Epilepsy – 2005 ILAE Report

• Seizure = a symptom
  – Defined as paroxysmal change in behavior due to abnormal electrical activity in the brain

• Epilepsy = a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition.

Fisher et al (2013). Epilepsia
A practical clinical definition of epilepsy—2013 ILAE Report

Epilepsy: a disease of the brain defined by any of the following conditions:

- 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

Fisher, R. et al. 2013. Epilepsia

Evidence based medicine:

Risks for recurring seizures after medical or surgical treatment for cavernous angioma with seizures

Chance of seizure freedom over 5 years of follow-up (3% surgery morbidity)  
Dammann P. J Neurosurg 2016
Seizure Classifications

Complex partial seizure with secondary generalization:
Causes of focal & generalized epilepsy: Evolving Understanding


Multiple microdeletions increase risks for GGE + mild intellectual disability (ID)

Mullen et al. *Neurology* 2013; 81: 1507-1514
CNV Inheritance is Complex and Varied in Patients with Both GGE and ID

Variable penetrance & expression in genetic generalized epilepsy:

Penetrance is defined as the percentage of individuals with a given genotype who exhibit the phenotype associated with that genotype.
Expressivity measures the extent to which a given genotype is expressed at the phenotypic level.
Treatment Options

Generalized Onset
  - Old
    • Valproate (VPA)
    • Phenobarbital (PHB)
  - New
    • Lamotrigine (LTG)
    • Topiramate (TPM)
    • Zonisimide (ZNA)
    • Levetiracetam (LVT)
    • Perampanel (PER)

Partial Onset
  - Old
    • Phenytoin (PHT)
    • Carbamazepine (CBZ)
    • Phenobarbital (PHB)
    • Valproate (VPA)
  - New
    • Tiagabine (TGB)
    • Levetiracetam (LVT)
    • Lamotrigine (LTG)
    • Gabapentin (GBP)
    • Topiramate (TPM)
    • Oxcarbazepine (OXC)
    • Zonisimide (ZNA)
    • Pregabalin (PGB)
    • Lacosamide (LCS)
    • Retigabine (EZB)
    • Eslicarbazepine (ESL)
    • Perampanel (PER)

Mixed (Lennox-Gastaut)
  • Rufinamide
  • Clobazam
  • CBD

AED Efficacy

Newly diagnosed epilepsy n=470

1st AED
  • Seizure-free 47%
  • Uncontrolled seizures 53%

2nd AED
  • Seizure-free 13%
  • Uncontrolled seizures 40%

3rd AED
  • Seizure-free 1%
  • Uncontrolled seizures 39%

Duotherapy
  • Seizure-free 3%
  • Uncontrolled seizures 36%

Quality of life in Epilepsy: Decreases with adverse medication effect & depression

Gilliam. Neurology 2002;58:S9-S20

Anti-Seizure Medications

ASMs

Calendar year

1840 1860 1880 1900 1920 1940 1960 1980 2000

Bromide Phenobarbital Phenytoin Primidone

Carbamazepine Benzodiazepines
Patient Profile: individualized therapy

**Patient Factors**
- New onset vs refractory
- Seizure type G/P - Etiology
- Other meds - yes
- Co-morbid conditions - yes
- Age - 75
- Childbearing age
- Compliance

**Drug Factors**
- Side effects
  - Emergent
  - Dose related 😊
  - Idiosyncratic
  - Long term
- Drug interactions 😐
- Ease of use
- Escalation
  - Lamotrigine
  - Levetiracetam
  - Lacosamide

Caution with new Antiseizure drugs: Ezogabine/Retigabine

- > 2 yrs exposure, 10%: sclera, conjunctive, lips, nail beds and scattered
- Retinal pigment clumping, 30%
- Urinary retention: 2%

Garin S TJAMA Dermatol. 2014
Quarterly use and cost of AEDs used to treat epilepsy

IMS National Prescription Audit (NPA), IMS National Sales Perspective (NSP), and IMS National Drug and Therapeutic Index (NDTI).

Think Twice Before Switching Medications

The Epilepsy Foundation, www.epilepsyfoundation.org
## Generic Drug Costs at JHH

Price ranges for generic and brand AEDs per pill at Johns Hopkins Outpatient & Moore Clinic Pharmacies

<table>
<thead>
<tr>
<th>AED (Brand Name)</th>
<th>Generic</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine 200 mg (Tegretol)</td>
<td>$0.14</td>
<td>$1.03</td>
</tr>
<tr>
<td>Divalproex 250 mg (Depakote)</td>
<td>$0.19</td>
<td>$1.93</td>
</tr>
<tr>
<td>Gabapentin 600 mg (Neurontin)</td>
<td>$0.35</td>
<td>$3.52</td>
</tr>
<tr>
<td>Lamotrigine 25 mg (Lamictal)</td>
<td>$0.20</td>
<td>$4.86</td>
</tr>
<tr>
<td>Levetiracetam 250mg (Keppra)</td>
<td>$0.47</td>
<td>$3.54</td>
</tr>
<tr>
<td>Oxcarbazepine 600 mg (Trileptal)</td>
<td>$1.18</td>
<td>$6.25</td>
</tr>
<tr>
<td>Topiramate 25mg (Topamax)</td>
<td>$0.15</td>
<td>$2.85</td>
</tr>
<tr>
<td>Zonisamide 100 mg (Zonegran)</td>
<td>$0.32</td>
<td>$3.22</td>
</tr>
<tr>
<td>Levetiracetam ER (Keppra XR)</td>
<td>$1.00</td>
<td>$3.88</td>
</tr>
</tbody>
</table>

Source: www.rxpricequotes.com accessed May 11, 2010

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## Case series: seizures after Dilantin substitution

BE study: Taro generic carbamazepine (ANDA 074649)

Bioequivalence Using 400 mg Oral Dose (2x200 mg tablets) of Carbamazepine

Figure 2 – (C/D)
**Modified release-AEDs: Increased Food effects compared to IR**

**AUC of generic/reference products: Fasting & Fed BE studies (hr*ng/ml)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Modified release-AEDs: Increased Food effects compared to IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>0%</td>
</tr>
<tr>
<td>VPA</td>
<td>5%</td>
</tr>
<tr>
<td>GBP</td>
<td>10%</td>
</tr>
<tr>
<td>LTG</td>
<td>15%</td>
</tr>
<tr>
<td>LEV</td>
<td>20%</td>
</tr>
<tr>
<td>OXC</td>
<td>25%</td>
</tr>
<tr>
<td>TOP</td>
<td>30%</td>
</tr>
<tr>
<td>ZON</td>
<td>35%</td>
</tr>
<tr>
<td>Total (all drugs)</td>
<td>40%</td>
</tr>
</tbody>
</table>
Generic lamotrigine versus brand-name Lamictal in patients with epilepsy

Conclusions: generic antiseizure drugs

- Generic products are typically 75% cheaper than reference products and so should be used by most patients.
- Individual patients with seizures or possible adverse drug effects after formulation changes can be evaluated with seizure and pill-taking diaries & levels.
- Individual dosing needs often dominate possible product switching effects.
- A small number of AEDs have complex kinetics (phenytoin) or variable absorption (carbamazepine)—it may be best to use single formulations of modified release formulations of these drugs along with careful clinical monitoring.
New Surgical & Stimulation Approaches

- Laser ablation of amygdala/hippocampus for temporal lobe epilepsy & focal epileptogenic lesions
- Responsive neural stimulation for non-resectable focal epilepsy (critical motor/language cortex; two foci)

Thermal Ablation

- Stereotactic placement of probe to ablate small targets in brain responsible for seizures
- Hippocampal sclerosis
- Periventricular nodular heterotopia
- Cortical dysplasia
Ablation 1

Test Dose
3W for 32 sec

Laser Doses
10W for 170 sec
12W for 63 sec

Irreversible Damage Estimate
19mm by 13mm

Procedure Verification

Target Area
Irreversible Damage Estimate
Ablation

Pre-procedure Axial images
Visualase Image
Post-procedure
Patient #2

• Principles:
  • Select new AEDs by side-effect and efficacy profile: match to Pt.
    – lamotrigine not potent against seizures, but mild epilepsy
    – few cognitive side-effects
    – appropriate for patient
  • Allergic rx: variation between standard/new AEDs

Neurostimulation for Epilepsy 2015

• Responsive neurostimulation (RNS™, Neuropace)
  – Safety and tolerability demonstrated in unblinded study that suggested efficacy
  – Recruitment 191 patients at 32 sites completed pivotal trial
  – Statistically significant reduction in seizures, 29% reduction in seizures during last 2 months of blinded period
  – FDA approval
Heterotopias

RNS Implant - JHMI

3 subdural strip arrays
1 depth array

JH RNS
Study Group

Memory chip
(EEG storage)

Mix signal (analog) chip
(takes in signals/digitizes/sends to digital chip)

Digital processor (100 kHz)

Implantable RNS

3.5 cm

Memory chip (EEG storage)
Seizure detection
Using proprietary software algorithms

Detection of spontaneous seizure triggers stimulation

Responsive stimulation

Current issues in epilepsy:

• Epilepsy and the elderly:
  – Most common group newly diagnosed with epilepsy
  – Special treatment considerations
  – Treat underlying vascular & health causes
• Sudden unexpected death with epilepsy (SUDEP)
  – Sudden death, usually nocturnal during seizures
  – 1/500 risk per year (1% per year if uncontrolled epilepsy)
  – Identifying risks & prevention

October 31, 2016
Incidences of Unprovoked Seizures in Developed Countries

“Microvascular” disease in “young” elderly patient with complex partial seizures

Exercise training increases size of hippocampus and improves memory in the Elderly

*Exercise induced increase in hippocampal volume is correlated with increase in serum BDNF, a mediator of neurogenesis in the dentate gyrus

Erickson et al. PNAS, 2011; 108: 3017-3022
Sudden unexpected death in epilepsy: Cumulative Risk of SUDEP from age of epilepsy onset


Sudden unexpected death in epilepsy (SUDEP)

• Tonic clonic seizures produce:
  – O2 desaturation
  – Post-ictal generalized EEG suppression
  – Peri-ictal autonomic alterations
• Patients sleeping facedown:
  – Immobility during post-ictal suppression period
  – Suffocation & apnea with post-ictal hypoxemia
  – Cardiac arrhythmias, need for resuscitation
• Role for seizure detection devices & intervention

October 31, 2016
EpiWatch research app

October 31, 2016

Seizure Detection:
Non-EEG seizure detection

• Alerting and logging (mobile devices)
  – Emergency care delivery, SUDEP intervention
  – Seizure frequency, triggers
  – Medication adherence and side effects

• Detect clinical manifestations
  – Convulsions, shaking (accelerometer)
  – Falls (gyroscope)
  – Heart rate increase in 80% (PPG)
  – Unresponsiveness (interactive UI)
US EpiWatch research participants

% change between initial HR and max HR

Legend
- Tonic Clonic (N=73)
- Complex Partial (N=172)
Seizure related movements & heart rate changes measured with EpiWatch

SUDEP Intervention

Caregiver Interventions:
- Turn on side
- Stimulate

Resuscitate

DANGER
Low Oxygen level
Summary:

- Epilepsy “disease” has special stigma/social challenges
- Many new medical & surgical treatments available for 40% with medication resistant epilepsy
- Changing demographic landscape: elderly
- Individual risk monitoring: SUDEP