Pharmacological Treatment of Non-Lesional 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</td>
<td>DSMB</td>
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<tr>
<td>Lilly</td>
<td>DSMB</td>
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<tr>
<td>Neuren Pharma</td>
<td>Research</td>
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<td>UCB</td>
<td>Research</td>
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Learning Objectives

• Understand current data on relative efficacy of antiepileptic drugs

• Understand use of broad spectrum antiepileptic drugs in non-lesional medication resistant epilepsy
ILAE Definition of Medication Resistant

Failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom
Verify Epilepsy Diagnosis and Identify Other Triggers

- Seizures vs non-epileptic (video/EEG)
- Partial vs generalized onset (video/EEG)
- Is a structural lesion present?
- Are other meds lowering threshold?
- Are illicit drugs or alcohol contributing?
- Is sleep deprivation occurring?
Should There Be a Difference In the Pharmacological Approach to These 3 Medication Resistant Patients?
Choosing Drugs for the Non-lesional Pre-surgical Patient

- Mechanism of action.
- Efficacy in clinical trials.
- Pharmacokinetics.
- Adverse effect profile.
<table>
<thead>
<tr>
<th>AED(s)</th>
<th>Sodium Channel</th>
<th>GABA</th>
<th>Excitatory Amino Acids/Other</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>+/-</td>
<td>alpha-2-delta</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Topiramate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vigabatrín</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>++</td>
<td></td>
<td>SV2A</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>++ (slow inactivation)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Ezogabine</td>
<td>K^+ channel</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Benzo</td>
<td></td>
<td>+</td>
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What do clinical trials say about choosing drugs based on mechanism of action?
Choosing Drugs for the Non-lesional Pre-surgical Patient

- **Mechanism of action.**
  - Make sure the patient has failed trials of drugs with different mechanisms of action
- **Efficacy in clinical trials.**
- **Pharmacokinetics.**
- **Adverse effect profile.**
Choosing Drugs for the Non-lesional Pre-surgical Patient

- Mechanism of action.
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Choosing Drugs for the Non-lesional Pre-surgical Patient

- Mechanism of action.
- Efficacy in clinical trials
  - Meta-analysis of RCT
  - Broad spectrum
- Pharmacokinetics.
- Adverse effect profile.
Comparisons Among AEDs: No Clear Choices for Focal Seizures

- Meta-analysis: Statistical analysis that combines or integrates results of several independent clinical trials
- Meta-analyses have shown trends without clear statistical “winners”
- Head to head trials:
  - VA COOP (recently diagnosed) phenytoin, carbamazepine superior to phenobarbital and primidone
  - VA COOP carbamazepine superior to valproate
  - Many non-inferiority studies, mostly in new onset
Summary ORs Generated Using a Fixed-Effects Model

Odds Ratio (95% CI), Log scale

50% Responders: New AEDs and Valproate

Odds Ratio for 50% Responders (95% CIs), Log scale

GBP: 2.29
LTG: 2.32
TGB: 3.03
TPM: 4.22
VPA: 3.33

50% Responders: New AEDs and Valproate

Meta-Analysis

LEV

OXC

ZNS

VNS

Odds Ratio for 50% Responders (95% CIs), Log scale

Marson AG Cochrane Collaboration 2001
Recent Meta-analysis of Antiepileptic Drugs (Bodalia 2013)
Caveats of Meta-analysis

- Relies on doses and titrations chosen for RCT, which may differ among grouped studies
- Populations may differ
- No qualifying studies for carbamazepine, phenytoin, or phenobarbital
- Most effective AEDs for seizures were usually least well tolerated
Could our patient with medication resistant non-lesional epilepsy have a misdiagnosed generalized epilepsy syndrome?
What Is Broad Spectrum Efficacy?

- Implies efficacy in both focal and generalized onset seizures (or no worsening)
- Useful if unsure of seizure type or syndrome, e.g., few seizures and normal evaluation
- Generalized onset patients may have focal EEG features, and focal onset patients may have EEG secondary bilateral synchrony

*Did our patient have adequate trials of one or more broad spectrum drugs?*
Secondary Bilateral Synchrony Mimics Generalized Onset

- Tukel and Jasper (1952)
  - 31 cases with parasaggital lesions and bilaterally synchronous spike-wave
  - Coined term: “secondary bilateral synchrony”

- Blume and Pillay (1985)
  - 57 cases of focal epilepsy with generalized discharges
  - Postulated multifocal lesions in most
Generalized Onset Epilepsy EEGs May Have “Focal” Features

- Many reports of focal EEG features in Juvenile Myoclonic Epilepsy
- Szaflarski et al (2013) used EEG-fMRI to show that generalized onset patients with valproate resistance had different localization of the generalized spike wave generators
- Sakurai et al (2010) used MEG to show focal default mode network initiation of spike wave in juvenile absence
- Matur et al (2009) found 34% of adults with IGE and absence had focal EEG
EEG: Focal vs Generalized

Image courtesy of J. Szaflarski, MD.
Not All AEDs Have Broad Spectrum Efficacy, But These Do (RCT)

- **Topiramate:**
  - new onset mixed population of partial and generalized onset
    TPM=CBZ=VPA
  - Lennox-Gastaut Syndrome
  - primary GTC

- **Levetiracetam:**
  - myoclonus with Juvenile Myoclonic Epilepsy and primary GTC

- **Lamotrigine:**
  - new onset mixed population of partial and generalized onset
    LTG=CBZ=PHT=VPA
  - Lennox-Gastaut Syndrome
  - Primary GTC

- **Valproate:**
  - effective in multiple syndromes but limited controlled trial data

- **Zonisamide:**
  - open label reports (Japan) but limited controlled trial data

- **Rufinamide, felbamate and clobazam:**
  - effective in Lennox Gastaut syndrome
Choosing Drugs for the Non-lesional Pre-surgical Patient

- Mechanism of action
- Efficacy in clinical trials
  - Make sure patient has failed several efficacious drugs
  - Make sure patient has failed one or more broad spectrum drugs
- Pharmacokinetics
- Adverse effect profile
Choosing Drugs for the Non-lesional Pre-surgical Patient

- Mechanism of action.
- Efficacy in clinical trials.
- Pharmacokinetics
  - Document adequate levels
- Adverse effect profile.
Choosing Drugs for the Non-lesional Pre-surgical Patient

- Mechanism of action.
- Efficacy in clinical trials.
- Pharmacokinetics.
- Adverse effect profile
  - Maximally tolerated doses, not just maximal recommended
  - Don’t count a drug failure due to idiosyncratic adverse effects
Choosing Drugs for the Non-lesional Pre-surgical Patient

- **Mechanism of action**
  - Make sure the patient has failed trials of drugs with different mechanisms of action

- **Efficacy in clinical trials**
  - Make sure patient has failed several efficacious drugs
  - Make sure patient has failed one or more broad spectrum drugs

- **Pharmacokinetics**
  - Document adequate blood levels

- **Adverse effect profile**
  - Maximally tolerated doses, not just maximal recommended
  - Don’t count a drug failure due to idiosyncratic adverse effects