Generalized epilepsies of unknown and genetic cause

Gregory Krauss, MD
Johns Hopkins University
Goals: Update on treatment of Generalized Epilepsies

1. Review of 1\textsuperscript{st} and 2\textsuperscript{nd} generation therapies
2. Treatment with new antiseizure drugs
3. Exploration of Precision Medicine with individualized therapies
Case #1

- 12-year-old girl experienced her first convulsion while at a pajama party at 8 am
- Stayed up most of the night before
- Had friends awaken to her jerking her arms and legs and then stiffening
- Incontinent of urine
- Lethargic afterwards, confused, generalized headache
- At ER: awakening, headache, non-focal exam; getting back to her normal self
What’s Next?

- Clinical exam
- EEG
- CT
- MRI
- Metabolic studies (Lab)
- Drug screen
- Lumbar puncture
One Week Later at the Neurologist

- Additional history
  - Occasionally “spacey,” but grades remain As and Bs
- Clumsy, particularly in the morning
- Tired, drops things, sometimes jerks after awakening
Case #1 (cont.)

- Sleep deprived EEG: bursts of generalized spike wave, 3 to 4Hz, normal background
- + Photic stimulation and HV induced spikes
MRI and EEG of 12 year old
Case #1 (cont.)

- **Diagnosis:** juvenile myoclonic epilepsy
  - Generalized clonic-tonic seizure
  - Myoclonic jerks
  - Absence

- **Lifetime Treatment**
  - Valproate
  - Lamotrigine
  - Topiramate
  - Levetiracetam
  - Perampanel
  - Zonisamide (*Not FDA approved, widely used*)
Primary Generalized Epilepsy (PGE)

- Non-lesional
- Normal general neurological function
- Often genetic factors
- Generalized seizure types:
  - Absence
  - Myoclonic
  - Tonic-clonic
Frequency of PGE syndromes: UK referral clinics, n=962

<table>
<thead>
<tr>
<th>Other syndromes (n = 250)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic–clonic seizures on awakening</td>
<td>54 (6%)</td>
</tr>
<tr>
<td><strong>Tonic–clonic seizures only</strong></td>
<td>189 (19.6%)</td>
</tr>
<tr>
<td>Pure photosensitive epilepsy</td>
<td>7 (0.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myoclonic epilepsies (n = 424)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>357 (37.1%)</td>
</tr>
<tr>
<td>Idiopathic myoclonic epilepsy</td>
<td>31 (3.2%)</td>
</tr>
<tr>
<td>CAE evolving to JME</td>
<td>25 (2.6%)</td>
</tr>
<tr>
<td>JAE/JME overlap</td>
<td>8 (0.8%)</td>
</tr>
<tr>
<td>Benign myoclonic epilepsy of infancy</td>
<td>3 (0.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absence epilepsies (n = 288)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood absence epilepsy</td>
<td>127 (13.2%)</td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>108 (11.2%)</td>
</tr>
<tr>
<td>Idiopathic absence epilepsy</td>
<td>46 (4.8%)</td>
</tr>
<tr>
<td>Eyelid myoclonia with absences</td>
<td>7 (0.7%)</td>
</tr>
</tbody>
</table>

**Nicolson et al. J Neurol Neurosurg Psychiatry 2004;75:75-9**
Treatment of PGE in UK referral clinics: Percent remission by seizure types

"Typical IGE": IGE with age of onset >3 years and <20 years. "Atypical" IGE: atypical absence and myoclonic epilepsies, or GTC seizures only, outside of the specified age of onset.

Nicolson et al. J Neurol Neurosurg Psychiatry 2004;75:75-9
TMS Hyperexcitability: an “epileptic Trait”

Paired pulse TMS: Indexing GABA A, B, glutamate synaptic activity
Cortical hyperexcitability also in patients with refractory generalized epilepsy & asymptomatic siblings

<table>
<thead>
<tr>
<th>JME</th>
<th>JAE</th>
<th>GE-TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short ISI Recovery Curves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long ISI Recovery Curves</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **JME**: Patients
- **JAE**: Siblings
- **GE-TCS**: Non-epilepsy controls

**Primary Generalized Tonic-Clonic Seizures**

<table>
<thead>
<tr>
<th>Drugs of Choice:</th>
<th>Some Alternatives:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Perampanel</td>
</tr>
</tbody>
</table>

**Absence Seizures**

<table>
<thead>
<tr>
<th>Drugs of Choice:</th>
<th>Some Alternatives:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethosuximide</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Valproate</td>
<td>Clonazepam</td>
</tr>
<tr>
<td></td>
<td>Zonisamide</td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
</tr>
</tbody>
</table>

**Atypical Absence, Myoclonic, Atonic Seizures**

<table>
<thead>
<tr>
<th>Drugs of Choice:</th>
<th>Some Alternatives:</th>
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<tbody>
<tr>
<td>Valproate</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Clonazepam</td>
</tr>
<tr>
<td></td>
<td>Felbamate</td>
</tr>
<tr>
<td></td>
<td>Clobazam</td>
</tr>
<tr>
<td></td>
<td>Rufinamide</td>
</tr>
</tbody>
</table>

1. Some of the drugs listed here have not been approved for such use by the FDA. Approved indications are included in the text.

## Treatment of refractory epilepsy: classification of evidence

<table>
<thead>
<tr>
<th>Rating of recommendation</th>
<th>Rating requirements</th>
<th>Rating of therapeutic article</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong>: established as effective, ineffective, or harmful</td>
<td>Requires at least 1 Class I study or 2 consistent Class II</td>
<td>Class I: Prospective, randomized, blinded, controlled clinical trial</td>
</tr>
<tr>
<td><strong>B</strong>: probably effective, ineffective, or harmful</td>
<td>Requires at least 1 Class II or 3 consistent Class III</td>
<td>Class II: Prospective matched group study with blinding</td>
</tr>
<tr>
<td><strong>C</strong>: possibly effective, ineffective, or harmful</td>
<td>Requires at least 2 consistent Class III studies</td>
<td>Class III: All other controlled trials with outcome assessment ind’t of pt population</td>
</tr>
<tr>
<td><strong>U</strong>: inadequate or conflicting data; unproven treatment</td>
<td></td>
<td>Class IV: Uncontrolled, case series, case reports, etc.</td>
</tr>
</tbody>
</table>

Adapted from French et al. Neurology 2004;62:1261-73
# First-line standard (1982-1989): Valproic Acid (VPA) monotherapy for JME

<table>
<thead>
<tr>
<th>Patients</th>
<th>N=</th>
<th>N=</th>
<th>%</th>
<th>Study Design</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/45 photosensitive, some pretreated</td>
<td>45</td>
<td>31</td>
<td>69</td>
<td>Open trial</td>
<td>1</td>
</tr>
<tr>
<td>15/17 GTCS, some pretreated</td>
<td>17</td>
<td>14</td>
<td>82</td>
<td>Open trial</td>
<td>2</td>
</tr>
<tr>
<td>9/11 GTCS, some pretreated</td>
<td>11</td>
<td>6</td>
<td>55</td>
<td>Case report</td>
<td>3</td>
</tr>
<tr>
<td>22/29 GTCS, 18/29 pretreated</td>
<td>29</td>
<td>28</td>
<td>97</td>
<td>Open trial</td>
<td>4</td>
</tr>
<tr>
<td>22/22 GTCS, untreated</td>
<td>22</td>
<td>21</td>
<td>95</td>
<td>Open trial</td>
<td>5</td>
</tr>
</tbody>
</table>

Janz, 1993

1 Covani et al, 1982  
2 Feuerstein et al, 1983  
3 Asconape, 1984  
4 Franzen, 1988  
5 Christe, 1989
Class I evidence: Topiramate treatment of “primary generalized tonic-clonic seizures”

- Refractory generalized tonic clonic sz
- Randomized (n=80) to treatment with drug or placebo
- 56% responder rate with TOP vs 20% with placebo
- No syndromic classification – 42.5% seizure types inconsistent with PGE (tonic, clonic, “drop”, atypical absence)

Biton V et al. Neurology 1999;52:1330-1337
Topiramate for “primary generalized tonic-clonic seizures”

<table>
<thead>
<tr>
<th>Baseline seizure type</th>
<th>Placebo (n=41)</th>
<th>Topiramate (n=39)</th>
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<tbody>
<tr>
<td>Tonic-Clonic</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Tonic-Clonic only</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Absence</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Tonic</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Drop attack</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Atypical absence</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Clonic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

n = 34

n = 80

Biton V et al. Neurology 1999;52:1330-1337
Juvenile Myoclonic Epilepsy

- Onset at 8-24 years; peak at 12-18 years
- Predominantly morning myoclonus, GTC, occasionally with absence sz
- Aggravating factors – fatigue, sleep deprivation and alcohol consumption
- VPA monotherapy preferred (Penry et al 1989)
- Efficacy of newer AEDs in case series
  - LTG, LEV, TOP, ZON
  - Clonazepam for myoclonic sz
Topiramate for “primary generalized tonic-clonic seizures”

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</tr>
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<td>8</td>
</tr>
<tr>
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</tr>
<tr>
<td>Atypical absence</td>
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<td>2</td>
</tr>
<tr>
<td>Clonic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

n = 80

n = 34

Biton V et al. Neurology 1999;52:1330-1337
Medically Refractory Primary Generalized Epilepsy

- Current definition – Lack of response to VPA
  - (or ETX if absence)
- Problems with diagnosis
  - Inappropriate AED – not drug resistant
  - Misdiagnosed secondary generalized seizures
  - Spectrum of partial/generalized epilepsy
  - Subtle symptomatic epilepsy
  - Non-syndromic seizure types
Time (weeks) to ≥ 50% reduction in PGTC seizure frequency. *P < 0.0001, lamotrigine XR (LTG-XR) versus placebo by log-rank test. The time to ≥ 50% reduction in seizure frequency was defined as the time a patient first achieved and maintained a ≥ 50%...
LEV suppression of photoconvulsive response

Photoconvulsive response, IPS 15, without LEV

Normal EEG, IPS 25, with LEV

Kasteleijn-Nolst Trénité et al, 1996
Levetiracetam – Class III Evidence

Johns Hopkins, Vanderbilt, Birmingham UK study: changes in frequency of generalized seizures

- Seizure free (n=22): 40%
- ≥50% reduction (n=42): 76%
- S.E./discontinued (n=8): 15%
Levetiracetam for PGE – Myoclonic seizure response

Responders  Seizure free  Discontinue

<table>
<thead>
<tr>
<th></th>
<th>LEV</th>
<th>PCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>58%</td>
<td>23%</td>
</tr>
<tr>
<td>Seizure free</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinue</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

International Epilepsy Congress, Paris, 2005
Zonisamide for generalized epilepsy in children in Japan

- New onset or diagnosis, monotherapy: 35/49 (78%) responders
- Drug-resistant, adjunctive: 8/54 (15%) responders
- Lennox-Gastaut: 26-50% responders
- Idiopathic generalized, monotherapy: 8/9 (89%) ‘excellent’ response*

*Baseline 1+ sz/month → seizure-free for 3+ months, or
Baseline <1 sz/month → seizure-free for 3x max seizure-free period

Glauser T, Pellock J. J Child Neurol 2002; 17:87-96
Seki T. Seizure 2004; 13S:S26-S32
Zonisamide – Class III Evidence*

- Biton and Bebin (2002) – Adjunctive therapy in patients with PGE
  - Multicenter, open-label
  - Age range: 4 – 50 years
  - 1-3 concomitant AEDs
  - 8 week titration to max 600mg/day
  - 8 week stable dose
  - Mean dose: 355mg (range 125-500mg)

<table>
<thead>
<tr>
<th></th>
<th>Median decrease in seizure frequency</th>
<th>Responder rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence n = 13</td>
<td>75%</td>
<td>66.7% (?)</td>
</tr>
<tr>
<td>Myoclonic n = 10</td>
<td>27.6%</td>
<td>40%</td>
</tr>
<tr>
<td>Tonic-clonic n = 9</td>
<td>75%</td>
<td>66.7% (?)</td>
</tr>
<tr>
<td>Overall (all types)</td>
<td>22.2%</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

*Also Jose Serratosa and others
Perampanel: A Selective Antagonist for the AMPA Subtype of Glutamate Receptors

5′-(2-cyanophenyl)-1′-phenyl-2,3′-bipyridinyl-6′(1′H)-one

Copyright © 2005 Lippincott Williams & Wilkins - All Rights Reserved.
PGTC Seizures: Change in Seizure Frequency per 28 Days\textsuperscript{a} and Seizure Freedom

Median change in PGTC Seizure Frequency per 28 Days

- Placebo (n=81): 38.4%
- Perampanel (n=81): 76.5%

Completed Maintenance seizure free

- Placebo (n=81): 13.9% (n=10)
- Perampanel (n=81): 36.8% (n=25)

\textit{Median percent change during Titration and Maintenance Periods vs Baseline}
Lacosamide: treatment for PGTCS

- Open-label pilot study: Tonic-Clonic, Myoclonic, Absence
- 16 weeks baseline (12-week retrospective, 4-week prospective)
- 6-week maintenance treatment (400 mg/day target dose)

**Results**
- 49 enrolled; 29 (74%) completed extension study

<table>
<thead>
<tr>
<th></th>
<th>Baseline Frequency (median)</th>
<th>Treatment Frequency (median)</th>
<th>Median Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absences (N=49)</td>
<td>4.65 ± 8.48</td>
<td>4.54 ± 9.13</td>
<td>0 days</td>
</tr>
<tr>
<td>Myoclonic (N=49)</td>
<td>4.66 ± 7.98</td>
<td>1.70 ± 5.08</td>
<td>0 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline Frequency (mean)</th>
<th>Change during Treatment (mean)</th>
<th>% Change</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-Clonic (N=49)</td>
<td>0.59 ± 1.18</td>
<td>−0.27 ± 1.05</td>
<td>−26.37% ± 156.16%</td>
<td>-100 – 700%</td>
</tr>
</tbody>
</table>

*N=25 No GTCs > 6 mo

Clobazam for Lennox Gastaut Syndrome:

Ng Y et al. Neurology 2011;77:1473-1481

©2011 by Lippincott Williams & Wilkins
SANAD: Time to exit (treatment failure) for generalized epilepsy therapy
AEDs: prevalence of major malformations

The North American AED Pregnancy Registry
Patient Profile-JME

Patient Factors

- New onset vs refractory
- Seizure type G/P - Etiology
- Other meds-
- Co-morbid conditions - no
- Age- 16, Gender - F
- Childbearing age - yes
- Compliance - ?

Drug Factors

- Side effects
  - Emergent
  - Dose related 😞
  - Idiosyncratic
  - Long term 😞
- Drug interactions 😞
- Ease of use 😊
- Escalation
- MOA

Levetiracetam
- Lamotrigine
- Zonisamide

Topiramate
- Valproate**
  [10% birth defect; inc.IQ decrease]
- Perampanel
Patient Profile

**Patient Factors**
- New onset vs refractory
- Seizure type G/P - Etiology
- Other AEDs – LEV, LTG
- Co-morbid conditions - no
- Age – 25-Male
- Childbearing age - no
- Compliance - ?

**Drug Factors**
- Side effects
  - Emergent
  - Dose related ☹
  - Idiosyncratic
  - Long term 😄
- Drug interactions ☹
- Ease of use 😊
- Escalation
- MOA
  - Valproic acid
  - Zonisamide
  - Perampanel
  - Topiramate
Apparent “medical-resistance” due to inappropriate drug selection

- Benbadis et al (2003) -
  - 58 patients with EEG-confirmed IGE
  - 28/58 (48%) were being treated with inappropriate AEDS (gabapentin, carbamazepine, tiagabine, etc)
  - Similar findings; marked response with VPA conversion (Panayiotopoulos)

Limitations of Syndromic Classification

- Tonic-clonic seizures
- Adult/early childhood absences
- Myoclonus without GTC
- Genotypic and phenotypic variability (e.g. GEF+)
- Subtle symptomatic (mild cognitive impairment)
Focal features in PGE: video-EEG study

- Retrospective review of 20 consecutive PGE patients
- Video-EEG monitoring:
  - 7/20 (35%) – Focal IEDs
  - 6/20 (30%) – Intermittent temporal slow waves
  - 7/20 (35%) – Focal clinical signs

GENETIC INFLUENCES IN >50% OF THE EPILEPSIES

Epi4K consortium:

Figure 1. Primary model analysis of familial genetic generalised epilepsy. The quantile-quantile plot for the 18,668 protein-coding genes had at least one case or control carrier (table 1). Qualifying variants were defined as a minor allele frequency of less than...

Ultra-rare genetic variation in common epilepsies: a case-control sequencing study

null, Volume 16, Issue 2, 2017, 135–143

http://dx.doi.org/10.1016/S1474-4422(16)30359-3
1) Excess ultra-rare variants in non familial IGE, links the genetics of common and rare, severe epilepsies

2) the variants responsible for epilepsy risk are exceptionally rare in the general population.

3) the emerging paradigm of targeting of treatments to the genetic cause in rare devastating epilepsies might also extend to a proportion of common epilepsies.

4) may allow clinicians to broadly explain the cause of these syndromes, and lay the foundation for possible precision treatments in the future.

Lancet Neurol. 2017 Feb;16(2):135-143.
Ethnically diverse sample: black
Epilepsy cases: yellow
Epi4K genetic analysis limited to European ancestry node B.
The genetic research results indicate whether a specific mutation phenotype has been identified and provides basic details on the functional consequences.

A description of the experimental data are provided along with details comparing the function of the mutated protein to the healthy protein.
The genetic research results indicate whether drugs have been identified that can address the functional consequence conferred by the genetic mutation. A list of the top compounds are provided with mechanisms of action(s) and associated drug classes. A list of antiepileptic drugs are categorized by extent of response.

Example: 5000 common drugs screened in “gain of function” variant inserted into neuronal culture: amitryptiline corrected channel dysfunction and N=1 clinical trial implemented by treating physician.
Summary: Medical refractory PGE (failed VPA or ETX)

- **Class I evidence:**
  - TOP $\rightarrow$ T-C
  - LTG $\rightarrow$ absence, T-C; ? JME
  - LEV $\rightarrow$ JME myoclonic & TC
  - Perampanel: IGE TC

- **Preliminary evidence:**
  - ZON: myoclonus, IGE TC, JME