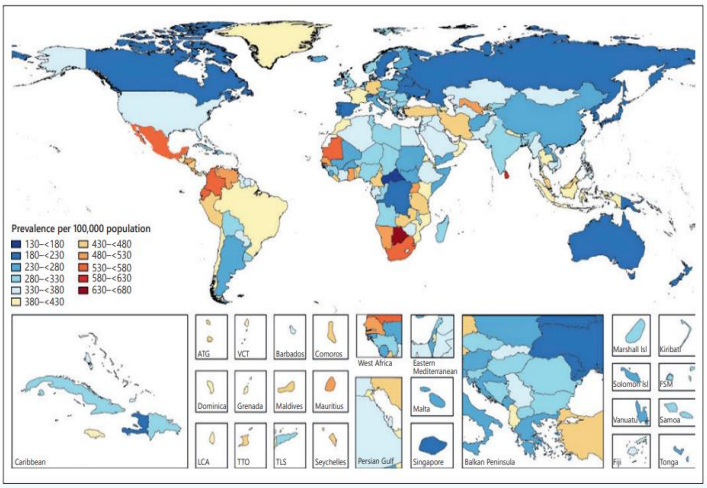
Natural History of Epilepsy

Panisra Sudachan, M.D.
Department of Pediatric Neurology
National Institute of Thailand

Outline

- Prognosis of first unprovoked seizure
- Prognosis of newly diagnosed treated/untreated epilepsy
- Prognosis of epilepsy syndromes
- Prognosis of drug responsive /resistance epilepsy
- Mortality

Epidemiology

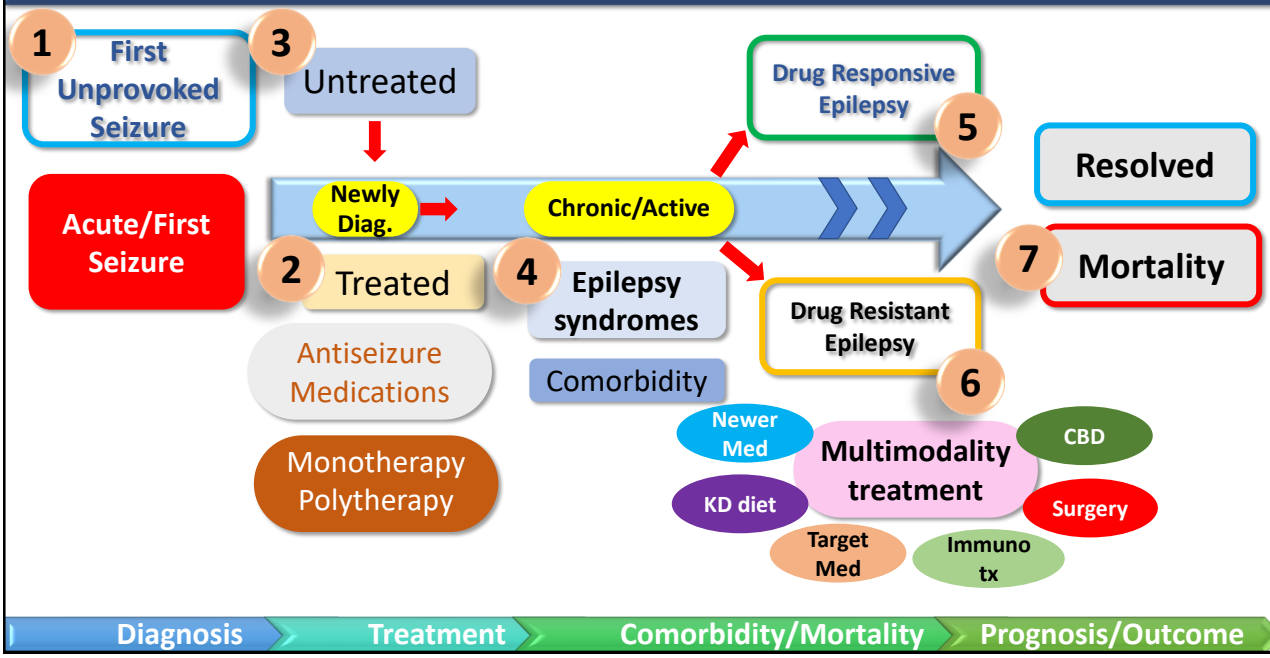


- the worldwide disease burden, about 46 million people.
- Nearly 80% of people with epilepsy reside in LMIC
- Cumulative annual incidence rate was 190 per 100,000 and the prevalence rate of active epilepsy was 7 per 1,000

Over all prognosis

Ettore Beghi, Neuroepidemiology 2020;54:185-191

Epilepsy Journey



1 First Unprovoked Seizure

First seizure definitions and worldwide incidence and mortality

W Allen Hauser [1], Ettore Beghi

Seizure recurrence

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

16-34%

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.

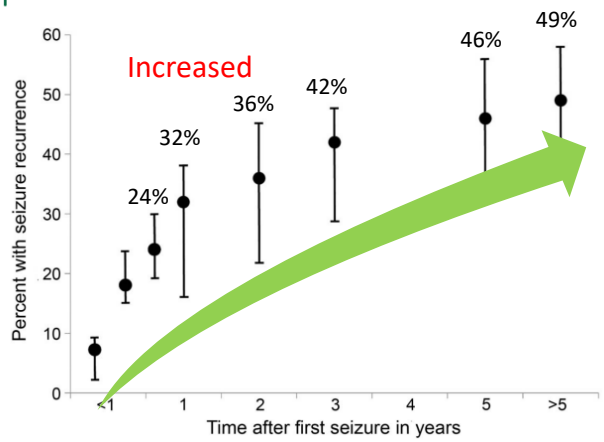
- seizure recurrence of
  - at 12 months 16%
  - at 24 months 21%
  - at 36 months 27%
- Extension of follow-up period
  - at 1 years 14%
  - at 3 years 29%
  - at 5 years 34%

SPECIAL ARTICLE

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



Risk of seizure recurrence

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. 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

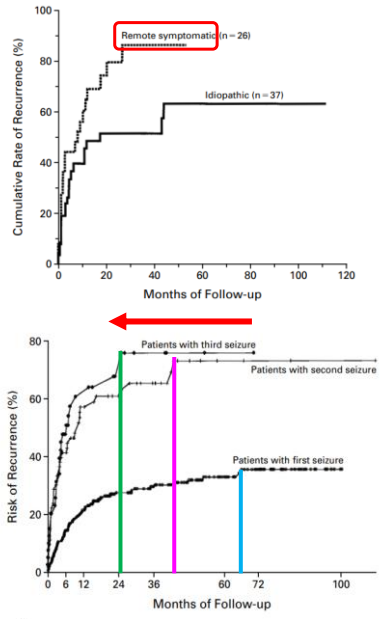
RISK OF RECURRENT SEIZURES AFTER TWO UNPROVOKED SEIZURES

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.

1. After a first unprovoked seizure, about 50% of recurrences occur within 6months of the initial seizure and 76-96% within 2 years.
2. After a second unprovoked seizure, the risk of a third seizure has been estimated at 73%
3. After a third seizure, the risk of a fourth seizure has been estimated at 76%

First Unprovoked Seizure

RISK OF RECURRENT SEIZURES AFTER TWO UNPROVOKED SEIZURES



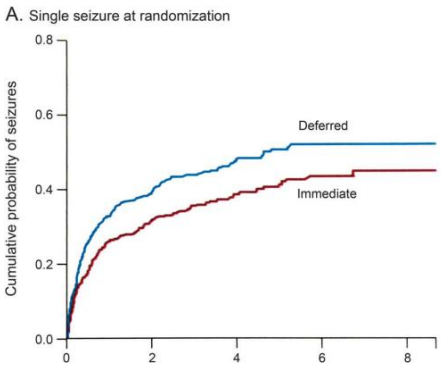
Cochrane Database of Systematic Reviews Review - Intervention New search

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. **50-96%=>21-45%**
- 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.

Research **2** **Newly Diagnosed**

Treatment

JAMA Neurology | Original Investigation

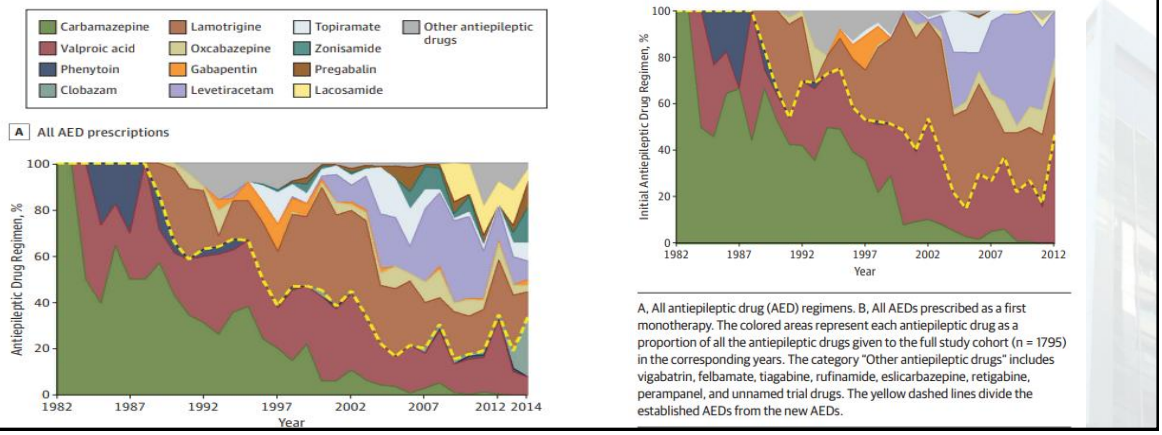
Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs

A 30-Year Longitudinal Cohort Study

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

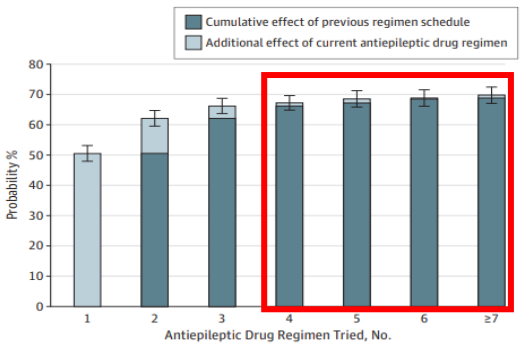
1795 newly diagnosed patients
- 80.2% Monotherapy
- 19.8% Polytherapy (>=2 AEDs)

Figure 1. Antiepileptic Drug Regimens Over the Study Period



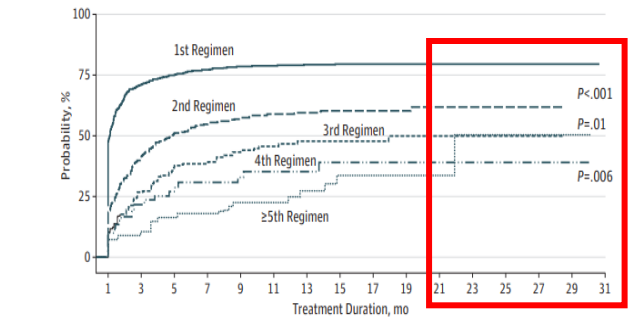
A, All antiepileptic drug (AED) regimens. B, All AEDs prescribed as a first monotherapy. The colored areas represent each antiepileptic drug as a proportion of all the antiepileptic drugs given to the full study cohort (n = 1795) in the corresponding years. The category "Other antiepileptic drugs" includes 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.

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

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

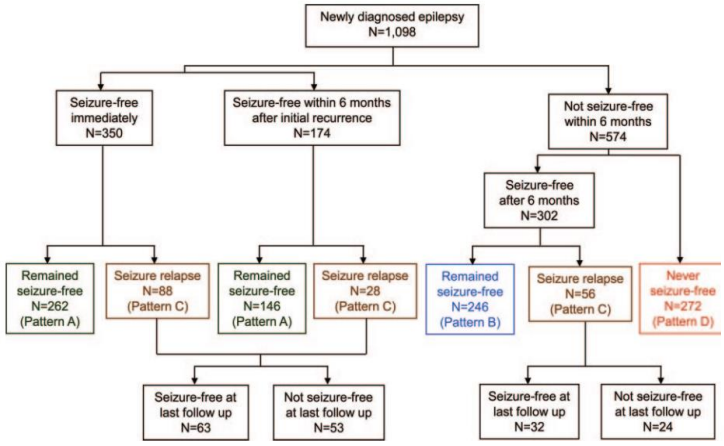
ARTICLES

Patterns of treatment response in newly diagnosed epilepsy

M.J Brodie et al.

Outcome Patterns

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



A. **Early remission**: remained seizure-free shortly after commencing treatment 62%

B. **Early phamacoresistance**: 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%

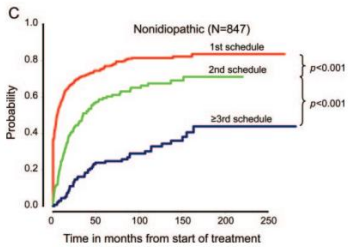
D. **Persistent seizures** despite repeated trials of different medications used singly or in combination 25%

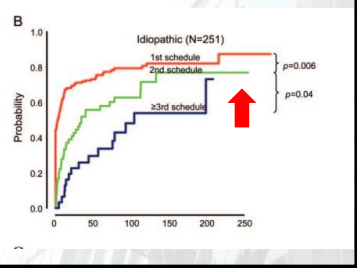
Prognosis of treated epilepsy (long term)

- 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





3 Prognosis of untreated epilepsy

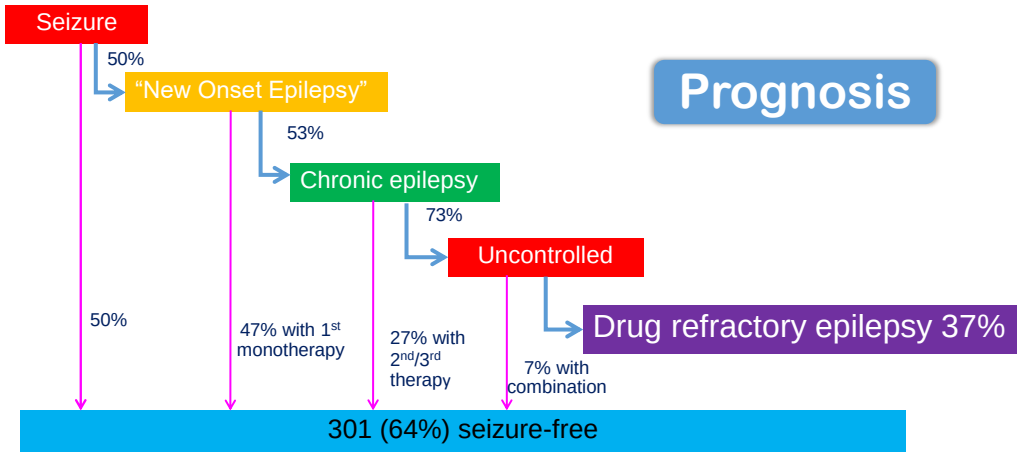
Zielinski, 1974; Keranen and Riekkinen, 1993; van Donselaar et al., 1997

- 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 <<<**

Achievement of seizure freedom in newly diagnosed epilepsy (n=470)



Kwan P& Brodie MJ N Engl J Med 2000; 342:314-9

Seminar in Epileptology

Epileptic Disord 2015; 17 (1): 243-53

The natural history and prognosis of epilepsy

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

4 **Epilepsy syndromes**

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.

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

Correspondence
American Academy of Neurology
guidelines@aan.com

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

5 **Drug Responsive Epilepsy**

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

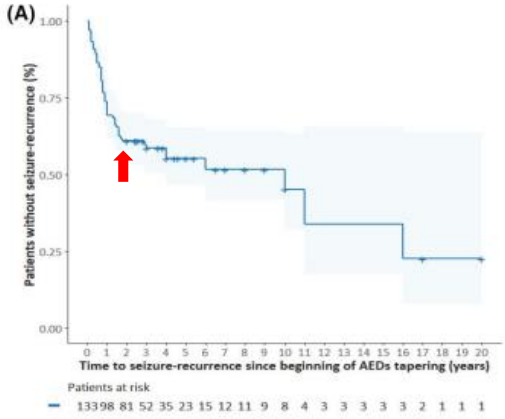
Epilepsia

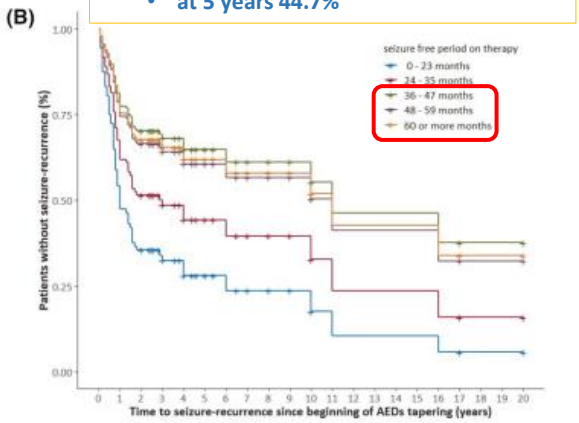
FULL-LENGTH ORIGINAL RESEARCH

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%





Epilepsia

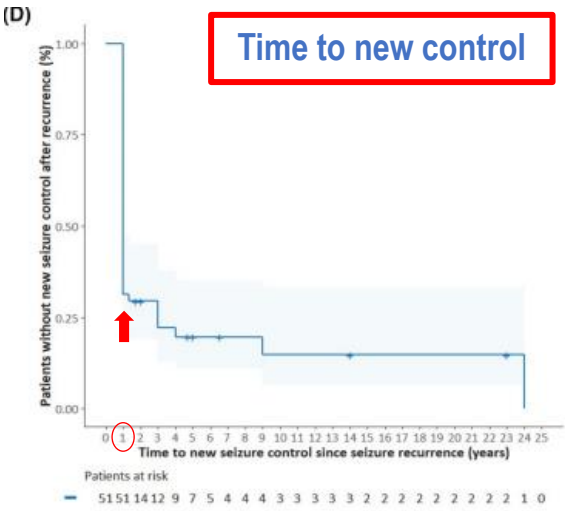
FULL-LENGTH ORIGINAL RESEARCH

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]

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)



Drug resistance in epilepsy

Emilio Perucca, Piero Perucca, H Steve White, Elaine C Wirrell

6 **Drug Resistant Epilepsy**

Lancet Neurol 2023; 22: 723–34

- **The pooled cumulative incidence of drug-resistant epilepsy was 20% - 32% (depends on study).**
- ***Incidence*: higher in children (25%) than in adult or mixed-age populations (15%), which might reflect different causes.**

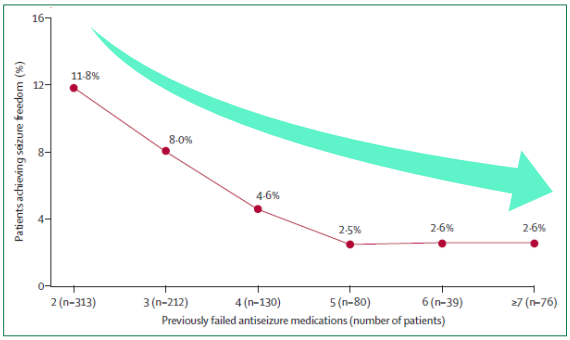
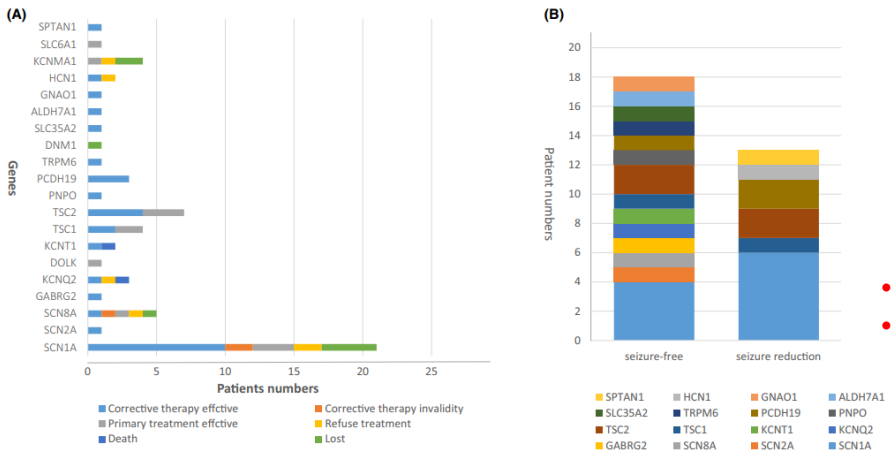


Figure 1: Seizure freedom rates after a newly added antiseizure medication, by number of previously tried antiseizure medications

not assess most recently developed ASM perampanel, brivaracetam, everolimus, cannabidiol, cenobamate, fenfluramine, and ganaxolone

a gradual shift from targeting of common epilepsy types to targeting of specific causes or syndromes, including **highly drug-resistant syndromes.**

DRE and genetic diagnosis



Change Treatment

- **50-53% SZ free**
- **75% SZ reduce**

FIGURE 2 The efficacy of adjustment treatment in genetic drug-resistant epilepsy (DRE) patients with "actionable" genes . A, The follow-up of 62 DRE patients with 23 "actionable" genes. B, After receiving corrective therapy, 18 DRE patients became seizure-free and 13 DRE patients achieved seizure reduction

DRE and Ketogenic Diet

Pharmacologic and Dietary Treatments for Epilepsies in Children Aged 1–36 Months

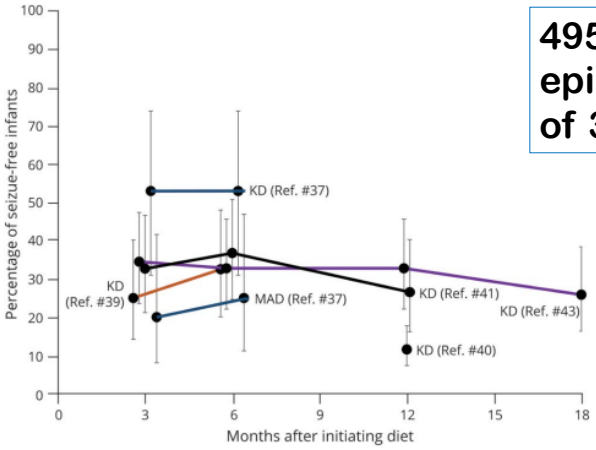
A Systematic Review

Jonathan R. Treadwell, PhD, Sudha Kilaru Kessler, MD, MSCE, Mingche Wu, MPH, Nicholas S. Abend, MD, MSCE, Shavonne L. Massey, MD, MSCE, and Amy Y. Tsou, MD, MSc

Correspondence
Dr. Treadwell
jtreadwell@ecri.org

Neurology® 2023;100:e16-e27. doi:10.1212/WNL.0000000000201026

Figure 2 Rates of Seizure Freedom After Dietary Treatments



495 children with non-syndromic epilepsy diagnosed before the age of 36 months

KD vs MAD MAD: modified Atkin's diet

SZ free

- 53%, 20% at 3 mo
- 53%, 25% at 6 mo

SZ reduction

- 58%,7% at 3 mo
- 71%, 28% at 6 mo

Review

Neuro-stimulation in focal epilepsy: A systematic review and meta-analysis

Henry C. Skrehot [a], Dario J. Englot [b], Zulfi Haneef [a,c,*]

Epilepsy & Behavior 142 (2023) 109182

0, USA
ngineering, and Biomedical Engineering, Vanderbilt Uni

Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis from the ILAE Surgical Therapies Commission

Lahoud Touma, Bénédicte Dansereau, Alvin Y. Chan, Nathalie Jetté, Churl Su Kwon, Kees P.J. Braun, Daniel Friedman, Lara Jehi, John D. Rolston, Sumeet Vadera, Lily C. Wong-Kisiel, Dario J. Englot, Mark R. Keezer

Neurology

Neuro-stimulation

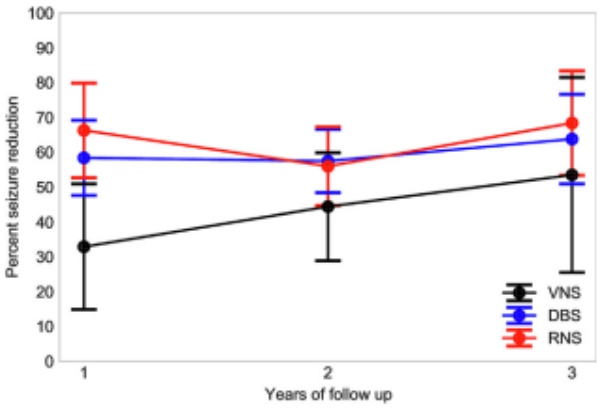


Fig. 5. Line graph showing mean seizure reductions in follow-up years 1, 2, and 3 for vagus nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation (DBS). Percentages are given in Table 1.

SZ reduction

VNS

- 34.7%

RNS :

- 53%, at 2 yr
- 66%, at 5 yr
- 75%, at 9 yr

DBS :

- 56%, at 2 yr
- 65%, at 5 yr
- 75%, at 7yr

Cochrane Library

Cochrane Database of Systematic Reviews

Surgery for epilepsy (Review)

West S, Nevitt SJ, Cotton J, Gandhi S, Weston J, Sudan A, Ramirez R, Newton R

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical treatment	Surgery				
Proportion free from seizures at 1 year	**71 per 1000**	**692 per 1000** (334 to 1000 per 1000)[a]	**RR 9.78** (4.73 to 20.21)	196 (2 studies)	⊕⊕⊝⊝ **low**[b,c]	RR > 1 indicates advantage for surgery One study measured freedom from seizures as 'all seizures impairing awareness', and another study measured freedom from seizures as ILAE Class 1
Proportion free from all seizures (including auras) at 1 year	**25 per 1000**	**375 per 1000** (52 to 1000 per 1000)[a]	**RR 15.00** (2.08 to 108.23)	80 (1 study)	⊕⊝⊝⊝ **very low**[b,c,d]	RR > 1 indicates advantage for surgery

7 Mortality

- ***Low*** *mortality risk*, but increased risk of death 2-3 x general population
- *LMIC >HIC*=>Treatment gap : ASM, surgery lack of access to health facilities and preventable causes.
- *DRE: Attributable to epilepsy or seizures*, important causes includes

: SUDEP, SE, unintentional injuries, and suicide

- *The incidence of SUDEP* :1.16 per 1,000 **The major risk factors** include:
  - generalized tonic-clonic seizures,
  - nocturnal seizures
  - persistence of seizures. (12%)

Epilepsia. 2015 November ; 56(11): 1700–1706.

Mortality, and life expectancy in Epilepsy and Status epilepticus—current trends and future aspects

Eugen Trinka[1,2,3*], Lucas J. Rainer[1,2], Claudia A. Granbichler[4], Georg Zimmermann[1,5,6] and Markus Leitinger[1]

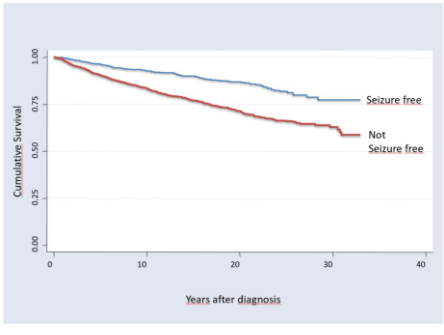


FIGURE 2
Kaplan maier survival curves of 3,334 patients in tyrol, Austria, with more than 30 years observation; overall 48,595 person years. Seizure free patients have a significant better overall survival (log rank test $\chi = 80.3$, $p < 0.0001$). (from Trinka, 2005 (79)).

frontiers | Frontiers in Epidemiology

Epilepsy Research 177 (2021) 106743

Contents lists available at ScienceDirect

Epilepsy Research

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

Review article

Dravet syndrome: A quick transition guide for the adult neurologist

Danielle M. Andrade [a,*], Anne T. Berg [b], Veronica Hood [c], Kelly G. Knupp [d], Sookyong Koh [e], Linda Laux [f], Mary Anne Meskis [c], Ian Miller [g], M. Scott Perry [h], Ingrid E. Scheffer [i], Joseph Sullivan [j], Nicole Villas [c], Elaine Wirrell [k]

[a] Adult Epilepsy Genetics Program, Division of Neurology, Krembil Brain Institute, Toronto Western Hospital, University of Toronto, Toronto, Canada

GUIDE TO TRANSITION PATIENTS WITH DRAVET SYNDROME TO ADULT CARE

Dravet syndrome (DS) is a rare infantile-onset severe developmental and epileptic encephalopathy. It is characterized by drug-resistant epilepsy, developmental delay, and a high risk of early mortality. More than 90% of patients with DS have a pathogenic variant in the *SCN1A* gene. DS is associated with an increased premature mortality of 17% by 20 years of age, mainly by sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE), but aspiration pneumonia and drowning also occur. Seizure detection devices and caregivers sharing the bedroom may reduce the risk of SUDEP, although there is no definitive evidence to support this.

Summary

Prognostic Outcomes

Prognosis of		
First unprovoked seizure	Seizure recurrence (Mixed children and adult) - at 12 months 16% - at 24 months 21% - at 36 months 27%	Seizure recurrence 24-49% (Adult study)
Treated epilepsy Untreated epilepsy	63.7% - seizure free (12 months or longer) *60%-5yrs, 58-65%-10 yrs, 70%-20 yrs follow up* Spontanuous remission: at least 50%	
Epilepsy syndromes	BECTS 89% CAE 56-93% JAE 62% JME 58%	West 33% Dravet 8% LGS 3% LKS 0%
Discontinued medications	45% relapse after AEDs discontinue	regained seizure control 82.4% 10% did not seizure control 7.8% developed drug-resistant epilepsy.
Drug resistance epilepsy Surgery	Incidence 20-32%	Add med after: 2 ASM- 11.8% (response rate) 3 ASM- 8% 4 ASM- 4.6%, > 5ASM-2.4-2.6%
Mortality	SUDEP 1.16 per 1000	LMIC, DRE (12%), Dravet syndromes(17%)