The Emerging Uses of 3 Recently FDA-approved Antiseizure Medications: Lacosamide, Rufinamide, and Clobazam

November 30, 2012

Howard P. Goodkin, MD, PhD
University of Virginia
Disclosures

• No financial disclosures
• This lecture presents the off-label uses of 3 antiseizure medications: lacosamide, rufinamide, and clobazam
Learning Objectives

Upon conclusion of this lecture, the participant will be able to

• list the common off-label uses of antiseizure medications in the treatment of epilepsy

• summarize the current published evidence that supports the off-label uses of lacosamide, rufinimade, and clobazam in the treatment of seizures and epilepsy
An FDA-approved drug may be labeled, promoted, and advertised only for those uses for which the drug’s safety and effectiveness have been established.
• The FD&C Act does not limit the manner in which a physician may use an approved drug. . . a physician may prescribe it for use or in treatment regimens or patient populations that are not included in approved labeling.

• “unapproved’ or more precisely “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in the medical literature.

• Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic interventions . . . For that reason, accepted medical practice often includes use that is not reflected in approved labeling.
Off-label drug use is common

- 21% of prescriptions were off-label (Radley et al, 2006)

Figure 1 Off-label prescription and degree of scientific support (data from Radley et al.)

Epstein and Huang, 2012; Radley et al, 2006
Off-label drug use is common

- **Gabapentin**
  - Off label prescriptions: 83%
  - Without strong scientific evidence: 66%

*Figure 1* Off-label prescription and degree of scientific support (data from Radley et al.)

Epstein and Huang, 2012; Radley et al, 2006
Off-label drug use: Physician’s Responsibility

• The off label use of a medication should be performed in “good faith, in the best interest of the patient, and without fraudulent intent”

• The off-label use of a medication is a matter of judgment that should be based on the answers to the following questions:
  – Are there on-label alternatives?
  – Is the off-label use rationale?
    • Is there published scientific evidence to support the off-label use?
    • What is the standard of care for this condition?
  – Is the off-label use in the patient’s best interest?

Committee on Drugs, American Academy of Pediatrics, 2002
Lacosamide

• On-label use (2008)
  • Tablets and oral solutions are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.
  • Injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizure in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible.

• Emerging uses
  • Generalized seizures in adults
  • Extension to children
  • Status epilepticus
Lacosamide: Generalized seizures in adults

- Case reports/series (e.g. 1, 2, 3)
- Harden et al, 2012
  - 18-82 years of age
  - 50 to 600 mg/day
  - Greater than 50% decrease in seizure frequency
    - 18/24 generalized tonic clonic seizures
    - 12/14 atonic seizures
- Adverse events included dizziness, rash, discoordination, psychiatric side effects (mood/anxiety), headaches.

(1) Zangalaldze & Skidmore, 2012; (2) Afra and Adamolekun, 2012; (3) Harden et al, 2012
Lacosamide: Extension to children

- Case reports/case series
  - Children with focal onset seizures (e.g. 1, 2)
  - Mixed population of children with focal and generalized seizures (e.g. 3, 4)

Lacosamide: Extension to children

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients Age (range)</th>
<th>Seizure Type</th>
<th>Patients experiencing ≥50% reduction in seizure frequency</th>
<th>Patients who discontinued therapy (%)</th>
<th>Mean Effective Dosage (mg/kg/day) (range)</th>
<th>Adverse effects reported during treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gavatha et al⁹</td>
<td>14 (3-18 yr)</td>
<td>Focal onset</td>
<td>5 (36%)</td>
<td>12 (67%) due to lack of efficacy at initial assessment 1 (6%) due to ADE</td>
<td>6.34 (1.7-10)</td>
<td>Somnolence (17%), irritability (11%), sleep disturbances (6%), pancytopenia (6%)</td>
</tr>
<tr>
<td>Guilhoto et al⁹</td>
<td>16 (8-21 yr)</td>
<td>Focal onset</td>
<td>6 (37.5%)</td>
<td>2 (12.5%) due to lack of efficacy 4 (25%) due to ADE</td>
<td>4.7 (0.5-8.8)</td>
<td>Nausea and vomiting (12.5%), headache (6%), blurred vision (6%), tics (6%), behavioral outbursts (6%), ataxia (6%), and depression (6%)</td>
</tr>
<tr>
<td>Heyman et al¹¹</td>
<td>17 (1.5-16 yr)</td>
<td>Focal onset, tonic, generalized tonic-clonic*</td>
<td>6 (35%)</td>
<td>6 (35%) due to lack of efficacy</td>
<td>12.39 (6.7-20)</td>
<td>Nausea (18%), dizziness (18%), restlessness (12%), fatigue (12%), headache (12%), increased appetite (6%), prolonged crying (6%)</td>
</tr>
<tr>
<td>Rastogi et al¹²</td>
<td>16 (1-16 yr)</td>
<td>Focal, atonic, tonic, tonic, clonic, myolonic, atypical absence*</td>
<td>8 (50%)</td>
<td>NR</td>
<td>9.4 (2.4-19.4)</td>
<td>nausea, vomiting, gastrointestinal intolerance, dizziness, headache, somnolence, facial edema (frequency not specified)</td>
</tr>
</tbody>
</table>

ADE, adverse drug event; NR, not reported
*Included patients with Lennox-Gastaut syndrome (LGS)
Lacosamide: Status epilepticus

- Case reports/series (e.g. 1-10)
- Albers et al, 2011
  - 7 patients with refractory SE
  - All cases of SE terminated within 24 hours of lacosamide IV
  - No serious side effects or adverse events
- Goodwin et al, 2011
  - 9 patients with refractory SE
  - No patient with resolution within study criteria of 4 hours
  - 2 patients decreased seizure frequency in the “days following”
  - Angioedema in two cases

Lacosamide: Status epilepticus

• Kellinghaus et al, 2011
  – Multicenter, retrospective analysis of 39 patients: GTCSE (n=6), CPSE (n=17) and SPSE (n=16)
  – Median age: 62 years (range 18-90 years)
  – Median bolus was 400 mg (range 200-400 mg)
  – Median time to lacosamide from SE onset was 30 hours (0.5 to 1440 hours)
  – No serious adverse events
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Treatment parameters and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Latency (h) onset SE – SE therapy</td>
<td>39</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.5 (57.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.75 (0.1–336)</td>
</tr>
<tr>
<td>Treatment before LCM with</td>
<td>37</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>37</td>
</tr>
<tr>
<td>LEV</td>
<td>33</td>
</tr>
<tr>
<td>PHT</td>
<td>14</td>
</tr>
<tr>
<td>Other AED</td>
<td>5</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>4</td>
</tr>
<tr>
<td>Latency (h) onset SE – LCM i.v.</td>
<td>116.5 (504.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30 (0.5–1440)</td>
</tr>
<tr>
<td>LCM Dosing (mg)</td>
<td>326 (200–400)</td>
</tr>
<tr>
<td>Bolus: mean (range)</td>
<td>424 (200–600)</td>
</tr>
<tr>
<td>Termination of SE by LCM i.v.</td>
<td></td>
</tr>
<tr>
<td>&lt;6 h after LCM i.v., No other AED after LCM</td>
<td>7/18%</td>
</tr>
<tr>
<td>&gt;6 h after LCM i.v., No other AED after LCM</td>
<td>10/26%</td>
</tr>
<tr>
<td>Further AED therapy needed</td>
<td>22/56%</td>
</tr>
<tr>
<td>PHT successful</td>
<td>5/13%</td>
</tr>
<tr>
<td>OXC/CBZ successful</td>
<td>4/17%</td>
</tr>
<tr>
<td>VPA/TPM successful</td>
<td>2/5%</td>
</tr>
<tr>
<td>Anesthesia successful</td>
<td>6/15%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Termination of SE</td>
<td>34/87%</td>
</tr>
<tr>
<td>Termination, no change in mRS</td>
<td>21/54%</td>
</tr>
<tr>
<td>No termination</td>
<td>5/9%</td>
</tr>
</tbody>
</table>

SE, status epilepticus; SD, standard deviation; LCM, lacosamide; AED, antiepileptic drug; PHT, phenytoin; LEV, levetiracetam; PHT, phenytoin; OXC, oxcarbazepine; CBZ, carbamazepine; VPA, valproate; TPM, topiramate; PHB, Phenobarbital; mRS, modified Rankin scale.
Lacosamide: Status epilepticus

- Hofler et al, 2011
  - Multicenter, retrospective analysis of 48 patients: CSE (n=11), NCSE (n=11), FSE (n=10), Seizure clusters (n = 17)
  - Median age 62 years of age (range 17-95)
  - Median bolus was 200 mg (range 200-400 mg)
  - Adverse events: pruritis and skin rash
    - Discontinuation in 1 patient
# Lacosamide: Status epilepticus

<table>
<thead>
<tr>
<th>Table 2. Dose and responsiveness of intravenous lacosamide in 48 patients with status epilepticus and seizure clusters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 48)</td>
</tr>
<tr>
<td>Treatment before LCM</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>LEV</td>
</tr>
<tr>
<td>PHE</td>
</tr>
<tr>
<td>VPA</td>
</tr>
<tr>
<td>Anesthesia</td>
</tr>
<tr>
<td>LCM dose (median, range)</td>
</tr>
<tr>
<td>Median initial bolus (mg, range)</td>
</tr>
<tr>
<td>Median loading dose/24 h (mg, range)</td>
</tr>
<tr>
<td>Order of LCM i.v.</td>
</tr>
<tr>
<td>LCM first</td>
</tr>
<tr>
<td>LCM second</td>
</tr>
<tr>
<td>LCM third</td>
</tr>
<tr>
<td>LCM fourth or later</td>
</tr>
<tr>
<td>Termination of SE/SC by LCM</td>
</tr>
<tr>
<td>LCM first</td>
</tr>
<tr>
<td>LCM second</td>
</tr>
<tr>
<td>LCM third</td>
</tr>
<tr>
<td>LCM fourth or later</td>
</tr>
</tbody>
</table>

SE, status epilepticus; SC, seizure clusters; LCM, lacosamide; LEV, levetiracetam; VPA, valproic acid; PHE, phenytoin.
Rufinamide

• On-label (2008)
  • Tablets is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 4 years and older and adults.

• Emerging uses
  • Other electroclinical syndromes
  • Adjunctive treatment of focal seizures in children and adults
Rufinamide: Other electroclinical syndromes

- Case reports/series
  - Dravet syndrome (e.g. 1, 3, 6, 9)
  - Epilepsy with myoclonic absence (e.g. 3,8)
  - Malignant migrating partial epilepsy (e.g. 4)
  - Myoclonic astatic epilepsy (e.g. 1,3,9)
  - West syndrome/Epileptic spasms (e.g. 2,5,9)
  - Multifocal encephalopathy with (bi)frontal spike-wave discharges (e.g. 9)
  - Symptomatic or cryptogenic generalized epilepsy, NOS (e.g. 1,3,8)

Rufinamide: Adjunctive treatment of focal seizures in children and adults

• Case reports/case series (e.g. 1, 2, 3)
• Double-blind placebo controlled trials (e.g. 4-7)
• Elger et al, 2010
  • 24-week multicenter Phase II clinical study
    – 647 patients
      » age 15 to 65 years
      » 1 – 3 antiepileptic medications
    – 12-week prospective baseline phase
    – 12-week randomized, double-blind, parallel-group, five-arm treatment phase

Rufinamide: Adjunctive treatment of focal seizures in children and adults

Subjects randomized
\[N = 647\]
Subjects receiving double-blind medication
\[n = 647\]

- **Rufinamide 200 mg/day**
  - **Completed**
    - \[n = 111\]
  - **Discontinued**
    - \[n = 16\]
    - AE \[n = 12\]
      - Unsat. effect \[n = 3\]
      - Other* \[n = 1\]
    - Other* \[n = 1\]

- **Rufinamide 400 mg/day**
  - **Completed**
    - \[n = 105\]
  - **Discontinued**
    - \[n = 20\]
    - AE \[n = 12\]
      - Unsat. effect \[n = 3\]
      - Abnorm. lab \[n = 1\]
    - Other* \[n = 4\]

- **Rufinamide 800 mg/day**
  - **Completed**
    - \[n = 110\]
  - **Discontinued**
    - \[n = 19\]
    - AE \[n = 12\]
      - Unsat. effect \[n = 4\]
      - Other* \[n = 3\]

- **Rufinamide 1600 mg/day**
  - **Completed**
    - \[n = 112\]
  - **Discontinued**
    - \[n = 21\]
    - AE \[n = 16\]
      - Unsat. effect \[n = 3\]
      - Other* \[n = 2\]

- **Placebo**
  - **Completed**
    - \[n = 116\]

*Other reasons included failure to meet protocol criteria, withdrawal of consent, poor compliance, and loss to follow-up.

Elger et al, 2010
Rufinamide: Adjunctive treatment of focal seizures in children and adults

- Primary endpoint – linear trend for dose response – was established at a minimally efficacious dose of 400 mg/day
- Mean responder rate ~15% for doses of 400 mg or greater
- %patients experiencing at least one AE was similar for placebo and rufinamide-treated patients (76.5% v 75.2%)

![Figure 3](image.png)

**Figure 3** Median seizure frequency ratio* by treatment group. *Seizure frequency ratio was defined as the seizure frequency per 28 days in the double-blind treatment phase divided by the seizure frequency per 28 days in the baseline phase.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>AEs observed at a frequency ≥ 10% in any treatment group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients, n</td>
<td>133</td>
</tr>
<tr>
<td>No. of patients with AEs, n (%)</td>
<td>100 (75.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (24.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (15.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 (9.8)</td>
</tr>
<tr>
<td>Infection (viral)</td>
<td>11 (8.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (8.3)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>4 (3.0)</td>
</tr>
</tbody>
</table>

Elger et al, 2010
Rufinamide: Adjunctive treatment of focal seizures in children and adults

- Biton et al, 2011
  - Multicenter, randomized, double-blind, placebo-controlled, parallel-group study
  - 357 patients,
    - Mean age 36.4 (12-77)
    - 15 patients <18 years
    - 1 to 4 AEDs
  - 56-day baseline phase
  - 12 day titration phase to a dose of 3,200 mg;
  - 84-day maintenance phase
  - Adverse event
    - Dizziness (26.7% vs 8.3%);
    - Fatigue (15.3% vs 10.0%);
    - Nausea (13.1% vs 5.0%);
    - Somnolence (12.5% vs 7.2%)
    - Diplopia (8.0% vs 1.1%)

- Responder rate: 32% vs 15%*

Biton et al, 2010
Clobazam

• On-label (birth date: 1970; approved 2011)
  • Tablets are indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

• Emerging uses
  • Other electroclinical syndromes
  • Monotherapy for focal seizures or generalized seizures in adults
  • Adjunctive therapy for focal or generalized seizures in adults and children
Clobazam: Other electroclinical syndromes

• Case series
  • West syndrome (e.g. 1, 2)
  • Dravet syndrome (e.g. 1, 3)
  • Myoclonic astatic epilepsy (e.g. 2, 3)
  • Landau-Klefner/CSWS (e.g. 1, 3)
  • Jeavons syndrome (e.g. 3)
  • Epileptic Encephalopathies, nos (e.g. 2)

(1) Sheth et al, 1995; (2) Silva et al, 2006; (3) Perry et al, 2012
Clobazam: Emerging Uses

- Drug-naïve adults with either focal or generalized seizures
  - Prospective case series (e.g. 1)
- Adjunctive therapy for focal or generalized seizures in adults and children
  - Case series (e.g. 2-17)
- Double-blind, placebo controlled trials (e.g. 18-21)

Clobazam: Adjunctive therapy in focal or generalized seizures

- Koeppen et al, 1987
  - Multicenter, double-blind, placebo-controlled, crossover trial
  - 129 patients
    mean age 33 years
  - Dosing: 10 to 40 mg/day
  - 20 seizure free
  - Adverse reactions:
    Drowsiness
    Dizziness
    Depressive mood
    Aggressiveness

<table>
<thead>
<tr>
<th>Sex</th>
<th>CLB/PLAC</th>
<th>PLAC/CLB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>35</td>
<td>73</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>33 ± 11</td>
<td>32 ± 13</td>
<td>33 ± 12</td>
</tr>
</tbody>
</table>

All seizure types

- Simple partial: 15, 19, 34
- Complex partial: 58, 57, 115
- Absence: 1, —, 1
- Tonic: 1, —, 1
- Tonic-clonic: 14, 15, 29
- Atonic: 1, —, 1

Koeppen et al, 1987
Clobazam: Adjunctive therapy in focal or generalized seizures

- Keen et al, 1990
- Double-blind, cross-over study
- 21 patients
  Mean age 11 (2-19)
- 0.5 mg/kg initial dose
  0.25 to 1 mg/kg
- 4 week pre-trail phase
  12 weeks/4 weeks
- 11 had > 50% reduction

<table>
<thead>
<tr>
<th>Table 1: Group Characteristics after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>NUMBER</td>
</tr>
<tr>
<td>SEX</td>
</tr>
<tr>
<td>— Female</td>
</tr>
<tr>
<td>— Male</td>
</tr>
<tr>
<td>AGE</td>
</tr>
<tr>
<td>— Mean</td>
</tr>
<tr>
<td>— Range</td>
</tr>
<tr>
<td>SEIZURES</td>
</tr>
<tr>
<td>— Generalized</td>
</tr>
<tr>
<td>— Partial</td>
</tr>
<tr>
<td>— Partial Generalized</td>
</tr>
<tr>
<td>INTELLECT</td>
</tr>
<tr>
<td>— Normal</td>
</tr>
<tr>
<td>— Abnormal</td>
</tr>
<tr>
<td>CENTRAL NERVOUS SYSTEM</td>
</tr>
<tr>
<td>— Normal</td>
</tr>
<tr>
<td>— Abnormal</td>
</tr>
<tr>
<td>DOSAGE</td>
</tr>
<tr>
<td>— Mean (mgm/kg)</td>
</tr>
<tr>
<td>— Range (mgm/kg)</td>
</tr>
<tr>
<td>SUCCESSES</td>
</tr>
</tbody>
</table>

Keen et al, 1990
Clobazam: Emerging Uses

- Status Epilepticus
  - Case series (e.g. 1,2)
- Febrile seizures
  - Randomized, control studies (e.g. 3,4) and prospective case series (e.g.5)

Conclusions: Impact on Clinical Care and Practice

• Off-label use can be essential in providing optimal medical care
• Case series suggest an emerging role for lacosamide in the treatment of generalized seizures in adults, children with epilepsy, and the management of status epilepticus
• Case series suggest an emerging role for rufinamide in the treatment of electroclinical syndromes other than Lennox-Gastaut syndrome
• Double-blind, placebo-controlled trials support an emerging role for rufinamide in the adjunct treatment of focal seizures
• Case series suggest an emerging role for clobazam in the treatment of electroclinical syndromes other than Lennox-Gastaut syndrome, certain forms of status epilepticus, and febrile seizures
• Double-blind, placebo-controlled trials support an emerging role for clobazam in the adjunct treatment of focal and generalized seizures