Emerging Trends in Epilepsy Medications: Choosing the Most Appropriate AED

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Incidence and Prevalence of Epilepsy in the United States

Community incidence¹: Rochester, Minn (1935–1984)

- Epilepsy affects more than 3 million people²
- 200,000 new cases of epilepsy diagnosed annually²

Choosing an Antiepileptic Drug (AED)

- Seizure type
- Epilepsy syndrome
- Pharmacokinetics
  - Drug interactions
  - formulation
- Concomitant medical/psychiatric conditions
- Adverse effects
- Cost
Success in AED regimens

Seizure free 47%
Monotherapy first AED

Not seizure free 36%
All regimens attempted

Seizure free 13%
Monotherapy 2nd AED

Seizure free 1%
Monotherapy 3rd AED

Seizure free 3%
Polytherapy

When Monotherapy Fails……..

Seizure Freedom with Adjunctive Therapy or Substitution Monotherapy in Patients with Inadequate Seizure Control on First Well-Tolerated AED

Patients (%)

<table>
<thead>
<tr>
<th>1st Failed AED + Adjunctive AED (n=42)</th>
<th>Substitution Monotherapy (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Factors Governing Neuronal Excitability

- Enhanced excitation (e.g., glutamate)
- $\text{Na}^+$ and $\text{Ca}^{2+}$-mediated currents (APs, PDS)
- Reduced inhibition (e.g., GABA)
- $\text{K}^+$ currents (membrane hyperpolarization)
- Changes in extracellular ionic fields ($\uparrow\text{K}^+$, $\downarrow\text{Ca}^{2+}$, change in extracellular space, etc.)
- Changes in pH (acidosis/alkalosis)
AED Mechanisms of Action

Inhibitory Synapse

- GABA
- GABA_A
- Cl^-
- Na^+
- K^+
- VGPC
- VGSC

Excitatory Synapse

- Glutamate
- AMPA
- NMDA
- mGluR
- Ca^{2+}
- Na^+
- SV2A
- VGCC
- VGSC

Intracellular signaling pathways regulating excitability in the postsynaptic neuron

VGSC = voltage-gated sodium channel; SV2A = synaptic vesicle protein; VGCC = voltage-gated calcium channel; VGPC = voltage-gated potassium channel; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate receptor; mGluR = metabotropic glutamate receptor.

Comorbid Disorders in Older Veterans with Epilepsy

- Dyslipidemia: 80%
- Hypertension: 53.8%
- Stroke: 52.7%
- Cardiac disease: 48.1%
- Diabetes: 28.3%
- Cancer: 23.8%
- Psychiatric disease: 21.6%
- Renal disease: 12.3%
- Liver disease: 2.7%
- Parkinson’s disease: 2.7%

Ramsay et al Epilepsia 2002;35(Suppl 8):91
Polypharmacy in Patients with Epilepsy: Age & Gender Effects

Mean Number Concomitant Meds

Years of Age

Gidal, French, Grossman Neurology 2009
Concomitant Medication use by Age

Favorable Tolerability and Convenient Dosing Are Essential for Compliance

Leading Cause of Noncompliance in Epilepsy Patients (n=102)

- Dosing Frequency: 25%
- Poor Tolerability: 55%
- Dosing Frequency and Poor Tolerability Equally: 20%

Noncompliance with AEDs is a major factor in breakthrough seizures and recurrence of seizures. Higher compliance rates are associated with QD dosing.

N = 24 patients followed for 2 to 37 weeks.

# Dosing Frequency & Medication Adherence in Chronic Disease

**TABLE 3** Traditional Meta-Analysis of Dosing Frequency Analyses of Taking, Regimen, and Timing Adherence

<table>
<thead>
<tr>
<th>Frequency of Dosing</th>
<th>N (% Groups [N of Patients] in Taking Adherence Analysis)</th>
<th>Taking Adherenceb (95% CI)</th>
<th>N (% Groups [N of Patients] in Regimen Adherence Analysis)</th>
<th>Regimen Adherencec (95% CI)</th>
<th>N (% Groups [N of Patients] in Timing Adherence Analysis)</th>
<th>Timing Adherenced (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily</td>
<td>33 (50.8) [n = 2,006]</td>
<td>93.0 (91.2-94.7)</td>
<td>35 (46.1) [n = 2,118]</td>
<td>81.8 (77.9-85.7)</td>
<td>20 (42.6) [n = 936]</td>
<td>76.9 (72.5-81.3)</td>
</tr>
<tr>
<td>Twice daily</td>
<td>22 (33.8) [n = 1,259]</td>
<td>85.6 (82.5-88.8)</td>
<td>24 (31.6) [n = 826]</td>
<td>74.2 (70.0-78.5)</td>
<td>16 (34.0) [n = 650]</td>
<td>59.3 (40.6-58.0)</td>
</tr>
<tr>
<td>Three times daily</td>
<td>9 (13.8) [n = 362]</td>
<td>80.1 (72.0-88.2)</td>
<td>13 (17.1) [n = 321]</td>
<td>62.8 (55.4-70.1)</td>
<td>8 (17.0) [n = 343]</td>
<td>35.9 (21.8-50.1)</td>
</tr>
<tr>
<td>Four times daily</td>
<td>1 (1.5) [n = 57]</td>
<td>84.4 (78.5-90.3)</td>
<td>4 (5.3) [n = 86]</td>
<td>68.2 (48.9-87.4)</td>
<td>3 (6.4) [n = 109]</td>
<td>18.8 (10.1-27.5)</td>
</tr>
</tbody>
</table>
AED Nonadherence Is Associated with Serious Clinical Events and Increased Medical Costs

Compared with adherent behavior, nonadherence is associated with:

- Threefold increased risk of death (HR, 3.32; 95% CI, 3.11-3.54; \( P < 0.001 \))
- Annual increase of over $2000 per patient in emergency department and inpatient costs (\( P = 0.001 \))

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence Rate Nonadherent</th>
<th>Incidence Rate Adherent</th>
<th>Ratio of Nonadherence to Adherence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED visits</td>
<td>1.48</td>
<td>0.99</td>
<td>1.50 (1.49-1.52)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1.34</td>
<td>0.72</td>
<td>1.86 (1.84-1.88)</td>
</tr>
<tr>
<td>MVA injuries</td>
<td>0.011</td>
<td>0.005</td>
<td>2.08 (1.81-2.39)</td>
</tr>
<tr>
<td>Fractures</td>
<td>0.54</td>
<td>0.45</td>
<td>1.21 (1.18-1.23)</td>
</tr>
<tr>
<td>Head injuries</td>
<td>0.37</td>
<td>0.50</td>
<td>0.73 (0.72-0.75)</td>
</tr>
</tbody>
</table>
ER vs IR
Theoretical Considerations

New AED Options
Ezogabine: Overview

- International non-proprietary name is retigabine
- FDA requested US non-proprietary name changed to ezogabine due to similarity to another product
  - Brand name filed with FDA is Potiga™ (Trobalt™ rest of world)
- Co-development between Valeant and GSK
- Submitted to FDA and EMA in October, 2009 for partial onset seizures
  - EMA granted approval on March 28, 2011 as adjunctive therapy for POS in adults aged 18 and older with epilepsy
  - GSK and Valeant submitted response to FDA “complete response letter” on April 15, 2011
- Extended release formulation is in development
Ezogabine: Mechanism of Action

First-in-class MOA:

- Ezogabine acts primarily through opening of neural voltage-gated potassium channels KCNQ2 and KCNQ3 (aka Kv7.2 and Kv7.3)
  - Genetic studies have found mutations in KCNQ2 and KCNQ3 that lead to benign familial neonatal seizures
- Kv7 channel family consists of five members that regulate the M current that opposes other depolarizing input to control neuron excitability
  - Ezogabine stabilizes Kv7 channels in open conformation, enhancing M current and hyperpolarizing the neuron
  - Ezogabine binds Kv7.2 through Kv7.5 potassium channels
    - Expression of the Kv7 channels in heart tissue and smooth muscle may be reasons for QT prolongation and urinary bladder issues


Ezogabine Pivotal Trials Primary Efficacy Endpoints: Median Percent Reduction in Seizure Frequency

**Median Reduction**

- Study 205: 13.1%, 23.4%, 29.3%, 44.3%
- Study 301: 17.5%, 27.9%, 39.9%, 35.2%, 44.3%
- Study 302: 15.9%, 20%, 27.9%, 39.9%

FDA EZG backgrounder: Food and Drug Administration, Center for Drug Evaluation and Research (CDER), *Peripheral and Central Nervous System Drugs Advisory Committee Meeting*, Potiga (ezogabine) Tablets Background Package, August 11, 2010.
## Ezogabine Pivotal Trials: Common Adverse Events ≥10%

### Incidence of AEs Across Controlled Epilepsy Trials

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=427)</th>
<th>EZG 600 mg/day (n=281)</th>
<th>EZG 900 mg/day (n=273)</th>
<th>EZG 1200 mg/day (n=259)</th>
<th>EZG TOTAL (n=813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>14.6</td>
<td>23</td>
<td>32</td>
<td>23.2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>12</td>
<td>15</td>
<td>24.5</td>
<td>26.6</td>
<td>22.0</td>
</tr>
<tr>
<td>Confusional State</td>
<td>2.6</td>
<td>4</td>
<td>7.7</td>
<td>16</td>
<td>9.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td>14.7</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>2.5</td>
<td>9.5</td>
<td>12.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Coordination</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>11.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>2</td>
<td>2</td>
<td>4.4</td>
<td>10.4</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**FDA EZG backgrounder:** Food and Drug Administration, Center for Drug Evaluation and Research (CDER), *Peripheral and Central Nervous System Drugs Advisory Committee Meeting*, Potiga (ezogabine) Tablets Background Package, August 11, 2010.
Preclinical studies with EZG demonstrated distended bladders and some with renal lesions believed to be secondary to voiding dysfunction and urinary retention

- Led to close monitoring of urinary function (including post-residual voiding) in trials

Renal and urinary disorder AEs were reported for greater proportions of patients in the EZG group than PBO group (17% vs. 12.9%) and may be dose-related

There were 5 SAE in 4 EZG-treated patients related to the urinary system (vs. 1 PBO)

- SAE included renal colic, urinary retention, and atonic bladder (patients continued treatment), and renal failure and urinary incontinence (discontinued treatment)
- One patient developed permanent sequelae from urinary retention and now has an apparent need for permanent need for self-catheterization
Perampanel (Fycompa): Mechanism of Action

**MOA:**

- Highly selective noncompetitive AMPA glutamate receptor antagonist
- Low affinity for kainate and NMDA receptors
- No competition with radio-labeled AMPA for binding to AMPA-type glutamate receptor
- Inhibits AMPA-induced increase in intracellular Ca\(^+\) in rat cortical neurons

### Perampanel (306) Adverse Events

**Incidence of treatment-emergent adverse events (TEAEs) (safety population)**

<table>
<thead>
<tr>
<th>TEAEs in &gt;5% of patients in any treatment group</th>
<th>Placebo (n = 185)</th>
<th>Perampanel 2 mg (n = 180)</th>
<th>Perampanel 4 mg (n = 172)</th>
<th>Perampanel 8 mg (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>18 (9.7)</td>
<td>18 (10.0)</td>
<td>28 (16.3)</td>
<td>45 (26.6)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>12 (6.5)</td>
<td>22 (12.2)</td>
<td>16 (9.3)</td>
<td>27 (16.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (8.6)</td>
<td>16 (8.9)</td>
<td>19 (11.0)</td>
<td>18 (10.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (2.7)</td>
<td>8 (4.4)</td>
<td>13 (7.6)</td>
<td>9 (5.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (2.7)</td>
<td>11 (6.1)</td>
<td>6 (3.5)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (1.6)</td>
<td>7 (3.9)</td>
<td>9 (5.2)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2 (1.1)</td>
<td>1 (&lt;1)</td>
<td>2 (1.2)</td>
<td>9 (5.3)</td>
</tr>
</tbody>
</table>

**WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS**

Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA. These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression.

Closely monitor patients particularly during the titration period and at higher doses.
Eslicarbazepine Acetate
Under Review: FDA
Eslicarbazepine: Overview

- Development and marketing by Sunovion

- NDA submitted to FDA in March 2009 based on 3 ex-US studies
  - FDA issued a Complete Response Letter in May 2010, reportedly requesting further studies that include US patients
  - US Phase III study recently initiated to support its NDA
  - Brand name filed with FDA is Stedesa™

Approved by EMA in April 2009 to market the
Eslicarbazepine: Chemical Structure

- Shares dibenzazepine nucleus with CBZ and OXC, but with 5-carboxamide substitute.
- ESL is structurally different at the 10,11 position.
  - Carbamazepine-10,11-epoxide believed partly responsible for adverse effects of CBZ.
Eslicarbazepine: Mechanism of Action

MOA:

- Binds and blocks voltage-gated Na\(^+\) channels
- Same drug class as carbamazepine and oxcarbazepine
- Compared with carbamazepine, oxcarbazepine, and R-licarbazepine, the S-enantiomer of licarbazepine (eslicarbazepine) demonstrated greater binding selectivity for the inactive state of the sodium channel over the resting state

Results from 3 Eslicarbazepine Pivotal Trials:
50% Responder Rates

800 mg and 1200 mg doses were statistically significant; 400 mg was not.

### Eslicarbazepine Pivotal Study #1 (BIA-2093-301): Safety Results

#### Summary of Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (n=102)</th>
<th>ESL 400 mg (n=100)</th>
<th>ESL 800 mg (n=98)</th>
<th>ESL 1200 mg (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>32 (31.4)</td>
<td>44 (44.0)</td>
<td>49 (50.0)</td>
<td>62 (60.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2.0)</td>
<td>4 (4.0)</td>
<td>14 (14.3)</td>
<td>14 (13.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (5.9)</td>
<td>5 (5.0)</td>
<td>9 (9.2)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0</td>
<td>2 (2.0)</td>
<td>7 (7.1)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (2.0)</td>
<td>6 (6.0)</td>
<td>9 (9.2)</td>
<td>10 (9.8)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (1.0)</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>6 (5.9)</td>
</tr>
</tbody>
</table>

*Treatment-emergent adverse events affecting >5% of patients and leading to discontinuation in >2% of patients in any treatment group.*