Epilepsy Update

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Epilepsy Update

• 3 New Anti-epileptic Drugs (AED’s) –
  • Rufinamide
  • Lacosamide
  • Vigabatrin
• 3 FDA Safety Alerts
  • Carbamazepine and Asian patients
  • AED and suicidality
  • Lamotrigine and aseptic meningitis
• Definition of Drug Resistant Epilepsy

Three new AED 2009
Rufinamide (Banzel™)
Lacosamide (Vimpat™)
Vigabatrin (Sabril™)

“New” – if patient hasn’t tried the medication it is “new” to that patient

Rufinamide (Banzel™)

• Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (≥ 4 years)

• Mechanism Of Action: Prolong inactive state of neuronal voltage-gated sodium channels
Rufinamide Kinetics
- $T_{\text{max}}$ 4-6 hrs
- Half life 6-10 hrs (BID dosing)
- Administer with food to improve absorption
- At higher doses, dose-limited absorption due to limited solubility
- Low 34% protein binding

Rufinamide Interactions
• Metabolized by carboxylesterases, not by P450
  – Weak CYP 3E1 inhibitor
  – Weak CYP 3A4 inducer
• AED interactions
  • Valproate increases RUF level up to 70%
  • RUF increases phenytoin level up to 21%
  • RUF decreases concentrations of: CBZ, LTG, PB
  • RUF is decreased by: CBZ, PHT, PB, Primidone
• Decreases estradiol concentrations (OCPs)

Reduction in Seizure Frequency

Rufinamide AEs With Incidence ≥ 5%

Lacosamide (VIMPAT®)
• Lacosamide tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years
• Lacosamide injection for intravenous use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years when oral administration is temporarily not feasible
Lacosamide Mechanism of Action

- Preclinical evidence suggests that Lacosamide works via:
  - Selectively enhancing slow inactivation of sodium channels

Lacosamide Kinetics

- Linear pharmacokinetics
- $T_{\text{max}}$: 1-4 hrs after oral administration
- $T_{1/2} \sim 13$ hrs; (BID dosing)
- 95% of the dose is excreted in the urine (40% as unchanged drug)
- Demethylation is the major metabolic pathway
- Low protein binding (<15%)
- Low drug-drug interaction potential

Adverse Events Lacosamide

<table>
<thead>
<tr>
<th>AE</th>
<th>Treatment Phase</th>
<th>Placebo (%) (n=234)</th>
<th>Lacosamide 200 mg/day (%) (n=270)</th>
<th>Lacosamide 400 mg/day (%) (n=471)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>Forced-attrition</td>
<td>7</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>2</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>Forced-attrition</td>
<td>6</td>
<td>7</td>
<td>10</td>
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<tr>
<td></td>
<td>Maintenance</td>
<td>5</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>Forced-attrition</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Forced-attrition</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
- Patients in these clinical trials were treated with 1 to 3 concomitant AEDs
- Discontinuation rates due to adverse events for patients treated with VIMPAT® 200 mg/day and VIMPAT® 400 mg/day were 8% and 17%, respectively, vs 5% for those receiving placebo

Lacosamide Oral Tablets: Dosing Schedule

- Oral VIMPAT® is available in 50-mg, 100-mg, 150-mg, and 200-mg tablets
- Therapeutic doses are 200-400 mg/day

- Dosing
  - Week 1: 50 mg BID
  - Week 2: 100 mg BID
  - Option to titrate at weekly intervals by 100 mg/day, given as 2 divided doses, up to 400 mg/day (200 mg BID)
    - Week 3: 150 mg BID
    - Week 4: 200 mg BID

Physiology of Voltage-Gated Sodium Channels

- Classical AEDs
- Repolarization
- Inactivated state = fast
- Inactivated state = slow
- Depolarization
- Regulation of sodium channel long-term availability

Lacosamide works via:
- Selectively enhancing slow inactivation of sodium channels

Preclinical evidence suggests that:
- Lacosamide is the major metabolic pathway
- Low protein binding (<15%)
- Low drug-drug interaction potential
- 95% of the dose is excreted in the urine
- $T_{1/2} \sim 13$ hrs; (BID dosing)
- Linear pharmacokinetics

Experimental evidence suggests that Lacosamide 200 mg/day and Lacosamide 400 mg/day were 8% and 17% vs 5% for those receiving placebo.

For the intent-to-treat population of the 3 pivotal studies (Studies 1, 2, and 3, respectively), median percent reduction from baseline to maintenance; †† for those receiving placebo.
**IV Lacosamide**
- Lacosamide injection use is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged ≥17 years when oral administration is temporarily not feasible.
- 200 mg of VIMPAT®/20 mL (Concentration: 10 mg/mL);
- Does not require additional dilution prior to administration or may be mixed with diluents
  - Compatible and stable with sodium chloride injection 0.9%, dextrose injection 5%, and lactated Ringer’s injection
- Infusion rate: At least 30 minutes
- 1:1 dose conversion (oral ↔ injection)

**Vigabatrin (Sabril)**
- Indicated for the treatment of Infantile Spasm
- Sabril is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing the peripheral visual field defect (pVFD). Sabril is not indicated as a first-line agent for CPS.

**Vigabatrin—Unique Mechanism of Action**
- GABA is an inhibitory neurotransmitter
  - VGB selectively and irreversibly inhibits GABA-T (prevents breakdown of GABA molecules)
  - Increases number of GABA molecules
  - Decreases seizure activity
- GABA-T enzyme

**Vigabatrin: Clinical Pharmacology**
- Orally absorbed, linear PK
- No clinically relevant effect of food, gender, race
- No clinically relevant drug-drug interactions
- Age-related $t_{1/2}$
  - Infants = 5.65 hr
  - Adults = 7.5 hr
- Plasma levels do not correlate with clinical effect

**Infantile Spasms (IS):**
- Age-specific convulsions disorder
- Children with IS exhibit the EEG patterns known as hypsarrhythmia
- IS was first described by West in 1841

**Vigabatrin: Spasm Cessation**

![Graph showing spasm cessation results](image_url)

Vigabatrin: Infantile Spasms:
- Soluble powder, oral administration
- Rapid titration to 125 - 150 mg/kg
  - 2-wk trial for efficacy
  - Duration of therapy: 3 - 12 mo or until age 1 year
- Key side effects
  - Drowsiness, risk of pVFD and MRI changes

VGB Complex Partial Seizure

Study 025 (N = 174)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Median Reduction</th>
<th>p-value vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>VGB 1 g/day</td>
<td>8.5</td>
<td>0.8</td>
</tr>
<tr>
<td>VGB 3 g/day</td>
<td>8.5</td>
<td>p = 0.0001*</td>
</tr>
<tr>
<td>VGB 6 g/day</td>
<td>8.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*p-value vs placebo.

Study 024 (N = 182)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Median Reduction</th>
<th>p-value vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>VGB 3 g/day</td>
<td>8.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

VGB Dosage and Administration
- Initial Dose is 500mg twice daily
  - Can increase by 500mg intervals weekly
  - Usual effective dose is 3g/day
- Renal Dosing
  - Vigabatrin primarily excreted through the kidney
  - CLcr 50-80mL/min decrease dose by 25%
  - 30-50mL/min decrease by 50%
  - <30mL/min decrease by 75%

Permanent Visual Field Defect
- Mild – not clinically significant (120° - 160°)
- Moderate – not clinically significant; can reliably detect change at the moderate level (60° - 120°)
- Severe – clinically significant (< 60°)

Constriction – concentric decrease in extent of field
VGB Peripheral Visual Field Defect Summary

Data from:
- Sanofi-Aventis Study MO71754/4020 — A multinational study of 524 evaluable vigabatrin-exposed epilepsy patients.
- Toronto Hospital for Sick Children Study — A single-center longitudinal electroretinogram (ERG) study of 246 infants with infantile spasms treated with vigabatrin.
- There are rare reports in the literature and from post-marketing surveillance of the pVFD occurring within 6 months of initiating Sabril therapy so the possibility of an earlier onset cannot be excluded.

Vigabatrin Summary

Unique MOA - VGB irreversibly inhibits GABA-Transaminase.

Effective with rapid onset:
- Decreases seizure frequency
- Complete seizure freedom (7% - 12%)

Generally well tolerated:
- Common AEs (fatigue, dizziness, somnolence)

Can lead to permanent Peripheral Visual Field Defect —

AED Selection For Seizure Type

Partial-Onset
- Simple
- Complex
- Secondarily generalized
  
PHT, CBZ, GBP,  
  TGB, OXC, PGB, LAC

Generalized Onset
- Tonic-clonic
- Myoclonic
- Atonic
- Absence

PB, PHT, CBZ, GBP,  
  TGB, OXC, PGB, LAC

VPA, FBM, LTG, TPM, ZNS, LEV, RUF, VGB

AED Meta-Analysis Efficacy

Odds Ratios for ≥50% Response (Responder Rate)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>2.3</td>
<td>1.9 - 2.6</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2.3</td>
<td>1.9 - 2.6</td>
</tr>
<tr>
<td>Zonisamide*</td>
<td>2.7</td>
<td>1.9 - 3.7</td>
</tr>
<tr>
<td>Oxcarbazepine*</td>
<td>3.0</td>
<td>2.5 - 3.7</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>3.2</td>
<td>2.6 - 4.0</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>4.1</td>
<td>3.5 - 4.9</td>
</tr>
<tr>
<td>Topiramate</td>
<td>3.6</td>
<td>3.1 - 4.1</td>
</tr>
<tr>
<td>Levetiracetam**</td>
<td>3.8</td>
<td>3.3 - 4.5</td>
</tr>
</tbody>
</table>

FDA ALERT: Carbamazepine CBZ

- Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis) with CBZ are significantly more common in patients with an allele, HLA-B*1502.
- The overall estimated risk of SJS/TEN associated with CBZ is based on countries with mainly Caucasian populations, and is fairly low, 1-6 per 10,000 new users, but is 10 times higher in some Asian countries.
- This allele HLA-B*1502 occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians.
- 10-15% may carry allele China, Thailand, Malaysia, Indonesia, Philippines & Taiwan
- 2 to 4% South Asians, including Indians have intermediate prevalence
- <1% low frequency, in Japan and Korea

FDA ALERT: Carbamazepine (CBZ)

- Patients with Asian ancestry from in which HLA-B*1502 is present should be screened for the allele before starting treatment with CBZ.
- If they test positive HLA-B*1502, CBZ should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions.
- Patients who have been taking CBZ for more than a few months without developing skin reactions SJS/TENS are at low risk of these events ever developing from CBZ.
FDA Alert: Suicidality and Antiepileptic Drugs

- Data from 199 placebo-controlled clinical studies covering eleven different antiepileptic drugs were reviewed and analyzed for reports of suicidal behavior (completed suicides, suicide attempts and preparatory acts) and suicidal ideation.

Carbamazepine, Felbamate, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Pregabalin, Topiramate, Valproate, Zonisamide

- Although the drugs listed above were the ones included in the analysis, FDA expects that the increased risk of suicidality is shared by all AEDs and that the class label changes.

Suicidality and Antiepileptic Drugs

Relative Risk and Risk Difference for Suicidality According to Trial Indication

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Drug</th>
<th>Relative Risk</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Events in 1000 Patients</td>
<td>Incidence of Events in 1000 Patients</td>
<td>Additional Drug Patients with Events in 1000 Patients</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.2</td>
<td>8.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Other</td>
<td>0.8</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>2.2</td>
<td>4.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

- The results were generally consistent among the eleven drugs.

FDA Drug Safety Communication: Aseptic meningitis associated with use of lamotrigine

- Fifteen cases reported a rapid return of symptoms following re-initiation of Lamictal; symptoms recurred within 30 minutes to 24 hours following re-initiation of Lamictal (mean of 5 hours).
- In these rechallenge cases, symptoms were frequently more severe after re-exposure.
- 25 reported cases contained data on cerebrospinal fluid (CSF) findings.
  - Mild to moderate pleocytosis (neutrophils > lymphocytes 1/3 of cases)
  - Normal glucose levels,
  - Mild to moderate increase in protein.
- Some of the patients treated with Lamictal who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases.
- In addition, some patients also had new onset of signs and symptoms of involvement of other organs (predominantly hepatic and renal involvement), which may suggest that some of the cases of Lamictal-associated meningitis were part of a hypersensitivity or generalized drug reaction.

Extended Release Formulations of AED

- Once Day - Phenytoin, Dilantin
- BID - Carbamazepine, Depakote ER, Keppra XR, Lamictal XR
### AED with IV Formulation

- **Phenobarbital**
- **Phenytoin** Dilantin/Fosphenytoin
- **Valproic Acid** Depacon
- **Levetiracetam** Keppra
- **Lacosamide** Vimpat

### Early Identification of Refractory Epilepsy

**Previously Untreated Epilepsy Patients (N=470)**

- Seizure-free with 1st drug: 47%
- Seizure-free with 2nd drug: 13%
- Seizure-free with 3rd drug or multiple drugs: 4%
- Not seizure-free: 36%


### Randomized Controlled Trial of Surgery for Temporal Lobe Epilepsy

- Canada – National Health system – intention to treat
- 80 subjects with long-standing medically intractable epilepsy
  - Many > 20 years
  - 40 in the surgical group and 40 in medical group
- 1 year follow-up
- 8% in medical arm seizure free (1 death)
- 64% in surgical arm seizure free
  - 10-15% little or no improvement
  - Significant improvement in HRQOL
  - Trend toward better social function


### Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons

**Temporal lobe and localized neocortical resections for epilepsy**

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.

“Patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center, although criteria for failure of drug treatment have not been definitely established.” Neurology 2003.
Drug Resistant Epilepsy
(Medically intractable, Refractory, Pharmacoresistant Epilepsy)

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies: Epilepsia 2010  P. Kwan et al

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.

AED’s on the Horizon

- Eslicarbazepine (Stedesa)
- Clobazam (Frisium)
- Retigabine (Potiga)
- Breviracetam
- E2007
- Ganaxolone
- Carisabamate?
- Phenobarbital