Clinical Use of New Antiepileptic Drugs: Lacosamide, Ezogabine, Rufinamide, and Clobazam

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Disclosure

Eisai  Data Monitoring Board
Lundbeck  Data Monitoring Board
SK LifeScience  Data Monitoring Board
Sunovion  Consultant
Supernus  Consultant
UCB Pharma  Consultant, Research Support
Vertex  Research Support
Learning Objectives

1. Know an indication, by seizure type or syndrome, for lacosamide, ezogabine, rufinamide, and clobazam.

2. Select an appropriate drug for “drop attacks” in the Lennox-Gastaut syndrome.
Case

• A 38-yo woman has 2 complex partial seizures/month despite levetiracetam 3000 mg/day. She has had an allergic rash to phenytoin and carbamazepine, and had cognitive difficulty with topiramate 100 mg/day. Zonisamide at 400 mg/day and pregabalin 600 mg/day did not improve seizure control when added to levetiracetam.

• Seizure monitoring revealed bilateral independent temporal onsets.

• *Choose a treatment for her.*
Is it Worthwhile to Keep Trying New Medications in Refractory Epilepsy?

Responder rates (50% seizure reductions) as a function of newly administered AEDs failed due to lack of efficacy or adverse events

Even after numerous inefficient AEDs, at least 26.5% of patients will respond with a favorable outcome to a new AED\textsuperscript{2}

\textsuperscript{2} Schiller Y, Najjar Y et al Neurology 2008; 70: 54-65
"...no matter how many AED therapies have failed, there is always hope of a meaningful clinical remission in this population." - Callaghan 2008
LACOSAMIDE
Lacosamide

- Indication: adjunctive therapy of partial-onset seizures in patients 17 years of age or older*

- Mechanism: holds voltage-gated Na+ channels in their slow inactivated state longer.
Percent Reduction in Complex Partial Seizures with Adjunctive Lacosamide- Pooled Studies

Isojarvi, Faught, et al presented at ANA annual meeting, Baltimore, Oct 2009

Metanalysis of RCTs
The adverse event profile of lacosamide: A systematic review and meta-analysis of randomized controlled trials*

*Epilepsia*  
pages no-no, 10 JUL 2012 DOI: 10.1111/j.1528-1167.2012.03589.x  
Lacosamide: % Dose-Related Adverse Effects*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>200/day</th>
<th>400/day</th>
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</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Rash, somnolence, cognitive effects low and equal to placebo


Comment: The dizziness tends to be subjective, not true vertigo and not usually associated with ataxia. It may be worse when given with other Na+ channel drugs, e.g. CBZ (Faught, opinion)
The adverse event profile of lacosamide: A systematic review and meta-analysis of randomized controlled trials
Lacosamide: Clinical Use

• Labeled dosing: 50 bid week 1*
  \textit{Conservative dosing: 50 hs week 1}**
• Labeled titration: 100 mg/day/week
  \textit{Conservative titration: 50 mg/day/week}
• Labeled target: 400 mg/day (200mg b.i.d.)
  \textit{Conservative target: 200 mg/day initially, increase slowly to 400 mg or max tolerability}

*Product labeling, 2012,
**Opinion, Faught
Lacosamide: Pro and Con

Advantages
• B.I.D. dosing
• Renal excretion
• No interactions
• Low rate of somnolence, rash, cognitive effects
• IV available
• Adds well to LEV, TPM, PGN

Disadvantages
• Modestly effective: 20% greater reduction than placebo at 400 mg/day
• Dizziness
• Harder to add to PHT, CBZ, OXC, LTG – More dizziness
• Monotherapy unproven
• Levels not established

Opinion, Faught
EZOGABINE (US NAME)
RETIGABINE (EUROPEAN)
Ezogabine

- Approved for adjunctive therapy of partial-onset seizures in patients 18+ years of age
- Facilitates and prolongs $K^+$ channel opening, aiding repolarization of neurons and inhibiting repetitive firing*
- Voltage-gate $K^+$ channels are found in brain, heart, and bladder, but ezogabine targets mostly the Kv7.2 and Kv7.3 channel types; *not* important for heart function*

Ezogabine

Adverse Effects: somnolence, dizziness, confusion, other CNS effects, dose related. Urinary retention can occur.

17-29% withdrawal due to adverse effects in double-blind trials, vs 12.5% placebo (This difference is about average in clinical trials of AEDs)

Cardiac considerations

- Extensive ECGs during development program showed no effect on heart
- No ECG screening required
Bladder considerations

- Kv7.2 and Kv7.3 channels are present in bladder innervation
- 2% urinary retention in clinical trials of ezogabine, 8% some complaint of voiding difficulty*
- Consider another drug in patients with prostatism or other voiding problems

*Product labeling, 2012
FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) will be necessary for ezogabine, with the goal of informing healthcare professionals of the risk of urinary retention and the symptoms of acute urinary retention. Ezogabine caused urinary retention in clinical trials. Urinary retention was reported as an adverse event in 29 out of 1,365 (approximately 2%) patients treated with ezogabine. In all studies of patients with partial-onset seizures, including open-label studies, five patients required catheterization (four on ezogabine and one on placebo).
Ezogabine Dosing

- Effective dose range 600-1200 mg/day in THREE divided doses
- Recommended starting dose is 100 mg TID*. (Conservative start: 50 mg TID**)
Ezogabine Pros

- Novel mechanism
- No significant interactions
- Renally excreted
- Low rash rate
- Low cognitive complaint rate
- No apparent serious skin, blood, liver effects so far

Opinion, Faught
Ezogabine Cons

• Modestly effective: 23.1% greater reduction than placebo at 1200 mg/day
• Short elimination half life: TID dosing
• Urinary retention may limit use in some patients, especially older men

Opinion, Faught
RUFINAMIDE
RUFINAMIDE

- Indication: Adjunctive therapy of seizures associated with the Lennox-Gastaut syndrome in patients 4 years of age or older*

- Mechanism of action: Na+ channel blockade (and possibly other mechanisms since traditional sodium channel blockers are not very effective vs atonic seizures)

- *Product labeling
Lennox-Gastaut Syndrome
Drop Attacks

% Seizure reduction

Felbamate: P=.002
Lamotrigine: P=.02
Topiramate: P=.04

Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome.

Glauser, T; Kluger, G; Sachdeo, R; Krauss, G; Perdomo, C; Arroyo, S; MD, PhD

DOI: 10.1212/01.wnl.0000303813.95800.0d

Figure 2: Median percentage reduction in total seizure frequency and tonic-atonic seizure frequency (per 28 days during the double-blind phase relative to baseline).

Rufinamide- Reduction in generalized seizures associated with LGS.

Glauser T et al. Neurology, 2008; 70:1950-8
Rufinamide Drug Interactions

RUF Reduced BY:
• PHT
• PB
• CBZ

RUF Increased By:
• VPA

RUF Induces Metabolism of 3A4 metabolized drugs, reduces serum levels by 7-21%, e.g. PHT, CBZ, PB

Product Labeling, 2012
Rufinamide: Clinical Use

• **CHILDREN**: 10 mg/kg/day (divide into two doses)*
• Target: 45 mg/kg/day or max 3200 mg/day*
• **ADULTS**: 400 mg (200 mg b.i.d.)
  MAX 3200 mg/day*

*Product Labeling, 2012
CLOBAZAM

Seif-Eddeine H, Ng YT

Figure 1. Clobazam’s unique chemical design, indicating the presence of its nitrogen atoms in the 1 and 5 positions.
Clobazam

- Benzodiazepine, 5-substituted rather than 3-substituted (different affinity for various GABA receptor configurations)
- Designed to produce less somnolence and tolerance than other benzodiazepines
- Approved 2011 in US for adjunctive therapy of seizures associated with LGS, age 2+ (Approved Australia 1970)
Clobazam dosing

- Dose range children <30kg, start 5 mg/day, titrate up to 20 mg/day as needed*
- Dose range adults 10-40 mg/day as 2 divided doses, available as 5,10,20 mg*

  \textit{Conservative start: 5 mg hs x 1 week, increase by 5 mg/week to target 20mg/day}*  

*Product labeling, 2012  
*Opinion, Faught
Clobazam reduction in weekly “drop” seizures in Lennox-Gastaut syndrome. n = 239.

- 1.0 mg/kg = -68%
- 0.5 mg/kg = -49%
- 0.25 mg/kg = -41%
- Placebo = -12%

Ng YT et al. *Neurology* 2011; 77(15): 1473-81
Four New Drugs: Two for a Seizure Type, Two for a Syndrome

- **Lacosamide** - An add-on Na+-channel choice for partial-onset seizures, no interactions, good profile for cognition and behavior; dizziness is frequent.


- **Rufinamide and Clobazam** - Drugs for seizures associated with the Lennox-Gastaut syndrome. *(Often added to VPA and other options include FBM, LTG, and TPM)*
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- Choose a treatment for her.
Considerations

- A sodium channel blocker might complement levetiracetam’s mechanism, but lamotrigine and oxcarbazepine carry higher rash risk with previous ring-compound allergy. Lacosamide has a low rash rate.
- Valproate can cause weight gain and is teratogenic; she is premenopausal.
- A K+ channel facilitator, ezogabine, might complement levetiracetam.
Three things we really need in AED pharmacology

• An antiepileptogenic agent

• Delivery systems that minimizes patient adherence as a variable

• Other choices for generalized-onset seizures
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Impact on Clinical Care and Practice

• Two new options for adjunctive therapy of partial-onset seizures

• Two new drug mechanisms of action which may be useful

• Two new options for adjunctive therapy of seizures associated with the Lennox-Gastaut syndrome