Epilepsy: what to start and when to stop it

Neurology update

19th Nov 2014
Introduction

• Epilepsy is common (over 250,000 Australians) (1 in 50 children), sometimes chronic, condition with
  – physical risks
  – psychological
  – socioeconomic consequences
  – quality of life.
  – long term commitment, general practitioner (GP) and the specialist.
Definition

In 2005, ILAE proposed conceptual definition:
- disorder of the brain
- enduring predisposition to generate epileptic seizures

Practical:
- 2 unprovoked seizures >24 h apart
Recurrence risk after 1st unprovoked seizure

- Two year risk 40-52%
- 24% with no risk factor and normal EEG
- 65% remote neurological insult and epileptiform EEG
- Dutch Study: 10 children with epileptiform EEG patterns after their first seizure had a 2-year risk of 71%
- Two unprovoked non febrile seizures, the chance by 4 years is 73%, with a 95% confidence interval 60–90%

Berg AT, Shinnar S. The risk of recurrence following a first unprovoked seizure. Neurology 1991;41:965–72
2013, ILAE

Disease of brain

(1) At 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, occurring over the next 10 years

(3) diagnosis of an epilepsy syndrome.
PHARMACOTHERAPY OF EPILEPSY: The issues

- Is treatment justified? (likelihood of further seizures and its risks including SUDEP) vs (consequences, inconvenience, and risks of taking regular medication)
- Which AED/what to start?
- When should AED combinations be used?
- Risks associated AED treatment?
- How long should treatment be continued/When to stop?
Antiepileptic drug development

- AEDs
- Antiepileptic drug development
- Lacosamide
- Levetiracetam
- Tiagabine
- Topiramate
- Fosphenytoin
- Gabapentin
- Lamotrigine
- Vigabatrin
- Oxcarbazepine
- Zonisamide
- Ethosuximide
- Sodium valproate
- Carbamazepine
- Tiagabine
- Primidone
- Phenobarbital
- Phenoytoin
- Primodone
- Bromide
- Year
Major considerations in choosing an AED

- Type of seizure
- Type of epileptic syndrome
- Adverse effect profile
- Age & genetic background (pharmacogenomics)
- Ease of use (fast and easy dose titration)
- Specific co-morbidities
<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Other AEDs that may be considered on referral to tertiary care</th>
<th>Do not offer AEDs (may worsen seizures)</th>
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<tr>
<td>Childhood absence epilepsy or other absence syndromes</td>
<td>Ethosuximide</td>
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<td>Vigabatrin</td>
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<td>Juvenile absence epilepsy or other absence syndromes</td>
<td>Ethosuximide</td>
<td>Ethosuximide</td>
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<td>Vigabatrin</td>
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<td>Juvenile myoclonic epilepsy</td>
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<td>Clobazam(^a)</td>
<td>Carbamazepine</td>
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<td>Vigabatrin</td>
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<thead>
<tr>
<th>Benign epilepsy with centrotemporal spikes</th>
<th>Carbamazepine(^a)</th>
<th>Carbamazepine(^a)</th>
<th>Eslicarbazepine acetate(^a)</th>
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<tr>
<td></td>
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<td>Clobazam(^a)</td>
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<td>Levetiracetam(^a)</td>
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<td>Oxcarbazepine(^a)</td>
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<td>Sodium valproate</td>
<td>Vigabatrin(^a)</td>
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### AED options by seizure type

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First-line AEDs</th>
<th>Adjunctive AEDs</th>
<th>Other AEDs that may be considered on referral to tertiary care</th>
<th>Do not offer AEDs (may worsen seizures)</th>
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<tr>
<td>Generalised tonic–clonic</td>
<td>Carbamazepine&lt;br&gt; Lamotrigine&lt;br&gt; Oxcarbazepine&lt;br&gt; Sodium valproate</td>
<td>Clobazam&lt;br&gt; Lamotrigine&lt;br&gt; Levetiracetam&lt;br&gt; Sodium valproate&lt;br&gt; Topiramate</td>
<td>(If there are absence or myoclonic seizures, or if JME suspected)&lt;br&gt; Carbamazepine&lt;br&gt; Gabapentin&lt;br&gt; Oxcarbazepine&lt;br&gt; Phenytoin&lt;br&gt; Pregabalin&lt;br&gt; Tiagabine&lt;br&gt; Vigabatrin</td>
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<tr>
<td>Tonic or atonic</td>
<td>Sodium valproate</td>
<td>Lamotrigine&lt;br&gt; Rufinamide&lt;br&gt; Topiramate</td>
<td>Carbamazepine&lt;br&gt; Gabapentin&lt;br&gt; Oxcarbazepine&lt;br&gt; Pregabalin&lt;br&gt; Tiagabine&lt;br&gt; Vigabatrin</td>
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CONCLUSIONS

Ethosuximide and valproic acid are more effective than lamotrigine in the treatment of childhood absence epilepsy. Ethosuximide is associated with fewer adverse attentional effects. (ClinicalTrials.gov number, NCT00088452.)
SANAD study
Standard and New antiepileptic Drugs

• Unblinded RCT in hospital-based outpatient clinics in the UK
• Effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy
SANAD STUDY

• Lamotrigine is clinically better than carbamazepine for time to treatment failure outcomes
SANAD STUDY

- Study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy
SANAD STUDY

• Valproate is better tolerated than topiramate and more efficacious than lamotrigine, and should remain the drug of first choice for many patients with generalised and unclassified epilepsies.
UK NICE guidelines for the use of new AED

- If established drugs have failed
  - Typically carbamazepine or valproate
- If most appropriate older drug is contraindicated
- If older drugs could interact with other medications
- If older drugs are already known to be poorly tolerated by the patient
- If patient is a woman of child bearing potential
Risks associated with AED treatment

- Failure to achieve complete seizure control
- Dose-dependent CNS side effects (cognition, mood)
- Idiosyncratic reactions
- Chronic adverse effects (bone health, weight gain etc.)
- Adverse drug interactions
The devil that we do not know: Latency to discovery of some adverse effects

<table>
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<tr>
<th>Drug</th>
<th>Adverse Effect</th>
<th>Incidence</th>
<th>Latent Period</th>
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<tr>
<td>PHT</td>
<td>Osteomalacia</td>
<td>Up to 5%</td>
<td>1938-1967</td>
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<tr>
<td>FBM</td>
<td>Aplastic anaemia</td>
<td>1:4000</td>
<td>1993-1994</td>
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<td>VGB</td>
<td>Visual field defects</td>
<td>33%</td>
<td>1989-1997</td>
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Results: Patients carrying HLA-B*15:02 are at strongly increased risk for CBZ-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in populations where HLA-B*15:02 is common, but not CBZ-induced hypersensitivity syndrome (HSS) or maculopapular exanthema (MPE). HLA-B*15:02-positive patients with CBZ-SJS/TEN have been reported from Asian countries only, including China, Thailand, Malaysia, and India. HLA-B*15:02 is rare among Caucasians or Japanese; no HLA-B*15:02-positive patients with CBZ-SJS/TEN have been reported so far in these groups. HLA-A*31:01-positive patients are at increased risk for CBZ-induced HSS and MPE, and possibly SJS/TEN and acute generalized exanthematous pustulosis (AGEP). This association has been shown in Caucasian, Japanese, Korean, Chinese, and patients of mixed origin; however, HLA-A*31:01 is common in most ethnic groups. Not all patients carrying either risk variant develop an HSR, resulting in a relatively low positive predictive value of the genetic tests.
Tolerability in infants & children

• Valproate
  – Valproate hepatotoxicity
    • Increased below the age of 2 yrs
    • Polytherapy
    • Presence of associated psychomotor delay
      – Look for undiagnosed inherited metabolic diseases
        » Carnitine deficiency/ Alper’s disease

(Valproate interferes with mitochondrial function)
Side effects mandating stopping treatment:

- **Clobazam:**
  - Behavioral changes, irritability
- **Topiramate:**
  - Language disturbances, glaucoma
- **Levetiracetam:**
  - Mood and behavioral changes
- **Lamotrigine:**
  - Drug rash & SJ syndrome
- **Zonisamide:**
  - Mental slowing, hypohidrosis
- **Vigabatrin:**
  - Visual field defects
Dravet Syndrome (DS)

- Epilepsy syndrome with intractable seizures and cognitive/motor/behavior concerns that is highly associated with a sodium channel receptor mutation

- Clinical diagnosis of DS:
  - Seizure onset < 12 months of age
  - Prior to seizure onset: unremarkable PMHx, normal development, normal neuroimaging
  - Seizures
    - Pleomorphic seizure types
      - Generalized (GTC, myoclonic, atypical absence)
      - Focal (alternating unilateral hemiconvulsions, other)
  - Developmental issues (slowing/plateau/regression)
  - Co-morbidity: Ataxia/gait abnormalities, behavioral issues
| Dravet syndrome | Discuss with, or refer to, a tertiary paediatric epilepsy specialist | Clobazam<sup>a</sup>  
Stiripentol | Carbamazepine  
Gabapentin  
Lamotrigine  
Oxcarbazepine  
Phenytoin  
Pregabalin  
Tiagabine  
Vigabatrin |
|----------------|------------------------------------------------|------------------|
| Dravet syndrome | Sodium valproate  
Topiramate| | |
Case

• 5.5 year old girl presented with afebrile GTC
• Previously 3 febrile seizures
• Atonic drops started soon after first GTC
• Brief absences also occurred
• Perinatal history and development normal
• Interesting family: Extensive family history of epilepsy on father’s side (febrile and afebrile seizures)
WHEN FEBRILE SEIZURES ARE NOT FEBRILE SEIZURES

• GEFS + (Gen. Epilepsy febrile seizures plus)
  – Common under-recognised disorder
  – Autosomal dominant with high penetrance
  – Typical FS, FS + lasting longer, Afebrile GTCs most common
  – Occasionally absence, myoclonic, atonic
  – Focal seizures of frontal or temporal lobe in origin
  – Dravet’s syndrome overlap
  – Remits in adolescence 80%
  – Sodium channelopathy
Case

- 5 year old girl, unremarkable birth history
- Normal development
- Woke up with vomiting and head and eye deviation to right, unresponsive and clonic jerks of the right side followed by GTC
- The episode lasted 30 minutes followed by right hemiparesis for 4 hours
- One year later, similar night time seizure
- EEG
Panayiotopoulos Syndrome

1. Tonic eye deviation
2. N, R, Vomiting
3. Pallor + other autonomic
4. Ictal syncope

- 70% nocturnal
- Peak- 4 to 5 years
- Lasts longer; 44% > 30 min
- EEG focus-commonly occipital, variability ++
BECTS
[Benign Rolandic Epilepsy]

- Most common partial epilepsy in childhood
- Onset 2-14 years; \(\frac{3}{4}\) 7-10 yrs
- Seizure frequency -
  - 10-20% have a single seizure
  - 20% have frequent seizures
  - < 2% have seizures into adulthood
- “No other” neurological issues
Ictal Semiology

- Focal facial sensorimotor
- Oro-pharyngolaryngeal
- Hyper salivation
- Speech arrest
- Clonic upperlimb

70% nocturnal
60% retained awareness
Lasts 1-2 min
Sec. Generalized - 30-50%
Epileptic Encephalopathy of Late Childhood

A spectrum of diseases

1. Landau-Kleffner syndrome
2. CSWS Syndrome

- Gradual cognitive/behavior deterioration
- Acquired language impairment
- Seizures
- Dramatic activation of epileptiform abnormalities in slow wave sleep
Our son was normal in every way until the age of 2 years. At first he seemed to be losing his hearing but not for environmental sounds. We thought that he was going deaf, but the hearing test was normal... When he was 3 years old he didn't say anything for over a month. He improved for a few months and then he had a minor seizure

» From the internet description by a mother
Boy aged 8 with Landau-Kleffner syndrome with occasional focal seizures

Awake

Asleep

---

300 μV

1 sec
Case

• 3 year old girl referred to specialist with staring spells
• History: brief episodes of staring and eyelid fluttinger and uprolling of eyes, unresponsiveness, no aura or post-ictal phase
• EEG: number of episode captured with 3 Hz spike and wave pattern
• Ethosuximide: stomach upset and vomiting, whiny and sometimes aggressive
• Valproate: initial some improvement but then seizures recurred. Did not tolerate high doses (mood and behaviour). Thus added in Lamotrigine, which wasn’t effective
• Clobazam: side effects and very drowsy
• Acetazolamide, Zonisamide- failed
• Ketogenic diet
• Negative for glucose transporter gene mutation
• All the medications were weaned off.
When to stop

- “Remission”
- “Resolved”
- “Cure”
- Cochrane systematic review: Early discontinuation was associated with higher recurrence risk than late discontinuation in children
- Recommend 2 years
Is the child really seizure-free?

• Clinical criteria
• EEG: An epileptiform EEG is associated with a higher risk of relapse, the test is not reliable. Similarly, a normal EEG does not guarantee remission
• Treat children and not their EEG
Resolution of epilepsy

• The ILAE Task Force
  – age-dependent epilepsy syndrome but are now past the applicable age
  – those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years
• 70% of children with seizures who are seizure free for 2 or more years while on AED therapy will remain seizure free when medications are withdrawn
Fig. 1 The epilepsies: a simple clinical classification

**Idiopathic**
- Idiopathic partial
  - e.g. benign rolandic epilepsy
  - Normal brain; focal EEG changes

**Symptomatic**
- Symptomatic partial
  - e.g. following infarction
  - Abnormal brain; focal EEG changes

**Other**
- Other epilepsy syndromes including some without precise classification

**Idiopathic generalised**
- e.g. childhood absence epilepsy
  - Normal brain; generalised EEG changes

**Symptomatic generalised**
- e.g. brain dysmorphism
  - Abnormal brain; generalised EEG changes
Factors affecting relapse

Fig 2. Probability of remaining seizure free following discontinuation of antiepileptic drugs in children with seizures after a seizure-free period: effect of etiology on outcome, Kaplan-Meier curves comparing idiopathic cases with remote symptomatic cases.
# Epilepsy syndrome

## Table

<table>
<thead>
<tr>
<th>Epileptic syndrome</th>
<th>N</th>
<th>No. with Recurrences</th>
<th>%</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Primary generalized epilepsy</td>
<td>61</td>
<td>21</td>
<td>34</td>
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<tr>
<td>Childhood absence</td>
<td>26</td>
<td>5</td>
<td>19</td>
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<tr>
<td>Juvenile absence</td>
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<td>3</td>
<td>33</td>
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</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
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<td>0.006</td>
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<tr>
<td>Other primary generalized</td>
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<td>9</td>
<td>41</td>
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<tr>
<td>Partial epilepsy</td>
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<tr>
<td>Benign rolandic epilepsy</td>
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<td>&lt; 0.001</td>
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<td>Benign occipital epilepsy</td>
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<tr>
<td>Temporal lobe epilepsy</td>
<td>7</td>
<td>3</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Other partial epilepsy</td>
<td>26</td>
<td>8</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable partial epilepsy</td>
<td>17</td>
<td>5</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable idiopathic epilepsy</td>
<td>36</td>
<td>10</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Total idiopathic cases</td>
<td>165</td>
<td>48</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>
Age

Fig 3. Probability of remaining seizure free following discontinuation of antiepileptic drugs in children with seizures after a seizure-free period. Effect of age at onset on outcome: Kaplan-Meier curves. (A) Idiopathic cases. (B) Remote symptomatic cases.
Family history

Fig 4. Probability of remaining seizure free following discontinuation of antiepileptic drugs in children with seizures after a seizure-free period: effect of family history of epilepsy in first-degree relative on outcome in idiopathic cases. Kaplan-Meier curves.
EEG abnormalities

Fig 5. Probability of remaining seizure free following discontinuation of antiepileptic drugs in children with seizures after a seizure-free period: effect of slowing on the electroencephalogram (EEG) on outcome for idiopathic cases, Kaplan-Meier curves.
EEG abnormalities

• Higher risk of recurrence but only in children with idiopathic seizures.
• Most children with focal spikes had benign rolandic epilepsy.
• Excluding children with benign focal epilepsies of childhood, then only 11 children had focal spikes.
History of atypical febrile seizures

Fig 6. Probability of remaining seizure free following discontinuation of antiepileptic drugs in children with seizures after a seizure-free period: effect of a history of atypical febrile seizures on outcome in overall cohort, Kaplan-Meier curves.
## Risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset &gt; 12 yr</td>
<td>5.1</td>
<td>3.0, 8.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atypical febrile seizures</td>
<td>2.5</td>
<td>1.4, 4.4</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>Family history of seizures</td>
<td>2.4</td>
<td>1.3, 4.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Moderate-severe MR (IQ &lt; 50)</td>
<td>2.1</td>
<td>1.2, 3.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Slowing on electroencephalogram</td>
<td>1.6</td>
<td>1.0, 2.6</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Idiopathic group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset &gt; 12 yr</td>
<td>5.4</td>
<td>2.8, 10.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Family history of seizures</td>
<td>3.1</td>
<td>1.5, 6.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Slowing on electroencephalogram</td>
<td>2.4</td>
<td>1.2, 4.7</td>
<td>0.013</td>
</tr>
<tr>
<td>Atypical febrile seizures</td>
<td>2.8</td>
<td>1.1, 7.2</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Remote symptomatic group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset &gt; 12 yr</td>
<td>3.6</td>
<td>1.6, 8.3</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>Moderate-severe MR (IQ &lt; 50)</td>
<td>2.8</td>
<td>1.5, 5.2</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Absence seizures</td>
<td>0.4</td>
<td>0.2, 0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Atypical febrile seizures</td>
<td>2.0</td>
<td>1.0, 3.9</td>
<td>0.049</td>
</tr>
</tbody>
</table>

MR = mental retardation; CI = confidence interval.
Table 8. Risk of Seizure Recurrence 2 Years after Withdrawal of Antiepileptic Drug Therapy in Children as a Function of Number of Risk Factors Present

<table>
<thead>
<tr>
<th>No. of Risk Factorsᵃ</th>
<th>N</th>
<th>No. with Recurrences</th>
<th>%</th>
<th>2-Year Recurrence Riskᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic seizures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>97</td>
<td>14</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>1</td>
<td>54</td>
<td>27</td>
<td>50%</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>6</td>
<td>86%</td>
<td>71%</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>0</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td><strong>Remote symptomatic seizures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9</td>
<td>1</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td>15</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>23</td>
<td>62%</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>8</td>
<td>89%</td>
<td>78%</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>0</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
</tbody>
</table>

ᵃRisk factors are those from multivariable analysis (Table 7) and are different for idiopathic and remote symptomatic groups.
ᵇCalculated from Kaplan-Meier analysis.
How long do we maintain ‘epilepsy restrictions’?

• Never to swim unsupervised and to shower rather than bathe!
• Ausroads driving recommendations
Take home message

• Epilepsy may be diagnosed after one unprovoked seizure and treatment initiated
• 70% - full seizure control with treatment
• AED decision- Epilepsy syndrome, seizure
• Wrong selection can worsen seizure
• HLA- B-1502 in high risk population
• Remote symptomatic epilepsy - higher recurrence risk, >50% seizure free
Resources

• ILAE website-Classification, videos
• NICE, UK
• Epilepsy Action, Australia
• PEN, NSW