The Natural History of Epilepsy

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Why Study Natural History?

- *What is my risk of another seizure?*
- *Does this mean I have epilepsy?*
- *Should I start medication now?*
- *What does my future look like?*

First Seizure: Definitions

Acute Symptomatic

(Provoked)

Seizure in close temporal relation to brain/systemic insult (TBI, stroke, infection). Low intrinsic recurrence unless condition recurs.

Unprovoked

(Remote/Progressive)

No immediate precipitant. Single unprovoked seizure has ~36–45% relapse risk.

Epilepsy

(Definition)

Defined largely by recurrence risk. After 2 unprovoked seizures, risk of third is ≈73–76%.

First Seizure Incidence

Type	Incidence	Key Demographics
Acute Symptomatic	29–39 per 100,000/yr	Infants <1 yr, Elderly, Men. Causes: TBI, Stroke, Infection.
Single Unprovoked	23–61 per 100,000 p-y	Peaks <12 months and >65 years. Lifetime risk ~8-10% by age 80.

Hauser, Beghi. Epilepsia2008

Risk After a First Unprovoked Seizure

- Cumulative recurrence risk after first seizure:
  - ≈16% at 1 yr, 21% at 2 yrs, 27% at 3 yrs
- High-risk markers: (risk recurrent up to ≈60% at 3 years)
  - Epileptiform abnormalities
  - Remote symptomatic seizure
- Overall ≈40–50% after first; ≈75% after two unprovoked seizures

Hauser. NEJM 1982
Hauser, Beghi. Epilepsia 2008

Treatment Decision After First Unprovoked Seizure

- Immediate antiseizure medication (ASM) treatment
  - Short-Term Benefit: reduce the absolute risk of recurrence by 35%
  - Long-Term Limitation: unlikely to improve the long-term prognosis
- Risk vs. Benefit:
  - Risk of ASM adverse events ranges from 7% to 31%

Allan Krumholz. Neurology 2015

Definition of Epilepsy (ILAE 2014)

- **Defined** by either
  - At least two unprovoked seizures occurring >24 hours apart ***OR***
  - One unprovoked seizure and a probability of recurrence risk (at least 60%) ***OR***
  - Epilepsy syndrome
- **Resolved** when a patient has been seizure-free for at least 10 years and off ASMs for at least the past 5 years

Fisher, et al. Epilepsia 2014

Long-Term Remission: Population Data

- Overall prognosis generally ***favorable*** for the majority
- **70-80%** eventually go into long-term remission within the first 5 years (the NGPSE cohort)
- Likelihood of long-term remission **better in newly diagnosed** than in epilepsy
- Many patients achieving remission despite early active course

Sander. Epilepsia 2003
Beghi. Epileptic Disord 2015
Shorvon, Goodridge. Brain 2013

Course Patterns

Relapsing-Remitting

52%

The most common pattern. Seizures may return after periods of freedom.

Early Remission

25%

Quick control that is sustained.

Worsening/No Remission

~17%

8% had no remission, 9% showed worsening course.

Beghi, et al. JNNP 2019

Childhood-Onset Epilepsy

- 67% terminal remission (≥5 yrs, mainly off ASM)
- 19% never achieving 5-year remission (persistent drug-resistant)
- Late remission common; “slow responders” eventually seizure-free
- *Negative factors:* symptomatic etiology and intellectual disability

Sillanpää. Brain 2006

Syndrome Prognosis Categories

Category	Description & Examples
Excellent	Spontaneous remission likely *Ex: BECTS, Benign myoclonic of infancy*
Good	Easily controlled, relapse uncommon *Ex: Childhood absence, GTC on awakening*
ASM-Dependent	Controlled but relapse off drugs *Ex: JME*
Poor	Drug resistant, palliative care *Ex: LGS, Dravet, Tuberous Sclerosis*

Sander. Epilepsia 2003
Beghi. Epileptic Disord 2015

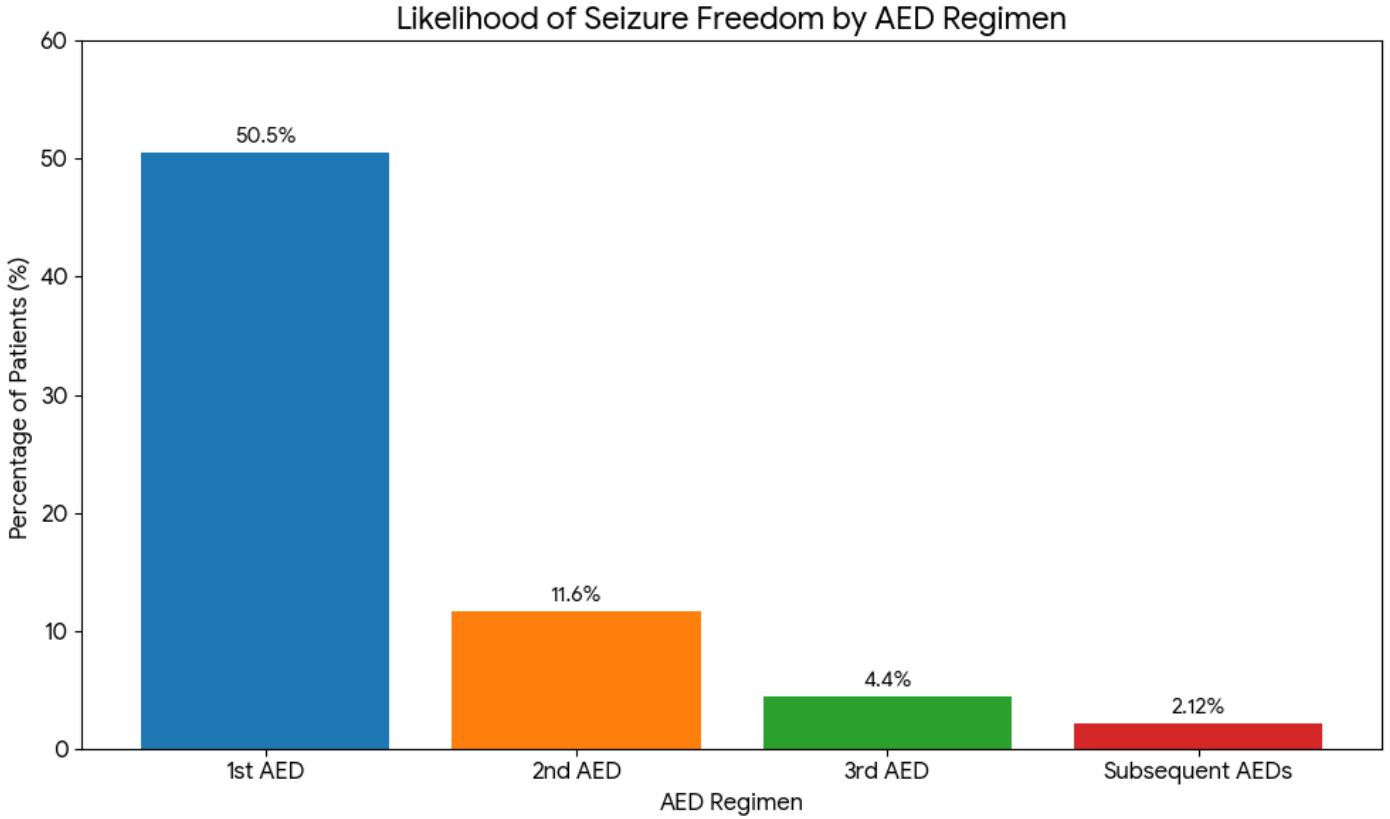
Treatment Outcomes in Newly Diagnosed Epilepsy

- Antiseizure Medications (ASMs) are the cornerstone of treatment
- ***≈40% of patients*** do not achieve seizure freedom
- ***Early response is a good guide*** to longer-term prognosis

Chen Z, Patrick K, Brodie MJ, Liew D. JAMA Neurol 2018

The Steep Decline in Efficacy

- *~60% seizure-free overall* **VS** *~40% of patients do not achieve seizure freedom*



Chen Z, Patrick K, Brodie MJ, Liew D. JAMA Neurol 2018

Drug-Resistant Epilepsy (DRE)

- Defined as *"failure of adequate trials of two tolerated and appropriately chosen and used AED schedules to achieve sustained seizure freedom"*
- Guide to referral to a specialized epilepsy center

Kwan P, Arzimanoglou A, Berg AT, et al. *Epilepsia* 2010

Clinical Predictors of DRE

- Etiology/neurologic deficits
  - Symptomatic etiology
  - Neurological dysfunction
  - Intellectual disability
- Early Seizure History
  - High seizure frequency during early treatment
  - High numbers of seizures before treatment

Giussani G, et al. Eur J Neurol 2016
Kwan P, Brodie MJ. NEJM 2000
Beghi. Epileptic Disord 2015

ASM Withdrawal & Relapse

Adults: After ≥2 years seizure-free, discuss risks and benefits of withdrawal

Children: Withdrawal may be considered after 18–24 months seizure-free

Benefits (Why stop?)

- Fewer side effects
- Better quality of life
- No long-term prognostic gain: Early/continued ASM does not improve long-term (>3 years) remission rates

Risks (Why wait?)

- Relapse rates: ~12–46%
- Timing: most relapses occur early
  - 2/3 within 1 year of taper, nearly 87% within 2 years.
- Consequences: relapse can lead to injury, loss of self-esteem, driving prohibition, and job loss

Beghi. Epileptic Disord 2015
Sillanpää, Schmidt. Seizure 2017
Gloss D, et al. Neurology 2021

Seizure Recurrence Predictors

- *Seizure-free period*
  - Seizure-free period on therapy < 2 yrs (HR 2.365)
- *Etiology*
  - Underlying neurological condition, symptomatic etiology, or persistent motor deficits
- *Abnormal interictal EEG*
- *Seizure consequences*
  - Recurrence risks include potential for injuries, loss of driving license, and psychosocial consequences

Beghi. Epileptic Disord 2015
Sillanpää, Schmidt. Seizure 2017
Gloss D, et al. Neurology 2021

Mortality and SUDEP

- Standardised mortality ≈2–3× general population overall
  - 10× mortality in symptomatic epilepsy with neurologic deficits
- Acute symptomatic seizures/status epilepticus → ≈19% 30-day case fatality
- Significant proportion of deaths seizure-related; SUDEP prominent cause
- Mortality reduction and safety counselling as core management goals

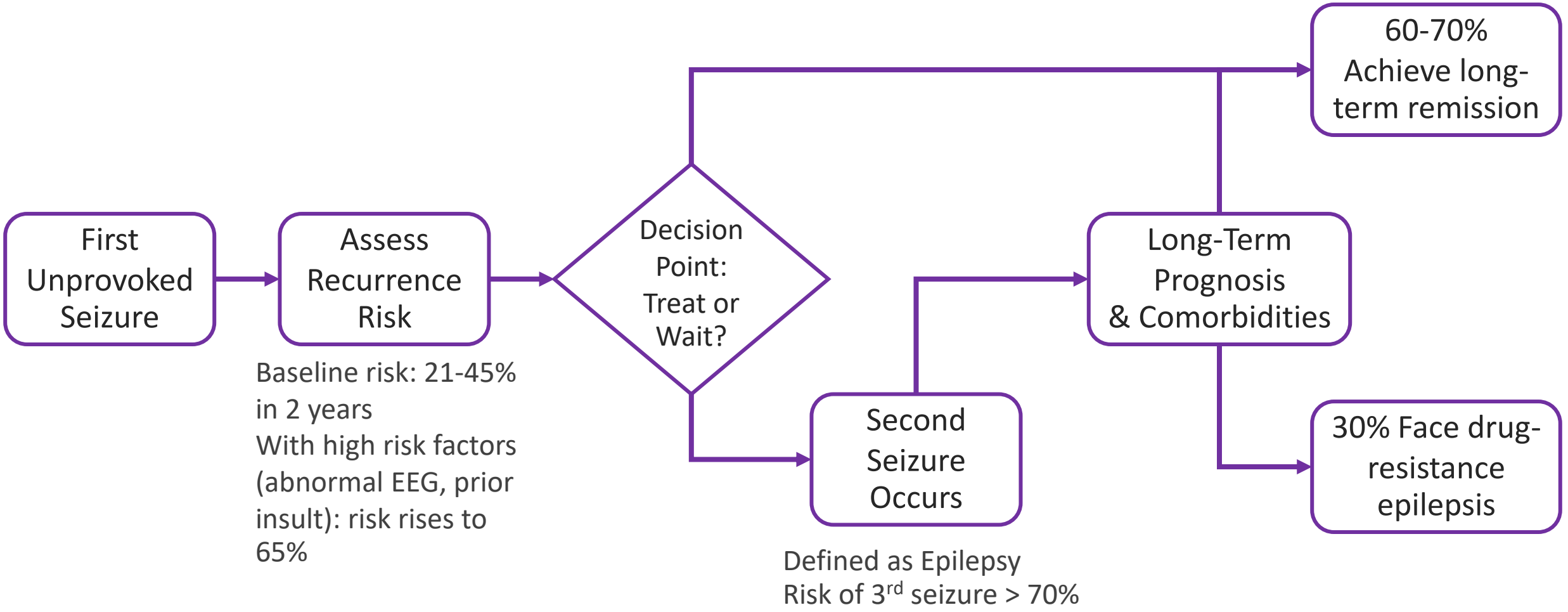
Sillanpää, Schmidt. Seizure 2017
Hauser, Beghi. Epilepsia 2008

Psychiatric Comorbidities and Prognosis

- Psychiatric disorders 2–3× more than normal population
- Anxiety (19%) depression (17%) as leading comorbidities
- Additional burden: bipolar disorder, psychosis, PTSD, ADHD, substance use
- Comorbidities worsening quality of life, adherence, and seizure outcomes
- Need for systematic screening and integrated neuropsychiatric care

Kwon, et al. JAMA Neurol 2025
Doherty, et al. BJNN 2022

Mapping the Patient Journey



Questions?

Thank you.