Natural History of Epilepsy

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Outlines

- Prognosis of first unprovoked seizure
- Prognosis of treated epilepsy/epilepsy syndromes
- Prognosis of untreated epilepsy
- Prognosis of epilepsy with discontinued medications
- Mortality

Epidemiology of Epilepsy

Ettore Beghi, Neuroepidemiology 2020;54:185-191

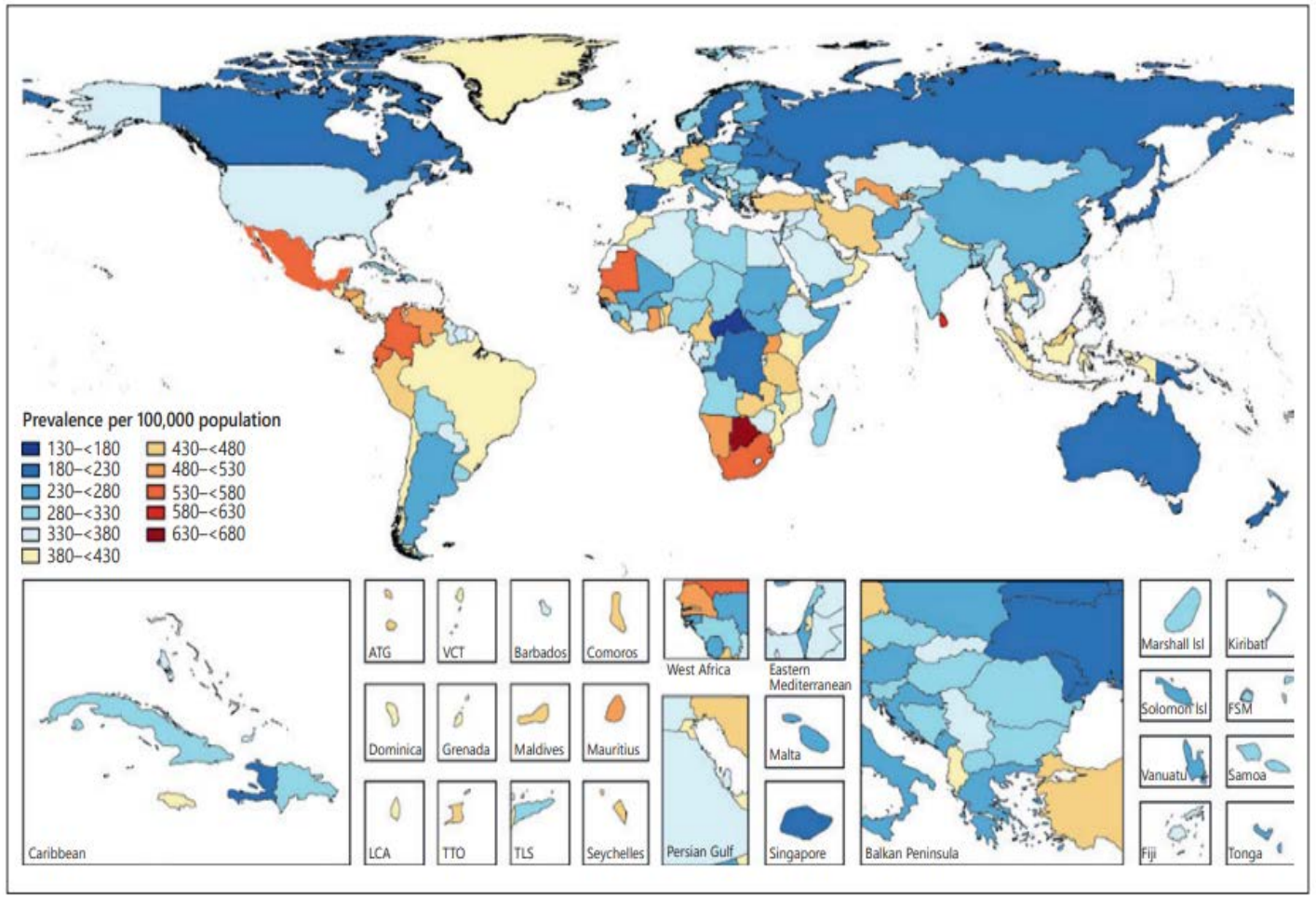
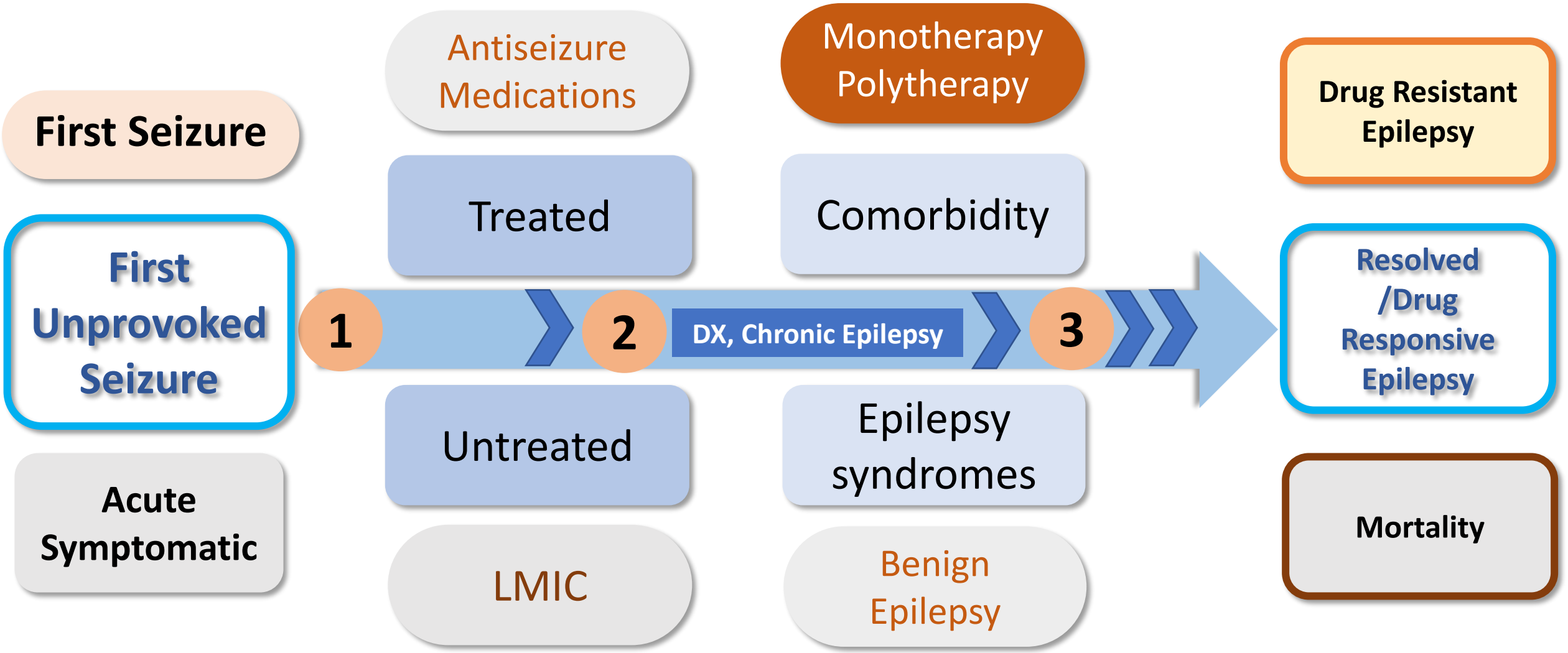


Fig. 1. Age-standardized prevalence (×100,000) of idiopathic epilepsy by country, 2016. With permission from Global Burden of Disease 2016 Epilepsy Collaborators [18].

- the worldwide disease burden, about 46 million people.
- Nearly 80% of people with epilepsy reside in LMIC
- Cumulative annual incidence rate was 190 per 100,000 and the prevalence rate of active epilepsy was 7 per 1,000

Epilepsy Journey



Diagnosis | Treatment gap | comorbidity | mortality

First Unprovoked Seizure

ILAE OFFICIAL REPORT

Epilepsia
The Journal of the International League Against Epilepsy

A practical clinical definition of epilepsy

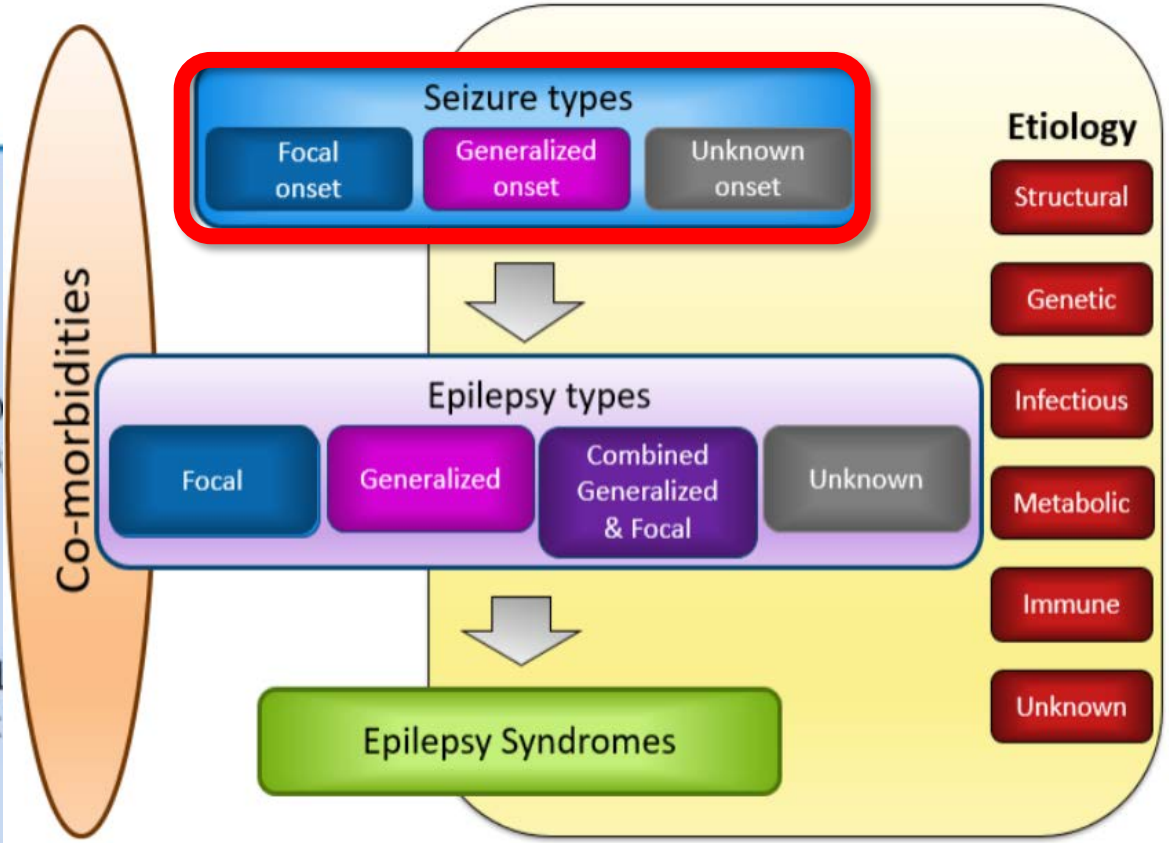
*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014

Epilepsy is a disease of the brain defined by any of the following conditions

1. A least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurrin over the next 10 years
3. Diagnosis of an epilepsy syndrome

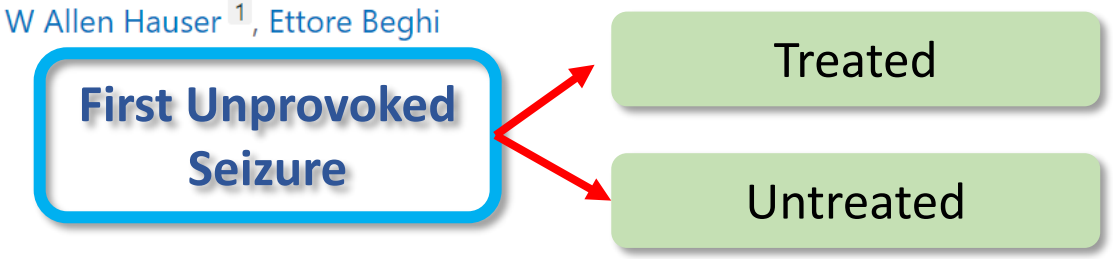
Epilepsy is considered to be resolved for individuals who had an age-dependent epil are now past the applicable age or those who have remained seizure-free for the last seizure medicines for the last 5 years.



First Unprovoked Seizure

First seizure definitions and worldwide incidence and mortality

W Allen Hauser [1], Ettore Beghi



Unprovoked seizures are seizures occurring in the absence of precipitating factors and may be caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures). Unprovoked seizures may be single or recurrent (epilepsy).

Seizure: European Journal of Epilepsy 90 (2021) 28–33

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Update on first unprovoked seizure in children and adults: A narrative review

María José Jiménez-Villegas [a,*], Lucas Lozano-García [b], Jaime Carrizosa-Moog [c]

[a] Clínica Somer, Rionegro, Antioquia, Colombia
[b] Department of Epilepsy Surgery and Neurophysiology, Instituto Neurológico de Colombia, Medellín, Colombia
[c] Child and Adolescent Neurology Service, Department of Pediatrics, Faculty of Medicine, University of Antioquia, Pediaciencias Research Group, Medellín, Colombia

Hauser et al.

- seizure recurrence of
  - at 12 months 16%
  - at 24 months 21%
  - at 36 months 27%

16-34%

- Extension of follow-up period
  - at 1 years 14%
  - at 3 years 29%
  - at 5 years 34%

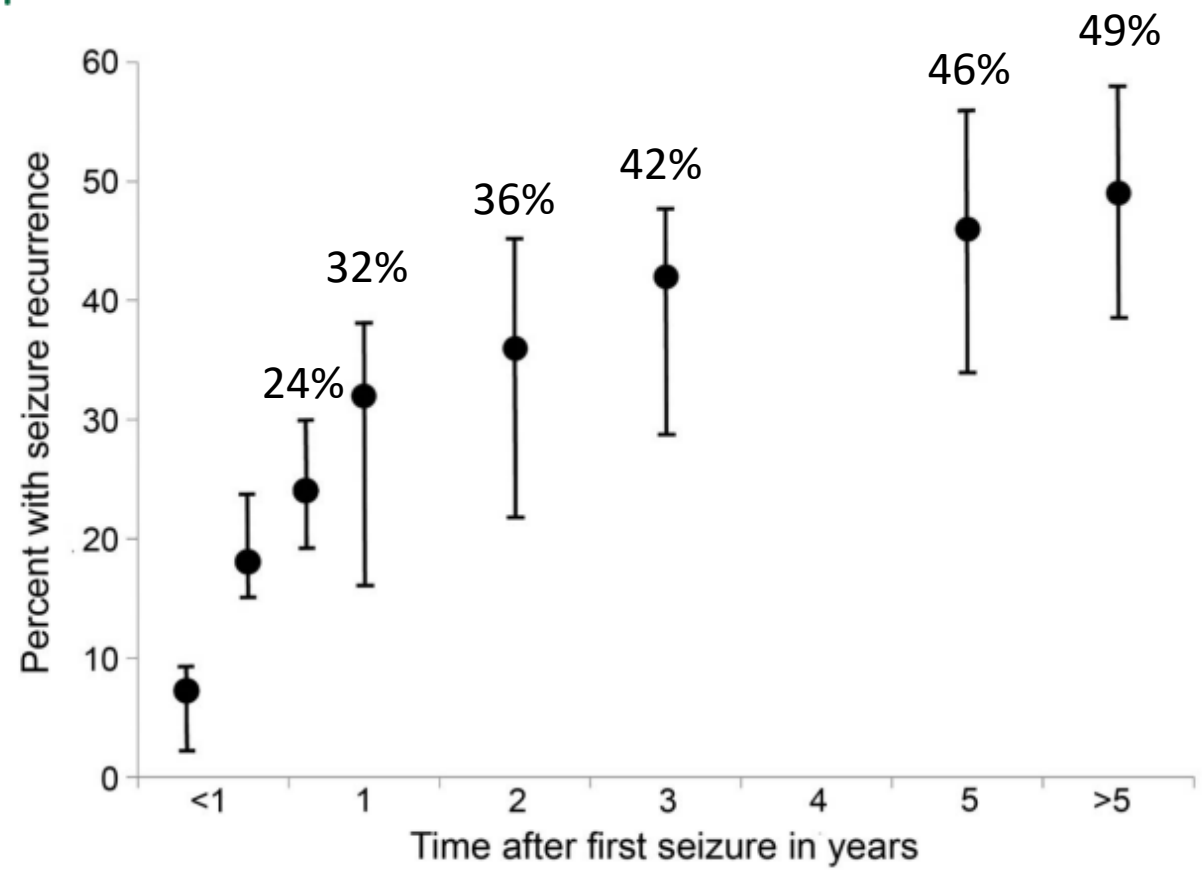
SPECIAL ARTICLE

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



The risk of seizure recurrence increases in :

1. Prior brain lesion or insult causing the seizure
2. EEG with epileptiform abnormalities (Adult 77%, children 66%) 16 hours
3. Significant brain-imaging abnormality
4. a nocturnal seizure

Yield of epileptiform electroencephalogram abnormalities in incident unprovoked seizures: A population-based study

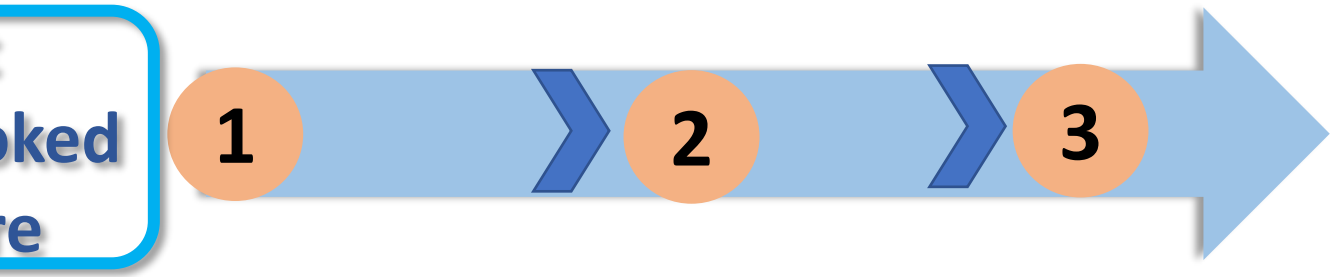
*Elisa Baldin, *†‡W. Allen Hauser, §Jeffrey R. Buchhalter, *‡Dale C. Hesdorffer, and *†‡¶Ruth Ottman

Epilepsia, 55(9):1389–1398, 2014
doi: 10.1111/epi.12720

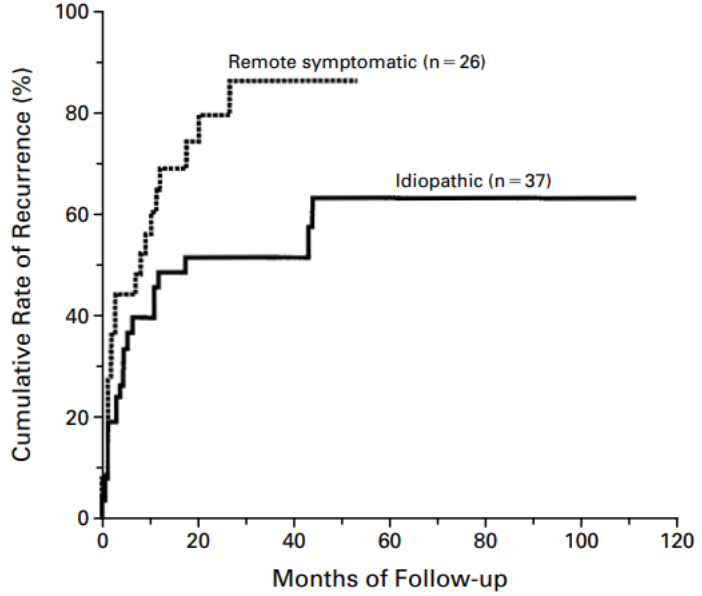
RISK OF RECURRENT SEIZURES AFTER TWO UNPROVOKED SEIZURES

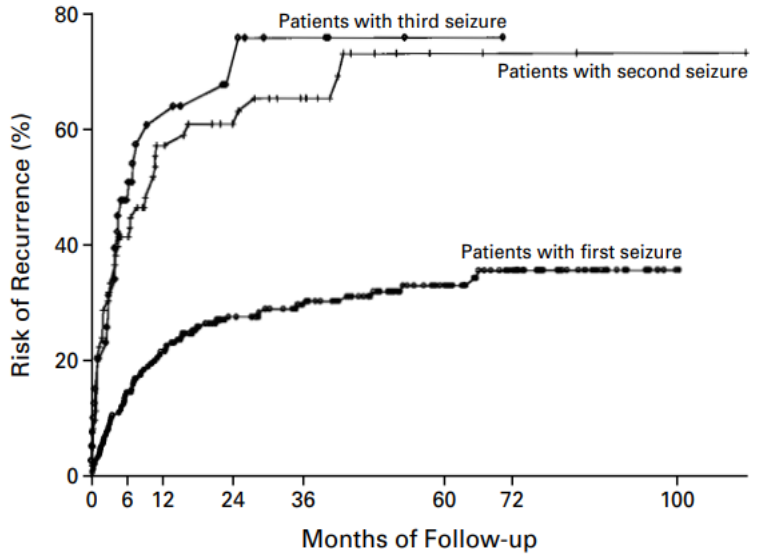
W. ALLEN HAUSER, M.D., STEPHEN S. RICH, PH.D., JU R.-J. LEE, PH.D., JOHN F. ANNEGERS, PH.D., AND V. ELVING ANDERSON, PH.D.

- After a first unprovoked seizure, about 50% of recurrences occur within 6months of the initial seizure and 76-96% within two years.
- After a second unprovoked seizure, the risk of a third seizure has been estimated at 73%
- After a third seizure, the risk of a fourth seizure has been estimated at 76%



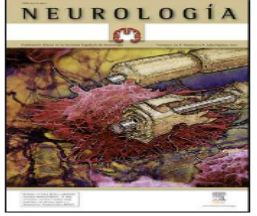
RISK OF RECURRENT SEIZURES AFTER TWO UNPROVOKED SEIZURES





NEUROLOGIA

www.elsevier.es/neurologia



CONSENSUS STATEMENT

Prognosis in epilepsy: initiating long-term drug therapy☆

Table 1 Scores on the prognostic index for recurrence from the MESS trial

	Prognostic index
Initial score	
One ES prior to first consultation	0
2 or 3 ES prior to first consultation	1
4 or more ES prior to first consultation	2
Add the following, if present	
Neurological disorder or deficit, learning disability, or developmental delay	1
Abnormal EEG (epileptiform discharges or slow waves)	1
Groupings by risk of ES recurrence	**Final score**
Low risk	0
Moderate risk	1
High risk	2-4

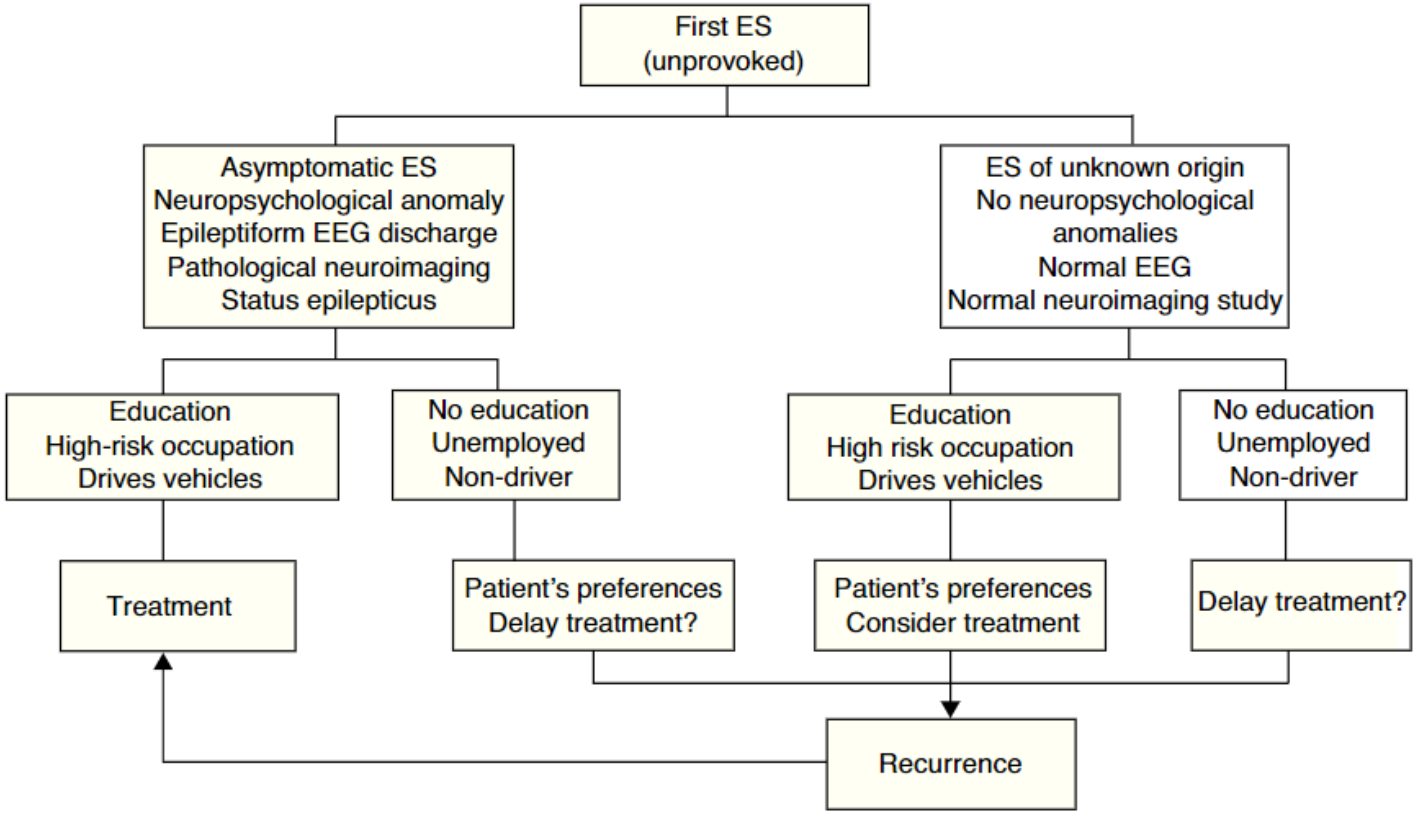


Figure 1 Therapeutic algorithm for first ES

Cochrane Database of Systematic Reviews | Review - Intervention

New search

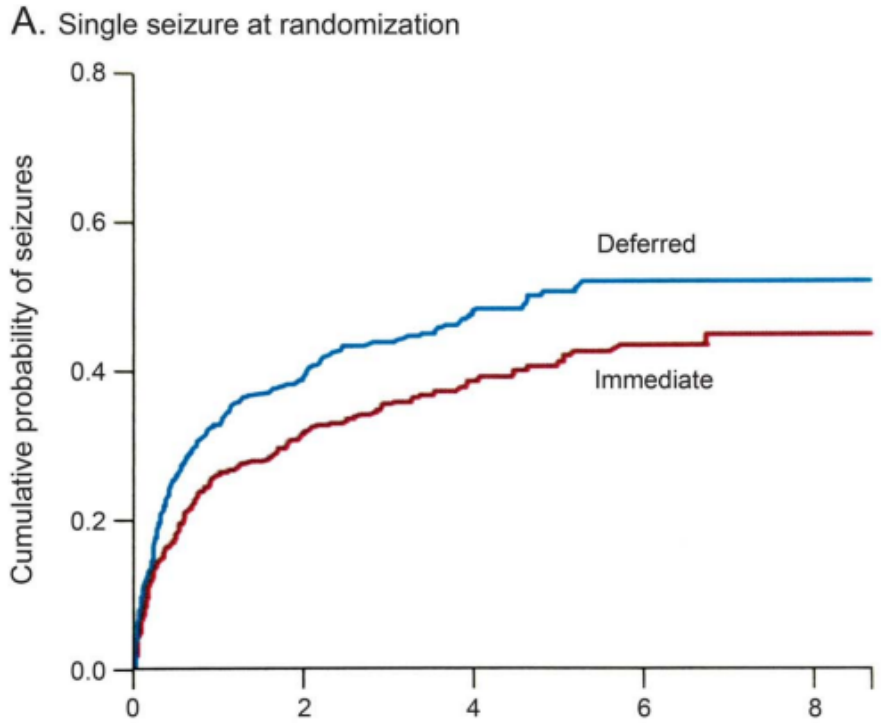
Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure

Maurizio A Leone, Giorgia Giussani, Sarah J Nevitt, Anthony G Marson, Ettore Beghi Authors' declarations of interest

Version published: 04 May 2021 Version history

https://doi.org/10.1002/14651858.CD007144.pub3

Figure 2 **Cumulative proportion of patients experiencing a seizure recurrence after randomization, comparing immediate vs deferred treatment**



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

A. Krumholz, MD[1,2]; S. Wiebe, MD[3]; G. S. Gronseth, MD[4]; D. S. Gloss, MD[5]; A. M. Sanchez, MD[1]; A. A. Kabir, MD[1]; A. T. Liferidge, MD[6]; J. P. Martello, MD[1]; A. M. Kanner, MD[7]; S. Shinnar, MD, PhD[8]; J. L. Hopp, MD[1]; J. A. French, MD[9]

- Risk for a recurrence relatively early, within the first 2 years (21%–45%), and especially in the first year.
- the risk appears to be lower for patients treated with AEDs

*__treatment reduces the risk of a subsequent seizure__, but does not affect the proportion of patients in remission in the long-term. ASM is associated with adverse events, with no evidence of reduction of mortality.

Treated Epilepsy

JAMA Neurology | Original Investigation

Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

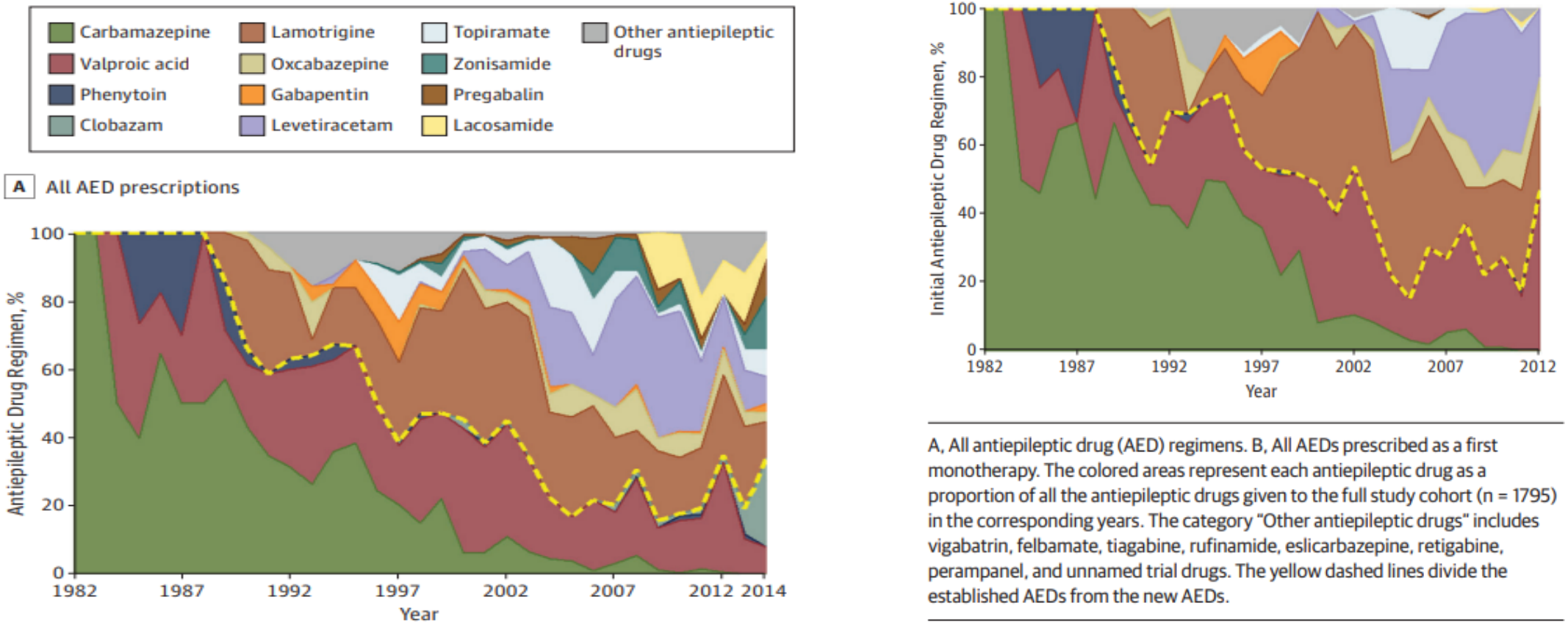
A 30-Year Longitudinal Cohort Study

Zhibin Chen, PhD; Martin J. Brodie, MD; Danny Liew, MD, PhD; Patrick Kwan, MD, PhD

1795 newly diagnosed patients

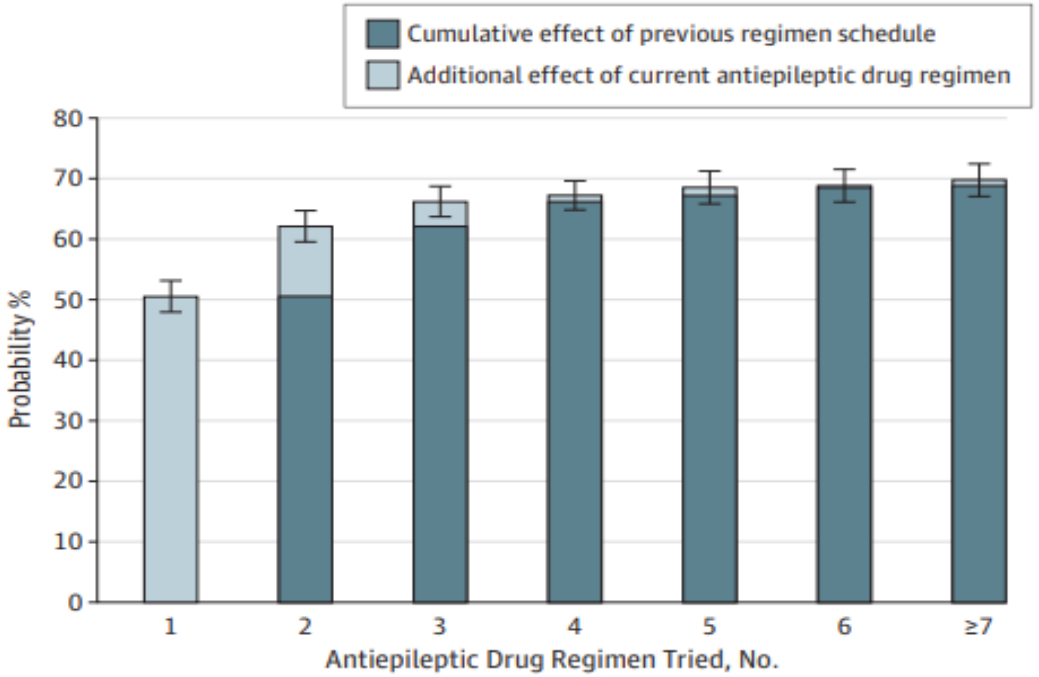
- 80.2% Monotherapy
- 19.8% Polytherapy (>=2 AEDs)

Figure 1. Antiepileptic Drug Regimens Over the Study Period



A, All antiepileptic drug (AED) regimens. B, All AEDs prescribed as a first monotherapy. The colored areas represent each antiepileptic drug as a proportion of all the antiepileptic drugs given to the full study cohort (n = 1795) in the corresponding years. The category "Other antiepileptic drugs" includes vigabatrin, felbamate, tiagabine, rufinamide, eslicarbazepine, retigabine, perampanel, and unnamed trial drugs. The yellow dashed lines divide the established AEDs from the new AEDs.

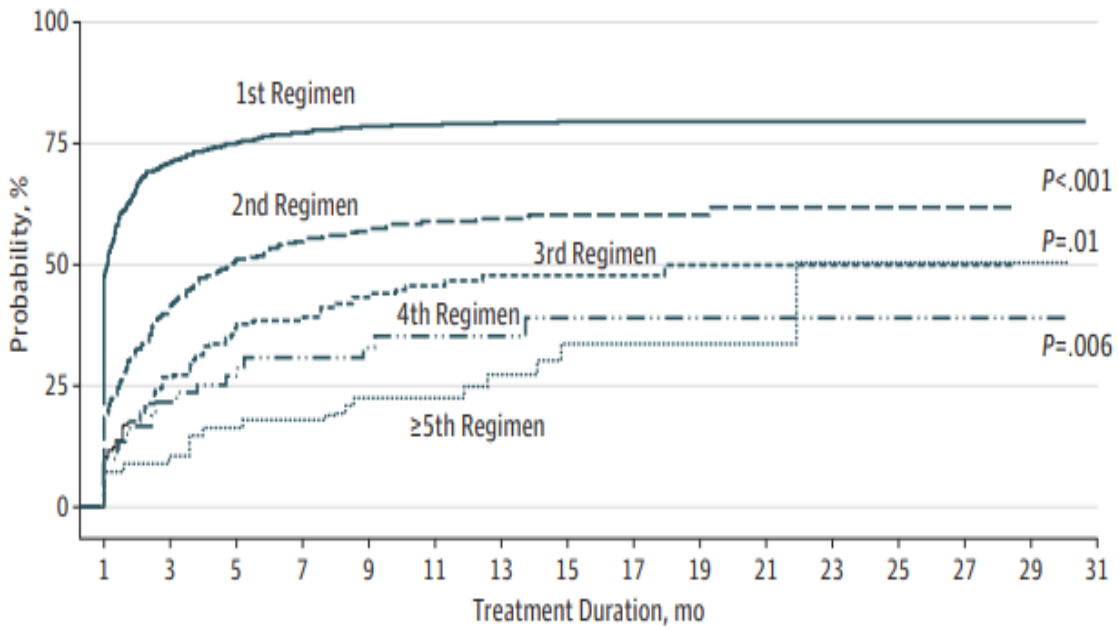
Figure 3. Increases in Probability of 1-Year Seizure Freedom for Each Additional Antiepileptic Drug Regimen Tried



The percentage of patients achieving seizure freedom via the first, second, third, fourth, fifth, sixth, and seventh AED regimens were 50.5%, 11.6%, 0.99%, 1.34%, 0.28%, and 0.94%, respectively. Please see Table 2 for numbers of patients achieving seizure freedom and total patients in each subgroup.

- 63.7% - seizure free (12 months or longer)
- 55.3% monotherapy, the rest, taking 2 or more drugs)

Figure 2. Cumulative Probability of 1-Year Seizure Freedom by Treatment Duration and Number of Antiepileptic Drugs Regimens Tried



No. at risk

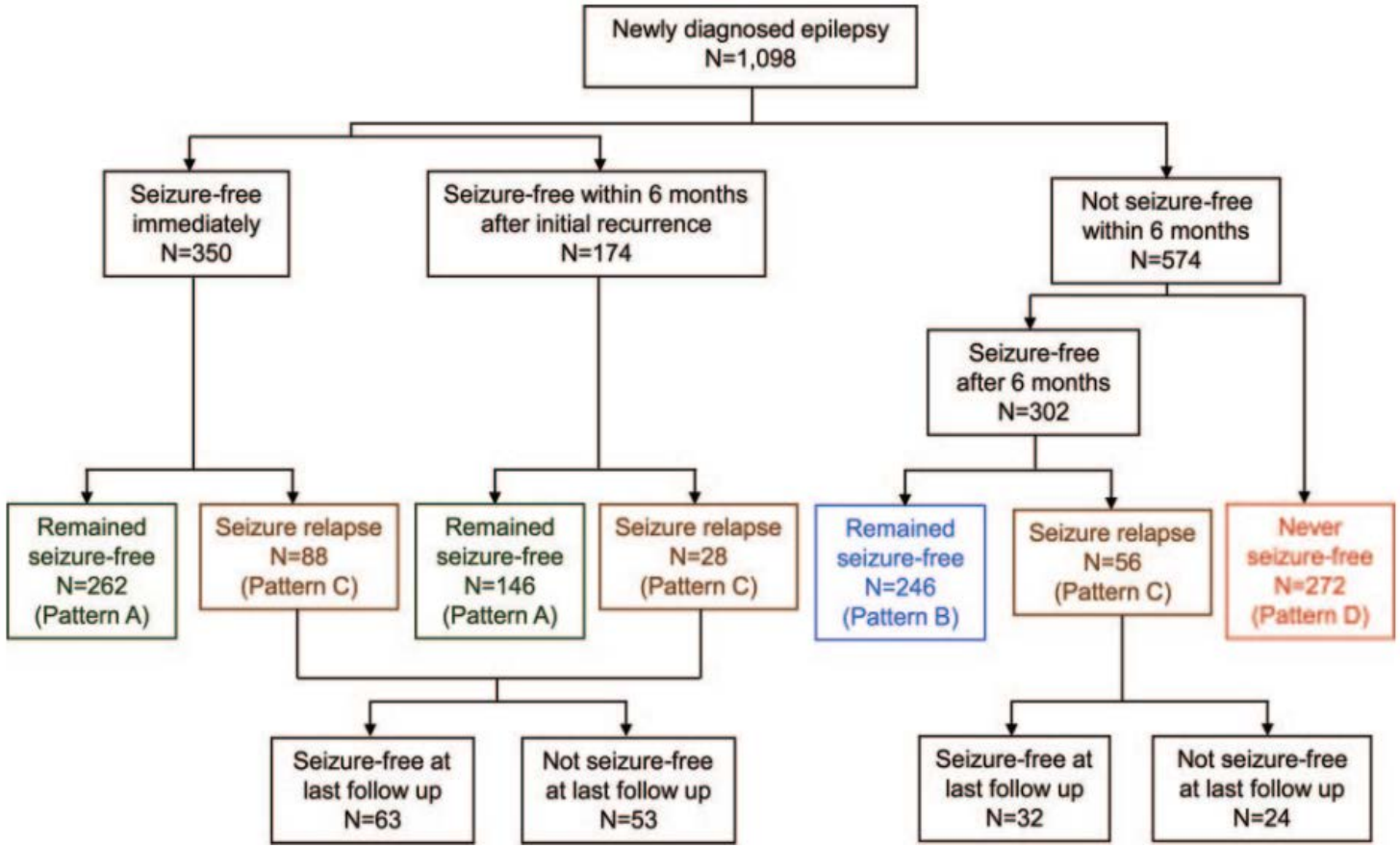
1st Regimen	1053	226	185	157	138	110	87	81	59	40	26	19	8	7	3	0
2nd Regimen	412	183	142	118	95	80	60	45	32	25	15	11	5	2	0	0
3rd Regimen	190	138	103	94	82	71	51	43	31	18	9	5	4	3	0	0
4th Regimen	69	55	47	38	26	22	19	18	12	12	5	4	2	2	1	0
≥5th Regimen	71	68	64	58	51	42	30	25	19	13	6	2	1	1	1	0

ARTICLES

Patterns of treatment response in newly diagnosed epilepsy

M.J Brodie et al.

ure 1 Patient flow throughout the study in terms of seizure outcome



4 outcome patterns in patients:

A. **Early remission**: remained seizure-free shortly after commencing treatment 62%
B. **Early phamaco-resistance**: less predictable although enter remission after a delay varying between 6 months and 18 years, 38%
C. **Remitting-relapsing course"** fluctuating between periods of seizure freedom and recurrence course 16%
D. **Persistent seizures** despite repeated trials of different medications used singly or in combination 25%

Seminar in Epileptology

Epileptic Disord 2015; 17 (3): 243-53

The natural history and prognosis of epilepsy

Ettore Beghi [1], Giorgia Giussani [1], Josemir W. San

Table 2. Long-term 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

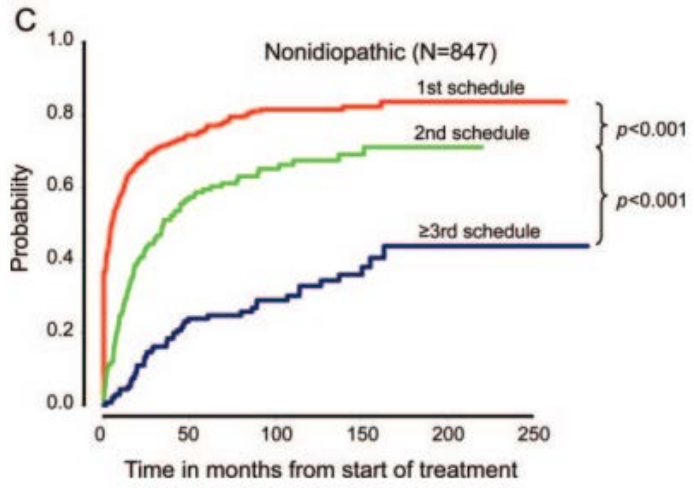
BECTS: benign childhood epilepsy with centrotemporal spikes; CAE: childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; LGS: Lennox-Gastaut syndrome; ESES: encephalopathy with status epilepticus during sleep; EGMA: epilepsy with grand mal on awakening.

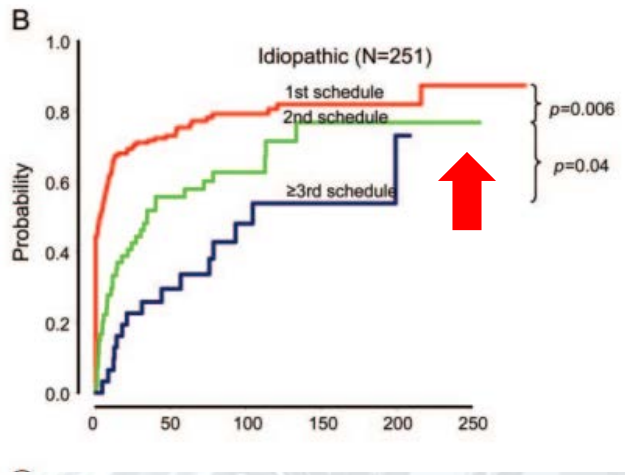
Prognosis of treated epilepsy

- About 60% of people with childhood-onset epilepsy will have a 5-year remission period, followed by withdrawal of antiepileptic drug (AED) treatment
  (Sillanpää and Schmidt, 2015).

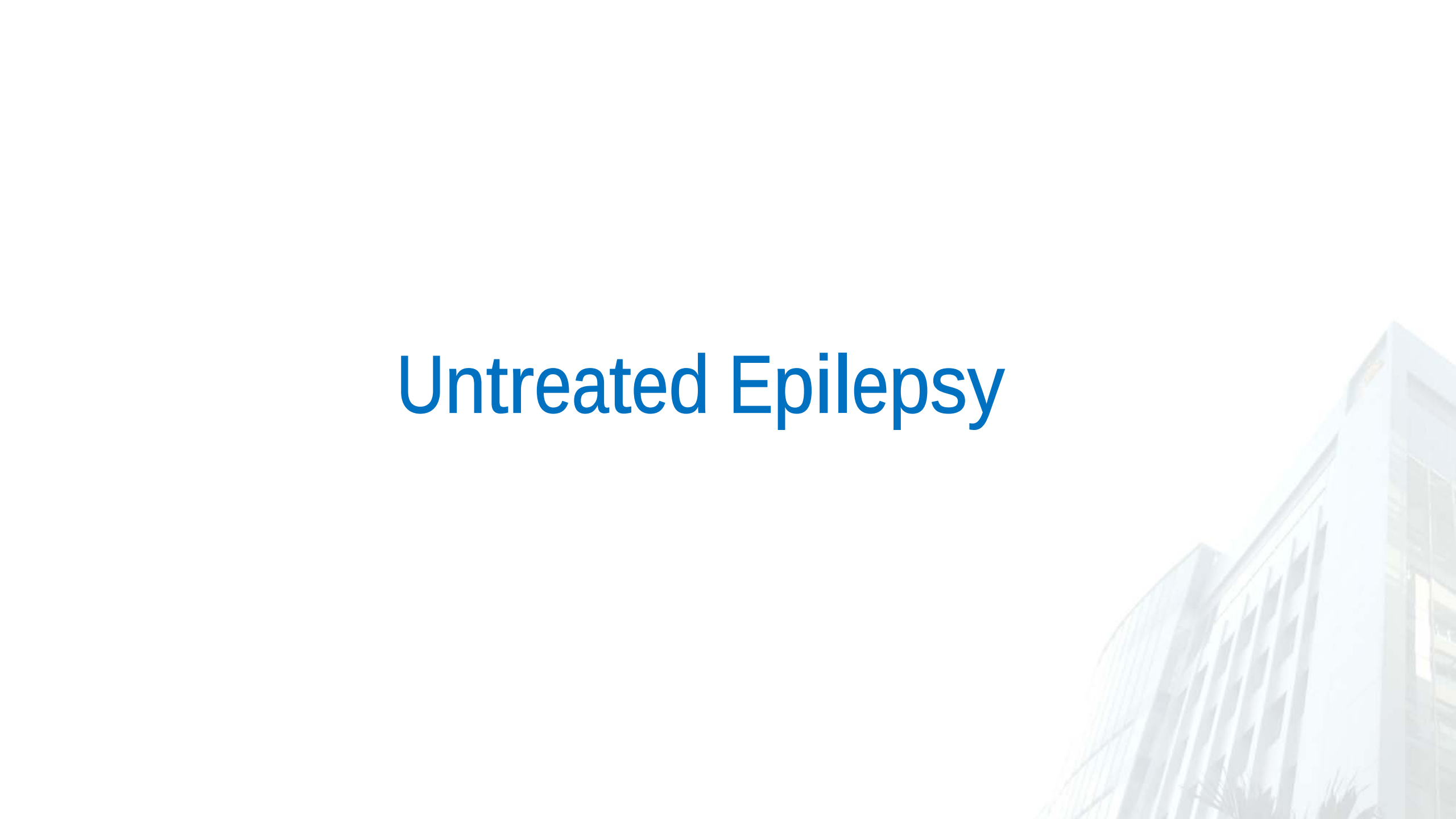
- Population-based studies on the long-term prognosis of treated epilepsy report a 58-65% cumulative five-year remission rate at 10 years
  (Annegers et al., 1979; Cockerell et al., 1997).

- About 70% by 20 years following





Untreated Epilepsy



Prognosis of untreated epilepsy

Zielinski, 1974; Keranen and Riekkinen, 1993; van Donselaar et al., 1997

- The prognosis of untreated epilepsy has been assessed only in resource-poor countries (*treatment gap ranging from 70 to 94%).*

Placencia et al., 1992

- a population-based **study in Ecuador**, the cumulative annual incidence was 190 per 100,000 and the prevalence of active epilepsy was 7 per 1,000, =>implies a remission rate of at least 50%.
- Similar prevalence rates of active epilepsy were found in **Nigeria** (**Osuntokun et al.**, 1987) and in **Ethiopia** (**Tekle-Haimanot et al.**, 1990). In a study in **Malawi** (**Watts**, 1992), the duration of active epilepsy was similar to that of industrialized countries.

>>> spontaneous remission of untreated epilepsy <<<

Ettore Beghi, Neuroepidemiology 2020;54:185-191

Discontinued Medications

SPECIAL ARTICLE

Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary

Report of the AAN Guideline Subcommittee

David Gloss, MD, MPH & TM, Kimberly Pargeon, MD, MA, Alison Pack, MD, Jay Varma, MD, Jacqueline A. French, MD, Benjamin Tolchin, MD, MS, Dennis J. Dlugos, MD, MSCE, Mohamad A. Mikati, MD, Cynthia Harden, MD, on behalf of the AAN Guideline Subcommittee

Neurology® 2021;97:1072-1081. doi:10.1212/WNL.0000000000012944

Correspondence
American Academy of Neurology
guidelines@aan.com

Remission & Medication withdrawal

The discontinuation of ASMs may be considered if:

- Seizure-free 2–5 years while taking ASMs (mean 3.5 years)
- Single type of partial seizure (simple partial or complex partial or secondary generalized tonic-clonic seizure [GTCS]) or single type of primary generalized seizures
- Normal neurologic examination results/normal IQ
- EEG normalized while taking ASMs

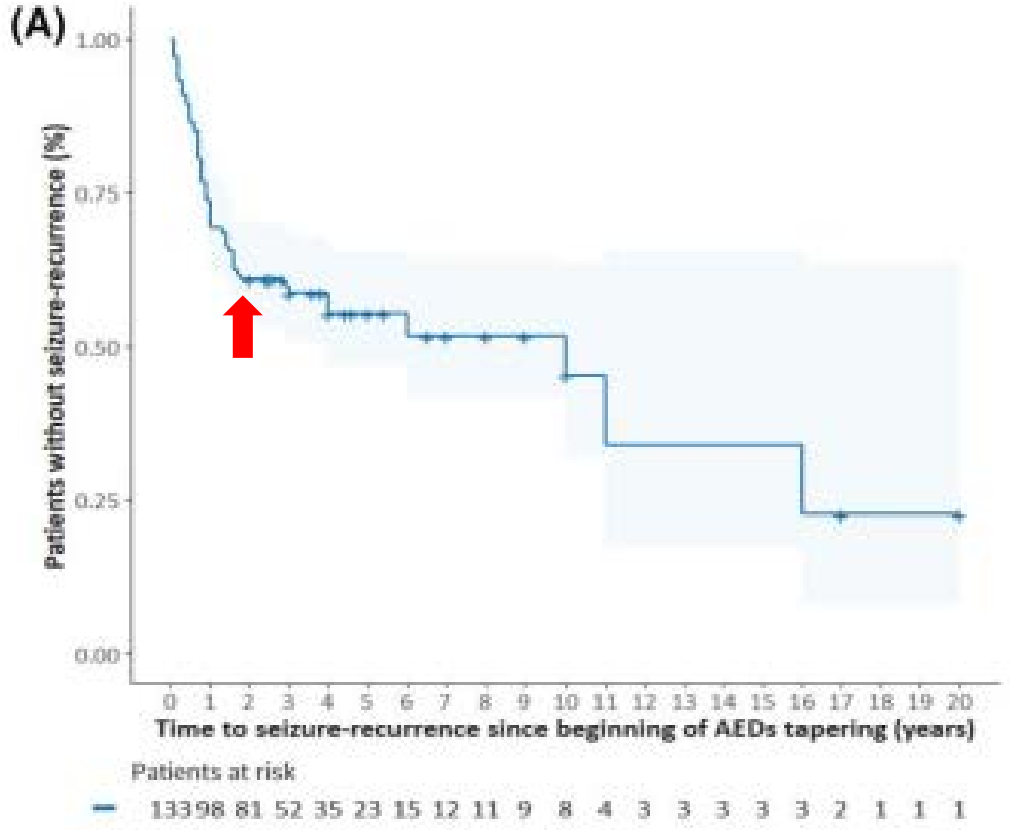
FULL-LENGTH ORIGINAL RESEARCH

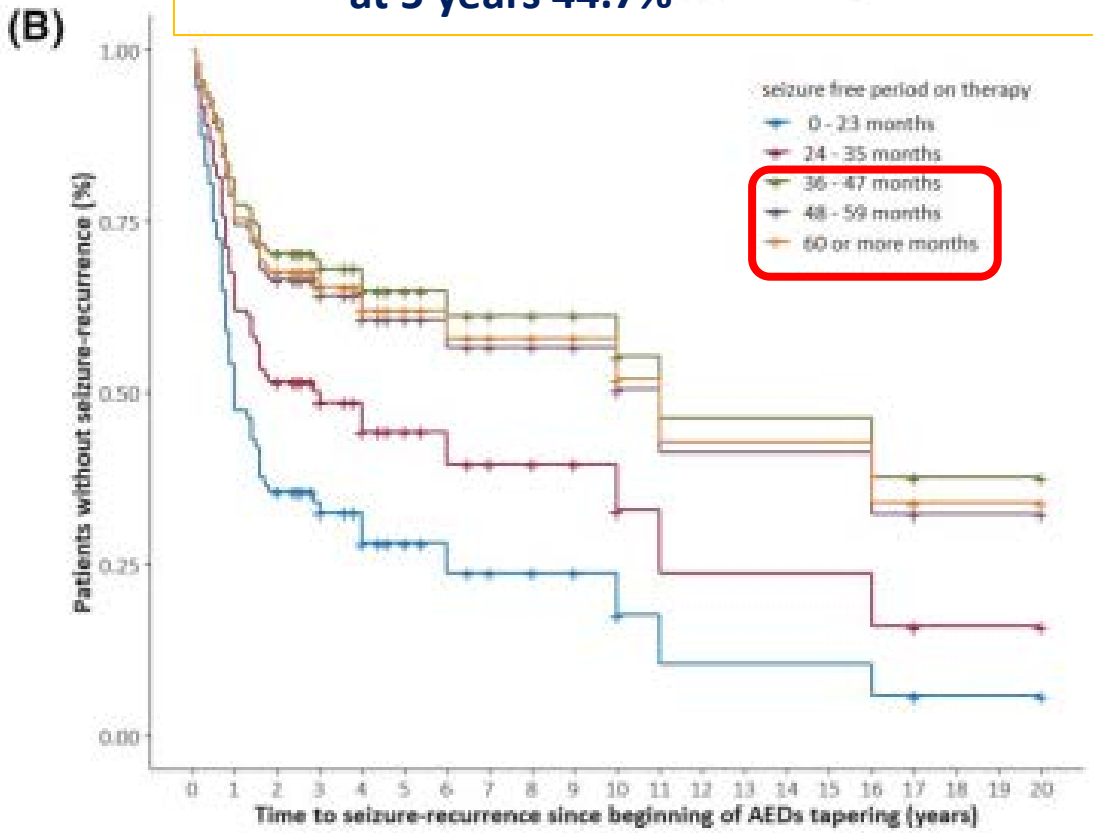
Epilepsia

Prediction of seizure recurrence risk following discontinuation of antiepileptic drugs

Margherita Contento[1] | Bruno Bertaccini[2] | Martina Biggi[1] | Matteo Magliani[1] | Ylenia Failli[1] | Eleonora Rosati[3] | Luca Massacesi[1,3] | Marco Paganini[3]

- N=133
- 45% relapse after AEDs discontinue
- cumulative risk of seizure recurrence
  - at 6 months 13.5%,
  - at 1 year 30.8%,
  - at 2 years 39.1%,
  - at 3 years 41.4%,
  - at 5 years 44.7%





FULL-LENGTH ORIGINAL RESEARCH

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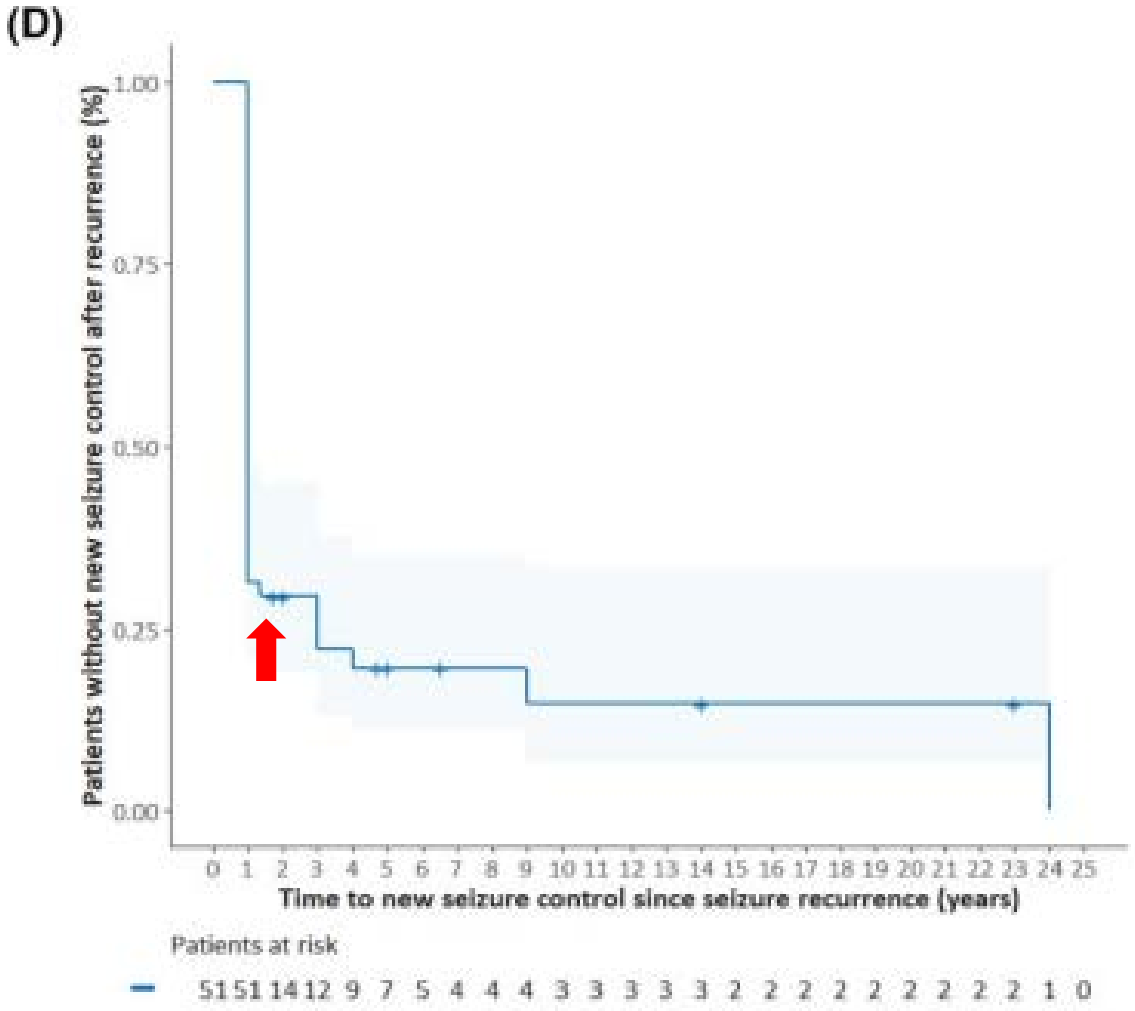
Probability of gaining a new seizure control after recurrence

- 51/133 patients, (relapse)
  - regained seizure control 82.4%,
  - 10% did not seizure control
  - 7.8% developed drug-resistant epilepsy.
- Patients gained new seizure control with **monotherapy 97.6%** (with the same AEDs at a higher/same/ lower dose



Mortality of Epilepsy

- PWE: low mortality risk, but increased risk of death than the general population
- Attributable to epilepsy or seizures, important immediate causes include SUDEP, SE, unintentional injuries, and suicide.
- Among deaths in HIC, standardized
- Indirect causes of death in LMIC include not only drowning and burns but also lack of access to health facilities and preventable causes.
- The incidence of SUDEP among people with epilepsy is 1.2 per 1,000

The major risk factors include:

- generalized tonic-clonic seizures,
- nocturnal seizures
- persistence of seizures.

Conclusion

- Epilepsy is a treatable condition. The overall prognosis of epilepsy is favorable in the majority of patients when measured by seizure freedom. Half of them continue to be seizure-free after treatment discontinuation
- Early response to treatment is an important positive predictor of long-term prognosis
- Pattern of treatment response of epilepsy patients –4 epilepsy outcomes
- Spontaneous remission of untreated epilepsy

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