Starting, Choosing, Mixing, Stopping Drugs in Epilepsy Management

Norman K. So
University of Washington, Seattle
2016 Review Course

DISCLOSURES

None

EPIDEMIOLOGY OF SEIZURES


<table>
<thead>
<tr>
<th>Incidence Rate</th>
<th>per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>44</td>
</tr>
<tr>
<td>First Unprovoked seizure</td>
<td>61</td>
</tr>
<tr>
<td>Acute symptomatic seizure</td>
<td>39</td>
</tr>
<tr>
<td>All seizures/epilepsy</td>
<td>100</td>
</tr>
</tbody>
</table>
EPIDEMIOLOGY OF SEIZURES

The data suggest:

Many persons who have a first seizure do not develop epilepsy

They include those with an unprovoked first seizure, and those with an acutely provoked seizure that does not denote an epileptic predisposition

Brain imaging (CT or MRI) should be considered routine (level B) with 15% abnormal in pooled analysis of 928 subjects

EEG should be considered routine (level B) with 51% abnormal in pooled analysis of 1766 subjects

Labs: CBC, Chemistry, tox screen, LP – insufficient data (level U)

IMAGING OF FIRST SEIZURE

King et al, 1998. 300 pts Melbourne, Australia

MRI abnormalities in: 38 of 277 (14%)

Tumor 17
Developmental anomaly 8
Hippocampal A/S 6
Cavernoma 2

CT Head missed 50% of lesions

MRI: 1.5 Tesla

Hakami et al, 2013. 764 pts Melbourne, Australia

Epileptogenic MRI abnormalities in: 177 (23%)

Tumor 26
Developmental anomaly 26
Hippocampal A/S 14
Cavernoma/AVM 26
Encephalomalacia 85

Nonepileptogenic abnormality 165 (22%)

MRI: 1.5 or 3 Tesla
SINGLE SCALP EEG AFTER FIRST SEIZURE

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Epilep</th>
<th>Non-Epilep</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>397</td>
<td>50%</td>
<td>5.5%</td>
<td>55.5%</td>
</tr>
<tr>
<td>FIRST Group, 1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melbourne, Australia</td>
<td>300</td>
<td>43%</td>
<td>25%</td>
<td>68%</td>
</tr>
<tr>
<td>King et al, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK, MESS</td>
<td>1331</td>
<td>46.5%</td>
<td>12.8%</td>
<td>59.3%</td>
</tr>
<tr>
<td>Marson et al, 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melbourne, Australia</td>
<td>936</td>
<td>17.6%</td>
<td>12.9%</td>
<td>31%</td>
</tr>
<tr>
<td>Hakami et al, 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SCALP EEG AFTER FIRST SEIZURE

An early EEG within 24 hours is more sensitive than delayed EEG

A 2nd Sleep Deprived EEG yields abnormalities in an additional 35% whose 1st EEG was normal

Both epileptiform and non-epileptiform focal slow wave abnormalities may confer an increased risk for recurrence (Hopkins et al, Lancet 1988: 721; Shinnar et al, 1990; Pediatrics 85: 1076)

RISK OF RECURRENCE AFTER FIRST SYMPTOMATIC SEIZURE

Hesdorffer et al, Epilepsia 2009; 50: 1102

Rochester, MN 1955-1984: 262 subjects with symptomatic seizures from stroke, TBI, CNS infection

(Acute defined as within 1 week of insult)

Risk of Subsequent Unprovoked Seizure

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Remote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>33%</td>
<td>71.5%</td>
</tr>
<tr>
<td>TBI</td>
<td>13.4%</td>
<td>46.6%</td>
</tr>
<tr>
<td>CNS infection</td>
<td>16.6%</td>
<td>63.5%</td>
</tr>
</tbody>
</table>

(all p<.01)
### Precipitants of Acute Provoked Seizures that are potentially reversible

- Metabolic disturbance: Glucose < 36 mg/dl, BUN > 100 mg/dl, Creatinine > 10 mg/dl
- Electrolyte Imbalance Na⁺ < 115 mg/dl, Ca²⁺ < 5 mg/dl, Mg²⁺ < 0.8 mg/dl
- Stimulant/other pro-convulsant drugs
- Sedative or ethanol withdrawal
- Sleep deprivation
- Fever ≥ 38.5°C
- Systemic infection

Cut off numbers from: Beghi et al (ILAE) Epilepsia 2010; 671

---

### Evidence-based Guideline: Management of an Unprovoked First Seizure in Adults


Neurology 2015; 84:1705

---

### Risk of First Seizure Recurrence

In Prospective Series after a First Seizure

Meta-Analysis by Berg & Shinnar 1991:
- 36% by 2 years (>80% risk of seizure recurrence occurs in first 2 years)

FIRST Trial (Italy) 1993:
- 51% by 2 years in untreated group

MESS Trial (MRC UK) 2005
- 39% by 2 years in deferred treatment group

Average ~ 40%
Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21%–45%) (Level A).
PROGNOSTIC INDICATORS OF SEIZURE RECURRENCE

• Partial seizures higher risk than generalized
• Seizure in sleep at higher risk of recurrence
• If in fact 1st seizure preceded by unrecognized seizures (Kim et al, MESS trial 2006)

Clinical factors associated with an increased risk for seizure recurrence include a prior brain insult such as a stroke or trauma (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), or a nocturnal seizure (Level B).

MULTIPLE SEIZURES or STATUS EPILEPTICUS AS FIRST SEIZURE AND RISK OF SEIZURE RECURRENCE

• Multiple seizures (in 24 hrs) at presentation
  Kho et al, Neurology 2006; 67:1047 p=0.8
• Status epilepticus
  Shinnar et al, 1990 (children) 1.3
  Ramos Lizana et al, 2000 (children) 0.6
  Hauser et al, 1990 (community) 1.79
  Hersdorffer et al, 2009 (community) 1.9

Thus 2 or more seizures in 24 hours may not increase the risk of recurrence, and considered as one event

Status epilepticus increases risk in adults but not necessarily in children

WHAT IS THE EVIDENCE ON TREATMENT OF FIRST SEIZURES?

<table>
<thead>
<tr>
<th>Seizure Rate</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Italian FIRST study</strong> (1993) 6 mos (n=397, CBZ, PHT, PB, VPA)</td>
<td>41% 24 mos 51%</td>
<td>17% 25%</td>
</tr>
<tr>
<td><strong>UK MESS study</strong> (2005) 6 mos (n=1443, CBZ,PHT, VPA, LTG) 24 mos</td>
<td>26% 39%</td>
<td>18% 32%</td>
</tr>
</tbody>
</table>

Early treatment reduces the risk of recurrence by 30-60%
META-ANALYSIS
An Evidence-based Approach to the First Seizure
Wiebe, Tellez-Zenteno, Shapiro Epilepsia 2008;49 (Suppl 1)

WHAT IS THE EVIDENCE ON TREATMENT OF FIRST SEIZURES?
Extended follow-up beyond 2 years:
FIRST Trial Group, Musicco et al, 1997
MESS Study Group, Marson et al, 2005
• 2 year remission rates (of 76%-81%) identical in treated and initially untreated (delayed treatment) groups followed beyond 2 years
• 50% of untreated patients remain seizure free
• Early treatment while effective does not protect against late development of epilepsy

AAN 2015 Recommendations
Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk for a seizure recurrence in the 2 years subsequent to a first seizure (Level B), it may not improve QOL (Level C).

Clinicians should advise patients that over the longer term (> 3 years) immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (Level B).

Patients should be advised that their risk for AED AEs ranges from 7% to 31% (Level B) and that these AEs are predominantly mild and reversible.
TO TREAT OR NOT TO TREAT AFTER A FIRST SEIZURE

In Children (American Academy of Neurology Practice Parameters 2003)

- Treatment with AED is not indicated for the prevention of the development of epilepsy
- Treatment with AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects

RISK OF RECURRENT SEIZURES AFTER 2 UNPROVOKED SEIZURES
Hauser et al, 1998

<table>
<thead>
<tr>
<th>Risk</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>A first seizure</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A second</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A third</td>
<td>76%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment Indicated after 2nd seizure
FDA APPROVED ANTI-SEIZURE DRUGS to 2016 (n 30+)

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd GENERATION</th>
<th>NEW from 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>felbamate '93</td>
<td>vigabatrin '09</td>
</tr>
<tr>
<td>clonazepam</td>
<td>gabapentin '93</td>
<td>lacosamide '09</td>
</tr>
<tr>
<td>clorazepate</td>
<td>lamotrigine '94</td>
<td>rufinamide '09</td>
</tr>
<tr>
<td>diazepam</td>
<td>topiramate '97</td>
<td>clobazam '11</td>
</tr>
<tr>
<td>ethosuximide</td>
<td>levetiracetam '99</td>
<td>pregabine '11</td>
</tr>
<tr>
<td>lorazepam</td>
<td>tiagabine '98</td>
<td>perampanel '12</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>oxcarbazepine '00</td>
<td>eslicarbazepine '13</td>
</tr>
<tr>
<td>phenytoin</td>
<td>zonisamide '00</td>
<td>brivaracetam '16</td>
</tr>
<tr>
<td>primidone</td>
<td>pregabalin '05</td>
<td></td>
</tr>
<tr>
<td>valproic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>valproate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(rarely used: methsuximide, phensuximide, ethotoin)

drug to be withdrawn in 2017

Choosing Among Drugs

Most formal trials look at Efficacy (seizure reduction) and Tolerability (adverse events, number staying on drug)

Phase III median Seizure Reduction Rates 1993-2013
**Comparison Studies of Old and New Antiepileptic Drugs**

No prospective double blind controlled study showed superior efficacy (seizure control rate) of newer drugs compared to the older. Several showed better tolerability and reduced discontinuation rates of newer drugs compared to the older. When older drugs (like CBZ) are taken in extended delivery formulations, tolerability improved to match newer drugs. A study showed PGB (pregabalin) to be more effective than LTG (lamotrigine) in refractory partial epilepsy, but another showed LTG better than PGB in newly diagnosed partial epilepsy.

1. Baulac et al, Epilepsy Research 2010, 91:10

---

**No Superiority of New AEDs in Efficacy for Seizure Control**

The SANAD Trials (UK) 2007

- **Partial Onset Epilepsy**
  - Hazard Ratio for 12 months remission

- **Generalized Epilepsy**

Data from: Marson et al, The SANAD Trial 2007, adapted by Löscher & Schmidt 2011

---

**Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: A systematic review and meta-analysis**

Epilepsia 2011; 52: 1280

Methods: analyzed 62 placebo-controlled and 8 head-to-head randomized trials, looking at Odd’s Ratio for responder rate (50% seizure reduction) and withdrawal rate.

Results:
- Responder rate: Highest topiramate, levetiracetam > all others > gabapentin, tiagabine
- Withdrawal rate: Highest oxcarbazepine, topiramte, least gabapentin, levetiracetam
- The frequency of the most common side effects is comparable among the new drugs

Conclusions: The differences are too small to allow a conclusion about which new drug(s) has superior effectiveness.
FACTORS INFLUENCING CHOICE OF AED

- Appropriateness for Focal v Generalized Seizures
- Cost ($10 or $1000 per month)
- Formulary (state, insurance, health system)
- Prior allergies
- Side effect profile
- Co-morbid state: weight, cognition, psychiatric, other
- Metabolic status: renal, hepatic
- Pharmacokinetics: once daily, bid, tid
- Rapid or slow titration
- Pregnancy or contraception

Choosing Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Broad-Spectrum Agents</th>
<th>Narrow-Spectrum Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Partial onset seizures</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Valproate</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Lacosamide*</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Ezogabine *</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Eskarbazepine*</td>
</tr>
<tr>
<td>Parempanel</td>
<td>Brivaracetam*</td>
</tr>
</tbody>
</table>

* New AEDs categorization may change

Hemodialysis effects on AEDs

<table>
<thead>
<tr>
<th>Hemodialysis clearance relates to solubility and plasma protein binding%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low clearance, No need post-HD dose supplementation: phenytoin, rufinamide, tiagabine, valproic acid/valproate</td>
</tr>
<tr>
<td>Intermediate clearance, unclear need for post-HD dose supplementation: carbamazepine, felbamate, lamotrigine, oxcarbazepine</td>
</tr>
<tr>
<td>High clearance, post-HD dose supplementation needed: ethosuximide, eslicarbazepine, gabapentin, lacosamide, levetiracetam, phenobarbital, pregabalin, primidone, topiramate, zonisamide</td>
</tr>
</tbody>
</table>

If in doubt, measure pre- and post-HD drug levels
Note free levels needed for phenytoin because of altered protein binding in renal failure, and maybe also for carbamazepine, valproate
Changing AED

Sz free

Kwan & Brodie 2000 (New onset) 24.5%

Schiller & Najjar 2008* (Mixed) 38.5%

Schmidt & Richter 1986 (Chronic) 12%

*76% new monotherapy, 24% add on

RESPONSE AS A FUNCTION OF PAST TREATMENT
Schiller & Najjar Neurology 2008; 70: 54

429 pts tried on 630 new AED treatments
89 newly diagnosed
Change Rx = 76%, Add Rx = 24%
Rx PB, PHT, CBZ, VA, GBP, LTG, TPM
Seizure free = terminal remission ≥ 1 yr

Predictors of Poor Response:
• partial v idiopathic generalized epilepsy
• duration epilepsy > 15 yrs
• seizure frequency >103 months

Patterns of Treatment Response in Newly Diagnosed Epilepsy
Brodie et al, Neurology 2012; 78:1548

1098 pts with newly diagnosed epilepsy started on AED (incl: those in prior reports 2000, 2006), diagnosed 1982 to 2006, followed up to 26 years in 2008

At last visit:
83% monoRx
17% combination

2nd regimen:
54% monoRx
36% combination
Lamotrigine Rash

AED-related rash in adult patients with epilepsy
from Arif et al, Neurology 2007

▲ = trend towards significantly higher than average rash rate of all other AEDs
(0.003<p<0.05)
▲▲ = rash rate significantly greater than average of all other AEDs
(p<0.003)
▼▼ = rash rate significantly lower than average of all other AEDs
(p<0.003)
▼ = trend towards significantly lower than average rash rate of all other AEDs
(0.003<p<0.05)

Specific Rash Cross-Sensitivity Rates
From Hirsch LJ et al, Neurology 2008

CBZ ↔ OXC (33-71%)
CBZ ↔ PHT (42-57%)
CBZ ↔ PB (27-66%)
PHT ↔ ZNS (21%)

No specific cross reactivity between LTG and any other AED

Drugs rarely associated with rash:
Valproate
Gabapentin
Pregabalin
Levetiracetam
Topiramate
Adding AED

Kwan & Brodie 2000 (New onset) 9.6%
Callaghan et al, 2007 (Intractable) 12%
Luciano & Shorvon 2007 (Intractable) 17%
after 3+ add on trials 28%
Many FDA Add-On studies (Intractable) 4-5%

Polytherapy Principles

\[
n!r!(n-r)!
\]
With 20 drugs 2 drug combinations = 190
With 25 drugs 2 drug combinations = 300
3 drug combinations = 1140 3 drug combinations = 2300
Share effectiveness for seizure type
Minimal pharmacokinetic interaction
Minimal additive side effects
Potential for synergism
? Different mechanisms of action

Adding Valproate to Lamotrigine: A study of their pharmacokinetic Interaction

Kanner AM, Frey M. Neurology 2000; 55; 588-591

28 patients with persistent seizures on stable LTG monotherapy, VPA added starting at 500 mg/d, then titrated upwards as needed to around 2000 mg/d LTG clearance ↓50% and T1/2 ↑50% on adding VPA LTG dosage needs to be lowered by 50% on start of VPA – (VPA inhibition of VPA clearance achieved with 250 mg/d) 6/28 (21%) became seizure free Adverse Effects: No rashes ➢ dizziness and diplopia 45% ➢ tremor 55%
VPA inhibits LTG metabolism within 1 hour – Yuen et al, Br J. clin. Pharmac 1992: 33; 511
**AED Hepatic Induction or Inhibition**

<table>
<thead>
<tr>
<th>AED</th>
<th>Selective CYP</th>
<th>Broad CYP</th>
<th>UGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>↑ 3A4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESM</td>
<td>↑ 3A4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>↑ 3A4</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td>↑ 3A4</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>↓ 2C9</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>FBM</td>
<td>↑ 3A4, ↓ 2C9</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>LCM</td>
<td>↑ 3A4, ↓ 2C9</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>+/− 3A4, +/−2C19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>↑ 3A4, ↓ 2C9</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>TPM</td>
<td>↑ 3A4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neither inducers nor inhibitors: LTG, GBP, PGB, TGB, LEV, LCM, ZNS

---

**Synergy**

*Greek: syn-ergos, συνεργός, meaning "working together"*

Defined as "The cooperative action of two or more stimuli or drugs" resulting in a different or greater response than that of the individual parts

- "additive" = sum of individual parts
- "supra-additive" = greater than the sum of the individual parts
- Pharmacokinetic = increase in duration or concentration of one or both drugs
- Pharmacodynamic = augmentation of desired effects independent of pharmacokinetic effects

---

**Lamotrigine substitution study: evidence for synergism with sodium valproate?**

<table>
<thead>
<tr>
<th>Phenytoin, Carbamazepine, or Lamotrigine</th>
<th>LTG mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT: 3.5 6.7</td>
<td>Mono: 5.5 8.2</td>
</tr>
<tr>
<td>CBZ: 3.6 8.2</td>
<td></td>
</tr>
<tr>
<td>VPA: 4.7 5.5</td>
<td></td>
</tr>
</tbody>
</table>

*LTG add on with conversion to monotherapy trial*
Comparative efficacy of combination drug therapy in refractory epilepsy
Poolos NP, et al. Neurology 2011; 78:52

N=148 residents state institution for developmental disability
Refractory (≥1 sz/yr after 2 AED trials). Focal or generalized
8 AEDs: LTG, VPA, CBZ, PHT, TPM, LEV, GBP, ZNS
Exclusions: PB, OXC, >3 AEDs, < 4 months trial, after surgery or VNS
Sz Freq/month, Sz Freq Ratio (SFR) comparisons across regimens

2 AED v 1 AED: SFR 0.81(0.68-0.98) p=0.03 n=145
2 Drugs can be better than 1
3 AED v 2 AED: SFR 1.07(0.88-1.30) p>0.05 n=76
3 Drugs not better than 2

Of 32 regimens: 1, 2, or 3 AED, with ≥ 5 pt exposures
Only LTG + VPA decreased SFR 0.52(0.40-0.66) p<0.001
as compared to all other combinations

Addition of Lamotrigine to:
Kanner AM, Frey M. Neurology 2000; 55; 588-591
Adding VPA to LTG: dizziness and diplopia 45%

Pooled Analysis of Lacosamide Trial Data
Grouped by Mechanism of Action of Concomitant AED
Saie et al. CNS Drugs 2010; 24; 1055
Additive Adverse Effects

**Somnolence**: nearly all AEDs except LTG, FBM  
**Dizziness/imbalance**: PHT, PRM, CBZ, OXC, LCM, LTG, TGB, PGB, PER  
**Blurred vision**: CBZ, OXC, LTG, LCM  
**Insomnia**: LTG, FBM  
**Tremors**: VPA, LTG  
**Weight gain**: CBZ, VPA, GBP, PGB, VGB  
**Weight loss**: FBM, TPM, ZNS  
**Mood changes**: ESM, PB, LEV, TPM, ZNS, PER

---

**Relationship Between Adverse Effects of AEDs with Number of Drugs**  
Canevin et al, SOPHIE group, Epilepsia 2010  
Adverse Event Profile in 809 pts with refractory epilepsy  

"AEs did not differ between monotherapy and polytherapy patients, and did not correlate with AED load, possibly as a result of physicians’ intervention in individualizing treatment regimens"

---

**RATIONALE FOR SELECTING DRUGS WITH DIFFERENT MECHANISMS IN POLYTHERAPY**  
Kwan & Brodie Seizure 2000  
470 previously untreated newly diagnosed patients with epilepsy

Na+ channel drugs: CBZ, PHT, LTG  
GABAergic drugs: TGB, VGB  
Multiple mechanisms: VPA, GBP, TPM
Predominant Mechanism of Action

| Fast Na | PH,T, CBZ, OXC, LTG, VPA, TPM, ZNS |
| Slow Na | Lacosamide (LCM) |
| Ca T type | ESM, VPA, ZNS |
| Ca α2δ voltage-gated | GBP, PGB |
| K | Ezogabine (EZG) |
| GABA | VPA, PB, Benzos, TFG, VGB (FBM, TPM) |
| Glutamate | FBM, LTG, TPM, perampanel (PER) |
| SV2 | LEV |

Pooled Analysis of Lacosamide by Mechanism of Action of Concomitant Drugs
Sake et al, CNS Drugs 2010

50% Seizure Reduction

At LCM 400 mg and 600 mg/d, statistically better 50% seizure reduction when added to Non-Na than Na-channel blockers

Potentially Difficult to Use Combinations

PHT+VPA: PH7 induces VPA metabolism (↓ to 50%). VPA displaces PHT (↓ total, ↑free)

PB+VPA: idiosyncratic hypersomnolence/encephalopathy

LTG+VPA: inhibition of LTG clearance, increased risk of rash

CBZ+LTG: hepatic induction of LTG clearance, additive dizziness and blurred vision

CBZ+OXC: doubling side effects: dizziness, diplopia

TPM+ZNS: doubling side effects: cognitive slowing, weight loss, kidney stones

LCM + Na+ drugs (PH,T,CBZ, OXC, LTG): dizziness, blurred vision, LCM metabolism inducible
**Encephalopathy when VPA is added to other AEDs**

Sackellares JC, Lee SI, Dreifuss. Stupor following administration of valproic acid to patients receiving other antiepileptic drugs. Epilepsia 1979; 20: 697


Noh Y, et al. Topiramate increases the risk of valproic-acid induced encephalopathy. Epilepsia 2012 (epub)

---

**Examples of Easier to Use Combinations**

- LEV added to all drugs
- LCM added to non-Na+ drugs*
- TPM added to non-inducing drugs other than ZNS, ?VPA
- GBP added to all drugs (partial seizures)
- PGB added to all drugs (partial seizures)
- Benzodiazepines as add on

*LCM potentiates dizziness from CBZ, LTG, OXC, PHT

---

**AED Combinations with Reports of Benefit**

*Some references: Deckers CLP et al. Review. Epilepsia 2000; 41: 1364

- PHT + PB* – focal seizures
- VPA + ESM* – absence seizures
- CBZ + VPA* – focal seizures with generalization
- LTG + TPM* – focal or generalized seizures
- VPA + LTG* – focal or generalized seizures
- + LEV – focal or generalized seizures
- + LCM – focal seizures (non-Na+ drugs)
- + AZM – generalized seizures
- + CZP – generalized seizures, nocturnal seizures
- + CLB – focal or generalized seizures
WHEN TO STOP ANTIEPILEPTIC
DRUG TREATMENT

–Children vs adults
–EEG findings
–Seizure type
–Epilepsy Syndrome
–Etiology
–Work and safety issues
–Patient perspective

Relapse Following Discontinuation of AEDs

A meta-Analysis (Berg & Shinnar 1994)
Age: Childhood* < Adult < Adolescent Onset
Remote Symptomatic v Idiopathic RR=1.55
Abnormal v Normal EEG RR=1.45
*Some advocate earlier drug withdrawal in children after 6 to 12 months remission

Relapse rates upon drug discontinuation, 1-2 years
seizure free after Epilepsy Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Yrs sz-free</th>
<th>Lobes</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt 2004</td>
<td>0.5-2</td>
<td>All</td>
<td>33.8% *</td>
</tr>
<tr>
<td>Berg 2006</td>
<td>1</td>
<td>All</td>
<td>39%</td>
</tr>
<tr>
<td>Menon 2011</td>
<td>0.25-1</td>
<td>Mesial Temp</td>
<td>24.8%</td>
</tr>
<tr>
<td>Menon 2012</td>
<td>2</td>
<td>Extratemp</td>
<td>41.5%</td>
</tr>
</tbody>
</table>

AAN Practice Parameter 1996
Neurology 1996; 47:600

May be considered if the pt meets the following profile:
• Seizure free 2 to 5 years on AEDs
  “The longer the seizure free duration, the better the prognosis”
• Single type of partial or generalized seizure
• Normal examination/normal IQ
• EEG normalized with treatment

Pooled relapse rates for Adults: 39%
Pooled relapse rates for Children: 31%
**Discontinuation of AED by Etiology**

**Favorable**
- Idiopathic
- Acute Symptomatic
- Unknown Cause

**Unfavorable**
- Symptomatic
- Remote Symptomatic
- Symptomatic Focal Epilepsies:
  - Mesial Temporal Sclerosis
  - Cortical Malformations
  - Post-Encephalitic

---

**Discontinuation of AED by Epilepsy Syndrome**

<table>
<thead>
<tr>
<th>Childhood Onset</th>
<th>Adolescence to Adult Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable</strong></td>
<td></td>
</tr>
<tr>
<td>Benign Rolandic</td>
<td><em>Oligoepilepsy</em> - Unclassified with few seizures</td>
</tr>
<tr>
<td>Benign Focal Epilepsies of Childhood</td>
<td></td>
</tr>
<tr>
<td>Childhood Absence</td>
<td></td>
</tr>
<tr>
<td><strong>Unfavorable</strong></td>
<td>Juvenile Myoclonic Epilepsy*</td>
</tr>
<tr>
<td>Dravet</td>
<td>Symptomatic Focal epilepsies</td>
</tr>
<tr>
<td>West Lennox-Gastaut</td>
<td></td>
</tr>
</tbody>
</table>

*Long term studies suggest that some patients with JME can remit of medications:*
- Baykan et al, 2008: 5/49 (10%) Mean 10.5 yrs Follow-up
- Camfield, 2009: 6/24 (25%) Mean 16 yrs Follow-up
- Gether et al. 2012: 6/31 (19%) Mean 39 yrs Follow-up
- Sarm et al. 2013: 11/66 (17%) Mean 44 yrs Follow-up

---

**Rate of Drug Withdrawal**

**Faster v Slower**

Ranganthan & Ramarathnam 2006 Cochrane Database Syst Review

Only 1 childhood study compared rapid (over 6 weeks) to slow taper (over 9 months)

"cannot derive any reliable conclusions regarding the optimal rate of tapering of AEDs"

Non-controlled Case Series

 Withdrawal seizures from abruptly stopping barbiturates, benzodiazepines
 Increased GTCS on abruptly stopping carbamazepine, oxcarbazepine
Discontinuation of AED Based on Original Indications after normal/non-epileptiform EEG

- AED started for prophylaxis of Head Trauma or Neurosurgery: withdraw by 1-3 months
- AED started for Single Acute Symptomatic Seizure from Head Trauma, Stroke, Neurosurgery: consider withdrawal after 12 months
- AED started after Single Unprovoked Seizure: withdraw after 1-2 years unless there are risk factors for recurrence
- AED started after First Remote Symptomatic Seizure: treat for 2 years then reconsider
- AED started for ≥2 Unprovoked Seizures: treat 2 years then reconsider
- AED after epilepsy surgery: can consider taper after 1 year (children) to 2 years (adults)

Personal Procedure for AED Discontinuation

Patient discussion and agreement
Advice on driving and activities
EEG while still on treatment
Withdraw one drug at a time
Taper each drug over 6 to 12 weeks or longer, based on dosage, type of medications, circumstances
Follow-up 1-3 months after a drug stopped (optional EEG)

THE END