Tailoring therapy to optimize care for Epilepsy

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- For discussion only -
Disclosures

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Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study

Seena Fazel, Achim Wolf, Niklas Långström, Charles R Newton, Paul Lichtenstein

Lancet 2013; 382: 1646-54

• Study of all people in Sweden diagnosed with epilepsy 1954 -2009 (n=70000), matched to up to 10 age- and sex-matched controls and unaffected siblings, followed up to the age of 56 years old
• Possible due to linkage of several national databases (census, patient register, cause of death register, multi-generation register) through unique national identification number
• Key findings:
• Mortality in people with epilepsy increased >10x after controlling for age, sex, income, marital, and immigration status
• Mortality increased for internal and external causes
• Ratios of psychiatric comorbidities 3-5x elevated in people with epilepsy (depression, alcoholism, substance misuse)
• Very high effect of psychiatric comorbidity on odds ratio for external causes of death
Comorbidities in epilepsy

- Diabetes type I (10 fold increase in NHNN cohort)
- Maternal mortality (11 x increase) + morbidity (preeclampsia, C-section, prolonged stay, 1-2 x increase)

Keezer M, in preparation
McDonald et al, JAMA Neurology 2015
Personal Impact of Epilepsy Scale

Category “Seizures”
1 Seizure recency
2 Severe seizure recency
3 Seizure severity
4 Seizures with lost awareness
5 Seizures bothersome
6 Seizure warning
7 postictal symptoms
8 Seizure related injuries
9 Seizure clusters

Category “Side effects”
10 Nr of medications
11 Anger / aggression
12 confusion / memory
13 Physical problems
14 Tiredness
15 Sleep
16 Headache€

Category “Comorbidities”
17 Depression
18 Anxiety
19 Thinking / memory
20 Work / school problems
21 Social limits
22 Transportation limits
23 Fear
24 Cost

25 Overall quality of life

• tool to quantify the impact of epilepsy longitudinally
• may help direct treatment decisions, especially in clinical settings with little time
• “the stroke scale for epilepsy”?

Fisher RS et al, Epilepsy & Behavior 2015
Predictors for pharmacoresistance

- Presence of multiple seizure types
- Etiology
- Positive family history
- Number of seizure before treatment
- Multifocal EEG abnormalities
- Inadequate response to initial therapy
- History of status epilepticus
- **ALL UNMODIFIABLE**
Predictors for pharmacoresistance

- Suboptimal AED choice
- Adherence
- Lifestyle factors
- MODIFIABLE
Psychiatric Comorbidities

**TABLE 1. Estimates of the prevalence of psychiatric disorders in patients with epilepsy**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence</th>
<th>General population</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>4% Seizure free</td>
<td>2–9% Women; 1–3% men</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>9–22% Uncontrolled/partially controlled</td>
<td>2–9% Women; 1–3% men</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>27–58% Medically intractable epilepsy</td>
<td>2–9% Women; 1–3% men</td>
<td>28</td>
</tr>
<tr>
<td>Depression</td>
<td>3–9% Controlled epilepsy</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>20–55% Recurrent epilepsy</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>~8–48%</td>
<td>5–17%</td>
<td>29</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3–50%</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Neurotic disorders</td>
<td>8%</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Psychosis</td>
<td>6–10%</td>
<td>1.5–2%</td>
<td>30, 35</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1 or 8%</td>
<td>2%</td>
<td>28, 29</td>
</tr>
<tr>
<td>Mania</td>
<td>Rare</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>ADHD</td>
<td>14–40%</td>
<td>~5%</td>
<td>36</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit-hyperactivity disorder.

* lifetime-to-date prevalence.

Includes dissociative disorder (2.5%), stress-related disorder (1.8%), anxiety-panic disorder (1.5%), and others (2.3%).

Likely combination of neurobiologic, psychosocial, and possibly iatrogenic effects

Bazil Epilepsia 2004
Gilliam Epilepsia 2002
Depression rather than seizure frequency is the major factor determining self-rated quality of life in people with pharmacoresistant epilepsy.
Pharmacologic properties of Pregabalin

- Acts on voltage gated Calcium channels in the brain, modulating neurotransmitter release
- Note: although structurally related to GABA, Pregabalin does not act on GABA-ergic mechanisms
- Absorption unaffected by meals
- Linear dose-uptake relationship in adults
- No hepatic metabolism, no induction, no inhibition
- >98% renaly excreted without being metabolised
- No protein binding
- No interactions with other drugs, including oral contraceptives
- No effect of PGB on CBZ, LTG, PHB, PHT, TPM and VPA

Ben Menachem, Epilepsia 2004
Bockbrader et al, Epilepsia 2011
Pregabalin compared to placebo as add-on in licensing trials: robust and dose-dependent seizure reduction

Brodie, Epilepsia 2004; Ramsay et al, Epilepsia 2009
Side effects in licensing trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency (%)</th>
<th>Withdrawals due to event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregabalin (n = 758)</td>
<td>Placebo (n = 294)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.5</td>
</tr>
<tr>
<td>Somnolence</td>
<td>20.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.9</td>
</tr>
<tr>
<td>Ataxia</td>
<td>13.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Weight gain</td>
<td>10.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>9.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.4</td>
</tr>
<tr>
<td>Headache</td>
<td>9.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Amblyopia (blurred vision)</td>
<td>9.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.4</td>
</tr>
<tr>
<td>Diplopia</td>
<td>8.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7</td>
</tr>
<tr>
<td>Tremor</td>
<td>7.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7</td>
</tr>
<tr>
<td>Thinking abnormal</td>
<td>7.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Some patients reported >1 adverse event.
<sup>a</sup>Significantly different from placebo.

French et al, Neurology 2003
Arroyo et al, 2004
Beydoun et al, 2005
Elger et al, 2003
Pregabalin effective in Asians with focal epilepsy (add-on, flexible dosing)

178 Korean adults, 75% on 3 AEDs

46% responder rate in PGB arm, 32% in placebo arm
7 patients discontinued PGB during study,
19 patients requested dose reduction due to side effects

Lee et al, Epilepsia 2009
Pregabalin well tolerated in Asians, too

- No idiosyncratic side effects
- Main side effects: Dizziness, Somnolence, Weight gain

<table>
<thead>
<tr>
<th>MedDRA preferred term</th>
<th>Pregabalin (N = 119)</th>
<th>Placebo (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All causality</td>
<td>Treatment-related</td>
</tr>
<tr>
<td>Dizziness</td>
<td>46 (38.7)</td>
<td>42 (35.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>26 (21.8)</td>
<td>26 (21.8)</td>
</tr>
<tr>
<td>Weight increase</td>
<td>14 (11.8)</td>
<td>14 (11.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (9.2)</td>
<td>11 (9.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (7.6)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>6 (5.0)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Tremor</td>
<td>6 (5.0)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (4.2)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Coordination abnormal</td>
<td>5 (4.2)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>3 (2.5)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (3.4)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>4 (3.4)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>3 (2.5)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>3 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>3 (2.5)</td>
<td>3 (2.5)</td>
</tr>
</tbody>
</table>

Lee et al, Epilepsia 2009
Audits in clinical practice I: Spain

- 101 adults, focal epilepsy
- 40% responders at 12 months
- 6% seizure free at 12 months
- Increase in seizure frequency in 4%

Main side effects:
- >10% weight gain seen in 26%
- Dizziness 20% (esp in combination with PHT, CBZ, OXC)
- leg edema 10%
- blurry vision 3%

No idiosyncratic side effects
Cognitive side effects rare

Reasons to discontinue at 12 months (total 40%):
- Inefficacy 16%
- Side effects 15%
- Worsening of seizures 9%
- 1 seizure-related death (drowning)

Carreno et al, Seizure 2007
Audits in clinical practice II: UK (Kings)

- 96 adults, 85 focal epilepsy
- 2 (0-4) concomittant AEDs
- 3 (1-9 previous AEDs)
- 30% ultimate responders (median 23 months)
- 10% incidental decrease in anxiety
- Increase in seizure frequency in 4%

Main side effects:
- >10% weight gain seen in 18%
- Dizziness 15% (esp in combination with PHT, CBZ, OXC)
- Drowsiness 17%

No idiosyncratic side effects
Cognitive side effects rare

Reasons to discontinue (total 45%):
- Inefficacy 30%
- Side effects 10%
- Inefficacy and side effects 9%

Valentin et al, Seizure 2007
Brandt et al, Seizure 2013
Audits in clinical practice III: UK (NHNN)

- 402 patients, 88% focal epilepsy
- 2 (0 - >4) concomittant AEDs
- Patients had failed median 8 AEDs

Retention higher in men than women:
- at 1 year 60% vs 45%
- at 2 years 46% vs 32%

Higher doses attained in men > women

40% discontinued PGB due to side effects:
- CNS-related (35%) and weight gain (12%)
- Women more likely to report side effects and stop PGB due to side effects
- Decision to stop PGB not linked to number of concomitant AEDs

Yen et al, Epilepsy Research 2009; Wehner et al, Seizure 2014
PGB non-inferior to LTG and Placebo as add-on in focal epilepsy: Randomized controlled double blind trial

- 97 centres in Europe, Australia, Canada
- Adults with pharmacoresistant focal epilepsy, on 1 - 3 AEDs, including at least one inducer, randomized to PGB or LTG or Placebo
- PwE had failed 4 (1-7) AEDs
- Note 2 phase design
- Note unusually high placebo response (53%) in one country contributing ~20% of patients

Most common side effects in PGB arm:
Dizziness (25%), somolence (20%), weight gain (9%), ataxia (9%).
No new adverse events

Baulac et al, Epilepsy Research 2010
PGB non-inferior to LEV as add-on in focal epilepsy: Randomized controlled double blind trial

• 71 centres in Europe, Asia, South America
• Adults with pharmacoresistant focal epilepsy, on 1 or 2 AEDs (largely CBZ, VPA, TPM, OXC), randomized to LEV or PGB
• Responder rates 59% for both LEV and PGB
• 8.4% on PGB vs 16% on LEV seizure free during maintenance phase
• Higher responder rates with lower(!) doses in both PGB and LEV group

Discontinuation tended to occur
• in the titration phase with PGB
• in the maintenance phase with LEV

Zaccara et al, Epilepsia 2014
People with 2 focal seizures, on treatment < 2 weeks
Pregabalin inferior to LTG in terms of efficacy: first seizure, first sGTCS occurred earlier on PGB than LTG

- Side effects overall similar in PGB and LTG
- Weight gain, somnolence more common in PGB
- Oropharyngeal pain more common in LTG

Kwan et al, Lancet Neurology 2011
However, mind the fine print:
Methodological issues in monotherapy trials

- Remember prognosis in newly diagnosed epilepsy
- 37% will do well, with no seizure over 1 year
- 25% will be pharmacoresistant
- Primary outcome was seizure freedom for 6 months, comparing essentially the first target dose

French, Lancet Neurology 2011
Brodie et al, Neurology 2012
Prognosis in newly diagnosed epilepsy

A: early and sustained sz freedom 37%
B: delayed but sustained sz freedom 22%
C: fluctuating 16%
D: never sz free 25%

Brodie et al, Neurology 2012
Pregabalin as monotherapy vs historic control
-Trial design developed to mandate FDA-US criteria-

Adults with uncontrolled epilepsy on 1 or 2 AEDs
Patients randomized to 600mg/d or 150mg/d (“pseudoplacebo”), predefined exit criteria:
- doubling of seizure rate at 2 or 28 days
- occurrence of status epilepticus
- re-occurrence of generalised tonic clonic seizures
- any other significant worsening

Main side effects in PGB 600mg/d:
Dizziness, somnolence (17% each)
Weight gain 16% vs 6% in 150mg/d

Trial stopped early because PGB 600mg/d did better “than expected”
(based on historic control design)

French et al, Neurology 2013
Data on Pregabalin in children are extremely limited

- Pregabalin safe and tolerated over 7 days at doses of up to 15mg/kg/d in children age 1 month to 6 years; pharmacokinetics suggest that 15mg/kg/d may be needed in children <30kg to reach an equivalent dose to 600mg/day in adults
- Follow up data in these children with epilepsy on 1-3 further AED pending
- 1 fetal malformation in 30 pregnancies exposed to Pregabalin monotherapy (Veiby G J Neurol 2014)

Mann et al, Epilepsia 2014
Pregabalin and cognitive side effects

Rates and predictors of patient-reported cognitive side effects of antiepileptic drugs: An extended follow-up

Asif Javed a, Brian Cohen a, Kamil Detyniecki b, Lawrence J. Hirsch b, Alexander Legge a, Baibing Chen b, Carl Bazil a, Kenneth Kato a, Richard Buchsbaum c, Hyunmi Choi a, *

Rates of patient-reported intolerable cognitive side effects <5% with Pregabalin in polytherapy and monotherapy; comparable to most other AEDs
positive outlier: Lamotrigine (2.5%)
negative outlier: Topiramate (22.8%)

Javed et al, Seizure 2015
Sleep and Epilepsy

• PwE, especially those with uncontrolled seizures of any kind, report worse quality of sleep than healthy controls
• PwE have increased sleep latency, increased number of arousals, more shifting between sleep stages, less REM-sleep, and less slow wave sleep compared to controls
• Sleep apnea and periodic limb movement disorder of sleep more common in PwE
• Poor sleep may increase seizure frequency, increase depression, contribute to memory problems in PwE, and decrease performance during daytime

Jain & Glauser, Epilepsia 2015
Effect of AEDs on Sleep

CRITICAL REVIEW AND INVITED COMMENTARY

Effects of epilepsy treatments on sleep architecture and daytime sleepiness: An evidence-based review of objective sleep metrics
Sejal V. Jain and Tracy A. Glauser

Epilepsia, 55(1):26–37, 2014
doi: 10.1111/epi.12478

• “Virtually all AEDs affect sleep architecture”
• AEDs with positive effect on sleep latency / sleep efficiency:
  Carbamazepine, Clobazam, Pregabalin, Gabapentin, Tiagabine
• AEDs that increase daytime sleepiness:
  Phenobarbitone, Valproate, Levetiracetam in high doses
• AEDs without effect on daytime sleepiness:
  Topiramate, Zonisamide
Pregabalin and dependency

- Pregabalin over-proportionally prescribed in imprisoned patients
- 50% of apprehended drivers had serum levels outside the recommended range, often in combination with other drugs
- Risk factors for abuse appear to be current or history of polytoxic drug misuse
- Physicians need to be aware of abuse potential and “street value” of Pregabalin

Gahr et al, 2013
Conclusion

• Few predictors of pharmacoresistance are modifiable, including adherence and lifestyle factors
• Pregabalin is effective and comparable to LTG and LEV as add-on therapy in pharmacoresistant focal epilepsy, with very early effect
• Pregabalin has a favorable pharmacokinetic profile, and is generally well-tolerated
• Somnolence, dizziness, and weight gain are the most common reported side effects, more common in women
• Pregabalin reduces anxiety in some people with epilepsy
• Role as monotherapy and in children to be defined