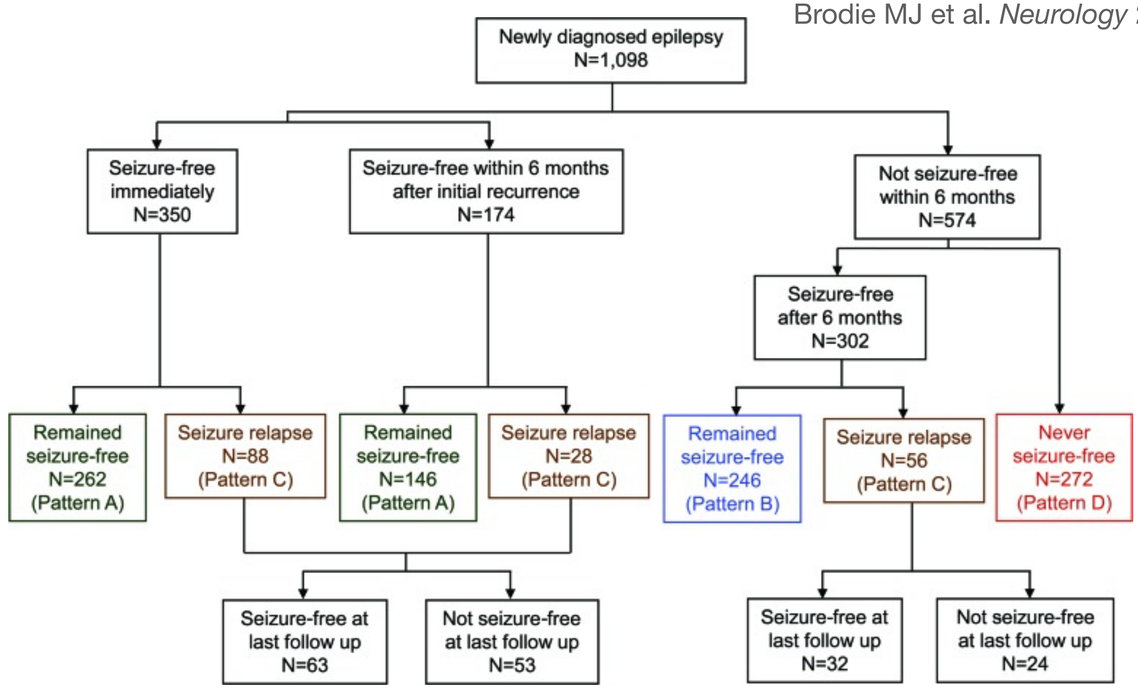
Sillanpaa & Schmidt. *Brain* 2006



A: 23/144 (16%)
B: 46/144 (32%)
C: 48/144 (33%); C1 20%, C2 13%
D: 27/144 (19%)

Western Infirmary in Glasgow, Scotland
32y (9-93)
follow-up 7.5y (4.7-12.0)
seizure-free: seizure-free period of a year of more

Brodie MJ et al. *Neurology* 2012



A: 408/1098 (37%)
B: 246/1098 (22%)
C: 172/1098 (16%); C1 9%, C2 7%
D: 272/1098 (25%)

The course of childhood-onset epilepsy over the first two decades: A prospective, longitudinal study

***†Anne T. Berg and ‡Karen Rychlik**

Epilepsia, 56(1):40–48, 2015
doi: 10.1111/epi.12862

Dynamic Process

A: 172/516 (33%); **B**: 51/516 (10%)

C: 267/516 (52%); C1 29%(drug-free 17%); C2 23%

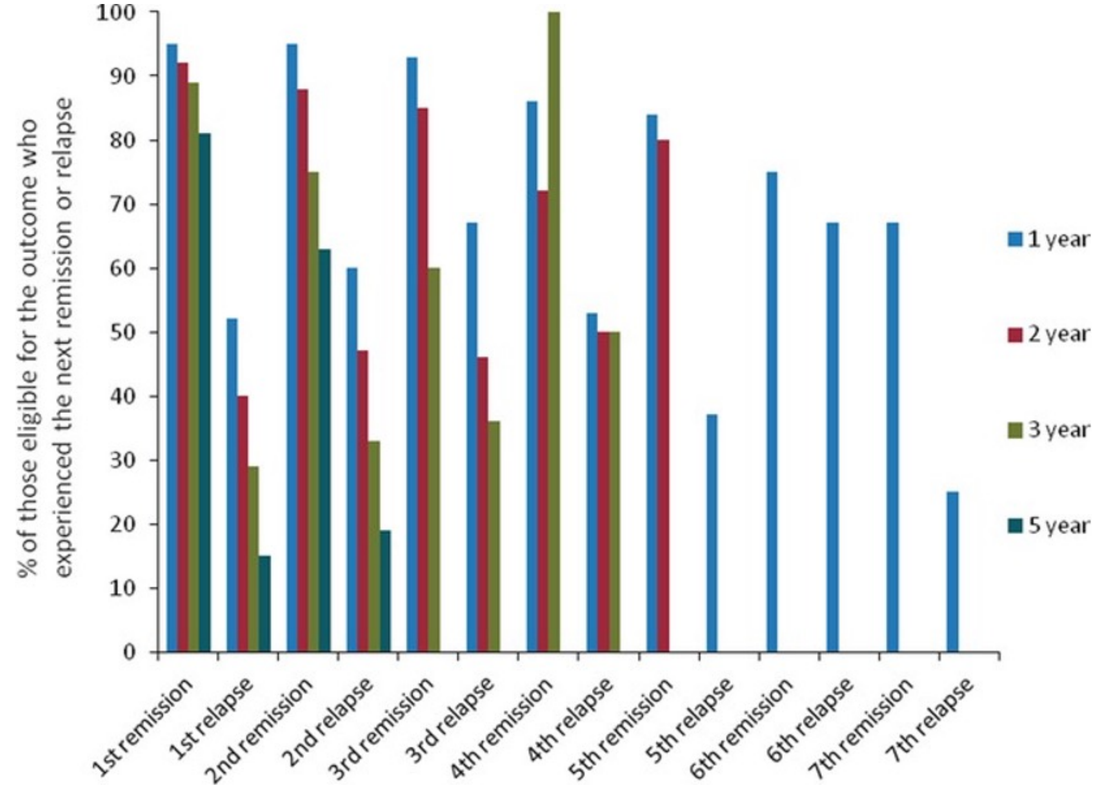
D: 26/516 (5%)

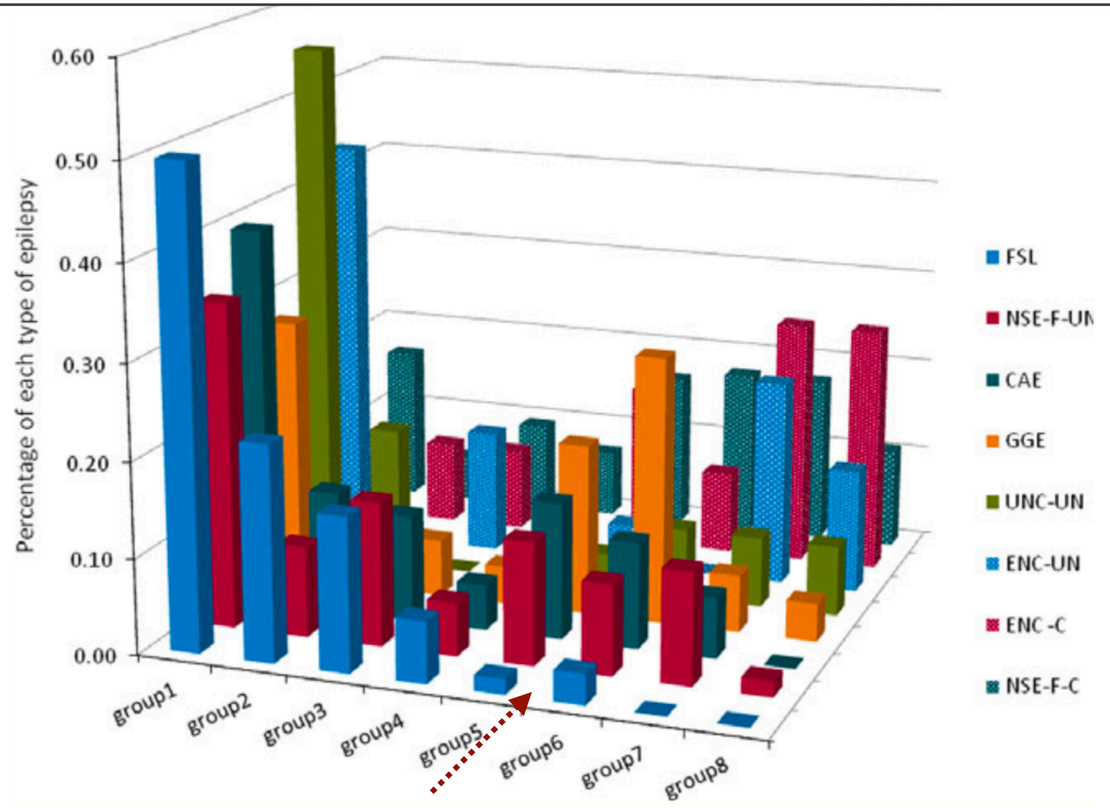
To determine remissions, relapses over two decades
child neurology practices in Connecticut
≤15y (childhood-onset epilepsy), 516 patients
follow-up 17y (13.5-18.7)

CR: seizure- and drug-free period of ≥5y

pharmacoresistance at any time 22.9%

complicated presentation: imaging abnormality, intellectual disability, neurologic deficit





Prognosis of Intractable Epilepsy

Likelihood of Seizure Remission in an Adult Population with Refractory Epilepsy

Brian C. Callaghan, MD,[1] Kishlay Anand, MD,[1] Dale Hesdorffer, PhD,[2] W. Allen Hauser, MD,[2] and Jacqueline A. French, MD[2]

To determine likelihood of remission in refractory epilepsy
University of Pennsylvania Epilepsy Center
Chart review in 2000, and monitored until 2003
246 patients who have DRE
DRE: failure of ≥2 ASM + seizure frequency ≥1/mo
40y (12-83), 59% female
epilepsy duration: mean 25y
Outcome: 6-mo remission
f/u: median 3.1y

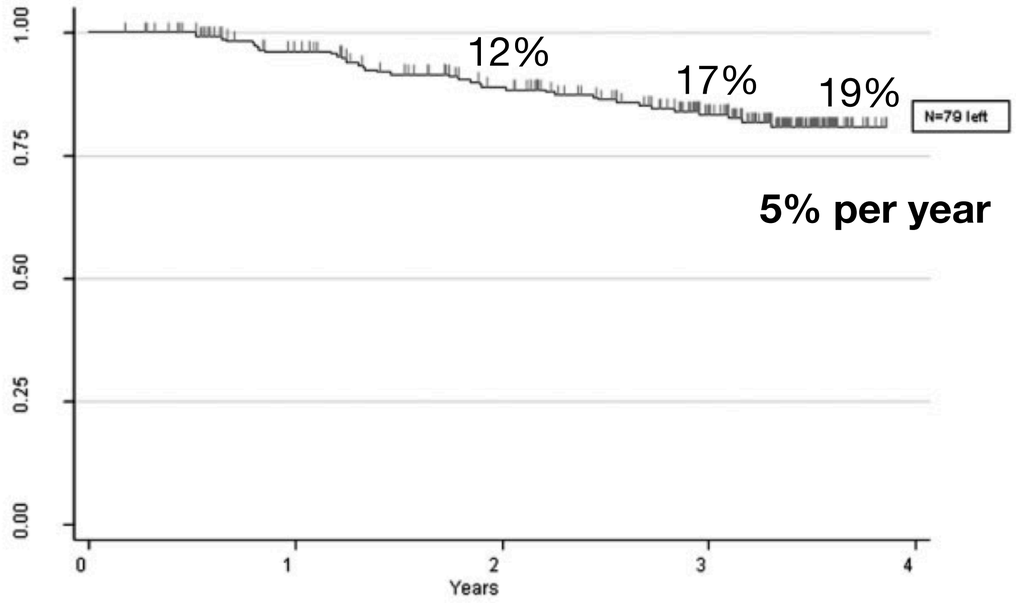


Fig 1. Cumulative probability of remission in the 246 drug refractory epilepsy patients. Cumulative probability of remission for the 37 in remission is 19.3% (95% confidence interval, 14.1–25.9%).

Still hope of seizure control even in patient not responded to multiple ASMs

Callaghan BC et al. *Ann Neurol* 2007

Prognosis after Treatment Withdrawal

Probability of seizure-free

- Children: 66-96% at 1y, 61-91% at 2y
- Adults: 39-74% at 1y, 35-57% at 2y

Risk factors:

- adolescent-onset
- focal seizures
- neurologic deficit/MR
- EEG at withdrawal (children)
- specific syndrome

Withdraw ASMs are at higher risk of relapse
Relapse rate was highest in first 12 mo (esp. in first 6 mo)
Recurrence can occur in those continuing therapy

330 patients, seizure free for ≥2y, on monotherapy

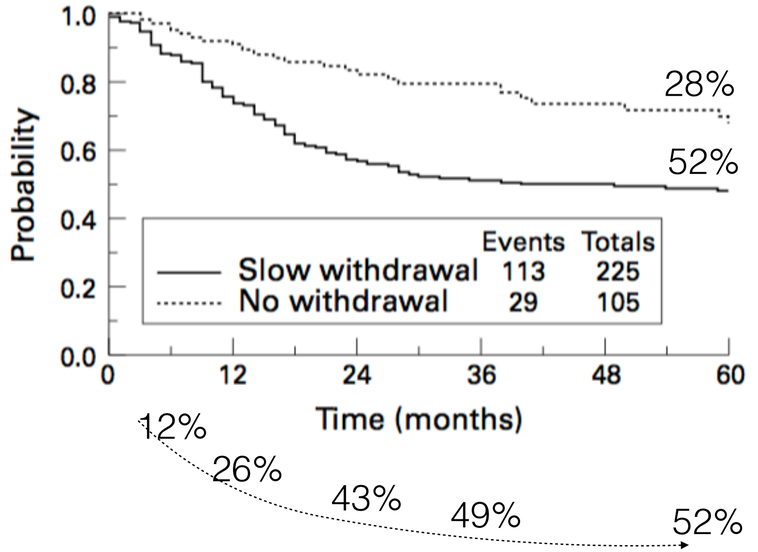


Table 2 Factors influencing the risk of seizure relapse in the multivariate model*

Factor	Hazard ratio	95% CI
Drug withdrawal:		
Yes	2.9	1.8–4.6
No	1	
Duration of active disease:		
2	1	0.3–1.0
3–5	1.6	0.6–3.7
6–10	2.3	1.0–5.3
>10	1	
No of years of remission at study entry:		
2	2.6	1.5–4.8
3–5	1.6	1.0–2.6
>5	1	
Abnormal psychiatric examination:		
Yes	2.1	1.3–3.6
No	1	
Epilepsy syndrome:		
Partial	1.1	0.8–1.6
Generalised	1	

*Other factors included in the model were age, sex, and education.

Specchio LM et al. *JNNP* 2002
Specchio & Beghi. *CNS Drugs* 2004

Untreated epilepsy

Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:320–325

The characteristics of epilepsy in a largely untreated population in rural Ecuador

M Placencia, J W A S Sander, M Roman, A Madera, F Crespo, S Cascante, S D Shorvon

house-to-house survey in rural area of northern Ecuador
1,029 epileptic seizure

Table 2 Treatment state for identified cases

	Active	*Inactive*	*Total*	
On treatment at time of the survey	121	NA	121	12%
Treatment only in the past	125	140	265	
Ever on treatment	246	140	386	37%
Never on treatment	329	314	643	
Total	575	454	1029	

NA = not applicable.

Results

Table 1 shows the age and sex distributions of the surveyed population and of the 1029 cases with a history of seizures. The lifetime prevalence of epileptic seizures was estimated to lie between 12·2/1000 and 19·5/1000 and the prevalence of the active condition between 6·7/1000 and 8·0/1000. The lower figures represent the 881 cases considered as definite and the higher figure is an adjusted figure, calculated by the addition of a further 378 cases estimated from the various quality control steps.[18] The annual incidence rates were similarly estimated to be between 122/100 000 and 190/1000 00 . These figures are fully discussed elsewhere.[18]

Spontaneous remission can be achieved even in those untreated

Mortality in Epilepsy

- Standardized mortality ratio (SMR): 2.2-2.6
- Etiologies of mortality:
  1. Deaths due to epilepsy
  2. Related to the cause of epilepsy
  3. Unrelated to epilepsy
- Risk: symptomatic epilepsy, neurologic deficit/learning difficulties, GTC, myoclonic seizure, severity of epilepsy

Epilepsy carries a greater risk of premature death!!!

Unrelated deaths
Neoplasms outside the central nervous system
Ischaemic heart disease
Pneumonia
Others

Related to underlying disease
Brain tumours
Cerebrovascular disease
Cerebral infection-abscesses and encephalitis
Inherited disorders, e.g. Batten's disease

Epilepsy-related deaths
Suicides 5x, severe epilepsy, TLE
Treatment-related deaths
Idiosyncratic drug reactions
Medication adverse effects
Seizure-related deaths
Status epilepticus up to 12.5%
Trauma, burns, drowning 1.2-6.5%
Asphyxiation, aspiration
Aspiration pneumonia after a seizure
Sudden unexpected death in epilepsy 2-18%

Ficker DM. *Epilepsia* 2000; Gaitatzis A & Sander J W. *Epileptic Disord* 2004

Conclusions

- Overall prognosis of epilepsy is *favourable* for majority
- *Etiology/syndrome of epilepsy is strongest predictor for remission*
- Epileptogenic process is “**dynamic**”, several factors are implicated in outcome
- Still hope of seizure control even in patient not responded to multiple ASMs
- People who need ASMs declare themselves early in withdrawal period
- Seizure remission can be achieved even in those untreated

ขอบคุณครับ

asoontornpun@gmail.com ; facebook: Birdy Soontornpun