Prognosis for New-Onset Epilepsy
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<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<tbody>
<tr>
<td>Upsher-Smith, Eisai, Acorda, UCB, Lundbeck, Pfizer</td>
<td>Consultation/advisory board member</td>
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Learning Objectives

• To understand the prognosis for long-term seizure control in new-onset epilepsy and specific epilepsy syndromes

• To review the evidence for the question of whether epilepsy prognosis is drug-specific
What kind of prognosis?

- Seizure outcome
- Treatment outcome (including side effects)
- Social function
- Occupational function
- Mortality
Seizure outcome prognosis

1) Overall epilepsy population
2) By syndrome
3) Course
4) Predictors
5) Is response/prognosis drug-dependent?
The magic number: 68%

- Brodie et al 2012: **68%** terminal (1-year) remission
- Cockerell et al 1997: **68%** in 3-year remission
- Lindsten et al 2001 (adults): **68%** 1-year remission (64% 3-year)
- Silanpää & Schmidt 2006 (kids): **67%** terminal (5-year) remission
Prognosis for primary generalized epilepsy

- Pediatric setting: 94% seizure-free (Silanpää & Schmidt 2006)
- Adult/adolescent setting: 64% seizure-free (Mohanrak & Brodie 2007)
- Adult/adolescent setting: 76% seizure-free (Kharazmi et al 2010)
Specific syndromes: CAE

1 year (Wirrell, Callenbach)
2 year (Loiseau, Trinka)
Specific syndromes: JAE

2-year remission measured in all studies
Specific syndromes: JME

- **75%** seizure-free for 2 years (Janz 1985)
  - 9% of patients successfully weaned off AEDs
- **68%** seizure-free for 5 years (Geithner et al 2012)
  - 19% successfully weaned off AEDs
- **67%** with "benign" course (Bakyan et al 2008)
  - Remainder either resistant (17%) or "pseudo-resistant" (16%)
Prognosis for symptomatic generalized epilepsy in kids

- 42% attained a 2-year remission (Berg et al 2001)
- 2/14 (14%) attained a 5-year remission (Silanpaa & Schmidt 2006)
- 28% with SGE attained 5 years of remission (Camfield x2 2007)
  - 24% died
- Variation by syndrome (LGS, myoclonic-astatic, West syndrome), but numbers for each are small
  - Better overall for myoclonic-astatic and for non-syndromic SGE
Prognosis for focal epilepsy syndromes

- BRE: 96% seizure-free for 5 years (Callenbach 2010)
- MTS: 42% in remission with Rx (Stephen et al 2001)
- MTS: 25% had 1-year remission with Rx (W-J Kim et al 1999)
- Cryptogenic focal epilepsy: 23% with terminal 5-year remission (Gasparini et al 2013)
Long-term course of epilepsy

- Early remission - within the first 6-12 months of Rx
- Delayed remission - ≥ 6 - 12 months from Rx
- Relapsing-remitting course - recurrent seizure following a period of seizure-freedom
- Resistant - never a period of sustained seizure-freedom (1 - 5 years)
Studies of long-term course

<table>
<thead>
<tr>
<th>Course</th>
<th>early remission</th>
<th>late remission</th>
<th>relapsing/remitting</th>
<th>resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silanpää &amp; Schmidt 2006 (n=144)</td>
<td>31%</td>
<td>32%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Brodie et al 2012 (n=1098)</td>
<td>37%</td>
<td>22%</td>
<td>16%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Predictors: age and # of seizures

Bonnett et al 2012

Figure 3: Relative hazard ratio plots for age and total number of seizures before randomisation for the time to treatment failure. Hazard ratio estimates with 95% CIs are shown for overall time to treatment failure, for age (A) and total number of seizures (B), and for time to treatment failure because of inadequate seizure control and because of unacceptable adverse events for age (C) and total number of seizures (D).
Predictors: # of drug failed

Brodie et al 2012

Schiller and Najjar 2008
Other prediction studies

- Gender?
  - Brodie et al 2012: best outcome in 42% of men, 31% of women

- Age
  - Found NOT to predict outcome in multiple studies, contradicting SANAD

- Partial seizures
  - Worse prognosis than for generalized tonic-clonic seizures
    - Diametric opposite of the surgical literature in resistant patients!
Predictors in kids (Berg et al 2001)

- **Good**
  - Idiopathic generalized epilepsy
  - Onset ages 5 - 9 years

- **Bad**
  - Remote symptomatic etiology
  - Family history
  - Higher initial seizure frequency (≥1/month)
  - Focal slowing on EEG

- Seizure frequency confirmed as prognostic sign in other studies
  - Others have been inconsistently found
Adult new-onset partial epilepsy trials
Two models of relative AED efficacy
Serial AED efficacy: seizure-free rates in resistant patients

- Brodie et al 2012: 15%
- Schiller & Najjar, 2008: 17%
- Callaghan et al, 2007: 15%
- Luciano & Shorvon, 2007: 15%

Resistance defined as failure of 2 AEDs in most studies.
Deficiencies in efficacy literature

- Can’t sort out spontaneous changes from drug successes
- No data in non-resistant patients to answer key question in sz-free patients:
- If a patient is seizure-free on an AED, how likely is she to remain seizure-free on a different AED?
  - Side effects -- acute, chronic, and beneficial
  - Pregnancy planning
  - Cost
Seizure recurrence and remission after switching antiepileptic drugs

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†Erika Stuckert, †Maromi Nei, and †Michael R. Sperling


SUMMARY

Purpose: Studies of seizure outcome in patients undergoing serial antiepileptic drug trials have all been uncontrolled, with no account made for the spontaneous changes in disease state that could confound the elucidation of drug effects. In addition, no study has ever looked at outcome following antiepileptic drug switch in seizure-free patients, despite the fact that this is done routinely in clinical practice. We aimed to address both of these issues.

Twenty patients (cases) were having seizures on their old drug; 6 (30%) entered remission after drug switch, compared to 8 of 40 matched controls (20%). The two groups differed at baseline in number of anticonvulsants previously failed, which was the most important factor for prognosis. After statistical adjustment to account for this, seizure-free patients had 6.53 times higher odds of seizure recurrence if switched to a new drug (95% confidence interval [CI] 1.02–61.19; p = 0.06). Non-seizure-free patients had 1.66 times higher odds of remission if they remained
Methods: case patients

- Patients with focal epilepsy being switched from monotherapy with an older AED (PHT, CBZ) to a newer AED (LEV, LTG, TPM)
- Enrolled into studies of serologic outcomes
- Many had been seizure-free on the older drug
- Categorized as seizure-free or not seizure-free prior to the switch
- Excluded those with < 6 months of monotherapy seizure outcome available before or after the switch
Methods: controls

- 2 controls matched to each case by consecutive retrospective chart review

- First two patients meeting these criteria:
  a. Office visit within 30 days of the case patient (index date)
  b. Same seizure status as the case prior to the index date
  c. On a single AED which was not changed at the index date
  d. Seizure outcome available 6 months after the index date

- Baseline differences in # of AEDs failed between cases and controls required statistical adjustment
## Results: 6 month seizure outcome

<table>
<thead>
<tr>
<th>Status at index date</th>
<th>Group</th>
<th>N</th>
<th>Seizure-free after index date</th>
<th>Recurrent seizures after index date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-Free</td>
<td>Cases (switched)</td>
<td>23</td>
<td>78.3%</td>
<td>21.7%</td>
</tr>
<tr>
<td></td>
<td>Controls (same Rx)</td>
<td>46</td>
<td>95.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Not Seizure-Free</td>
<td>Cases (switched)</td>
<td>20</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>Controls (same Rx)</td>
<td>40</td>
<td>20%</td>
<td>80%</td>
</tr>
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## Multivariate analysis of 6-month outcome

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free patients, controls vs. cases</td>
<td>6.53</td>
<td>1.02 - 61.19</td>
<td>0.06</td>
</tr>
<tr>
<td>Seizure-free patients, per previous AED failure</td>
<td>0.85</td>
<td>0.57 - 1.39</td>
<td>0.47</td>
</tr>
<tr>
<td>Non-seizure-free patients, controls vs. cases</td>
<td>1.66</td>
<td>0.36 - 8.42</td>
<td>0.52</td>
</tr>
<tr>
<td>Non-seizure-free patients, per previous AED failure</td>
<td>0.61</td>
<td>0.37 - 0.91</td>
<td>0.03</td>
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Summary

- Two-thirds of patients with epilepsy in remission at any given time
- 15-20% of patients have a relapsing-remitting course
  - About half of these are in remission at any given time
- CAE and BRE patients do better
- JAE, SGE, and MTS do worse
  - View that SGE and MTS can rarely be medically controlled is incorrect
Summary (cont.)

- Major predictors are # of seizures at time of Rx and # of drugs failed.
- However, "success" of serial drug trials likely due to spontaneous remissions.
- Good prognosis may, in about 1/6 of patients, be drug-dependent.
- Extent of overlap of the spectra of AEDs remains to be determined.