Antiepileptics: A focus on Perampanel (Fycompa®)

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Presented to: Dr. Diana Malaeb
Date: 28/2/2013
Abbreviations

- AED: antiepileptic drug
- EEG: electroencephalography
- SJS: Stevens Johnson syndrome
- VA: Valproic acid
- GABA: Gamma amino butyric acid
- NMDA: N-methyl D-aspartate
- AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
- CNS: central nervous system
Outline

- Introduction
- When to start AED
- Choosing an AED
- When to stop AED
- First generation
- Second generation
- Concurrent illnesses
- Perampanel
Introduction

- A seizure is defined by transient focal or generalized signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

- Focal seizures:
  - Originate within neuronal networks limited to one cerebral hemisphere.

- Generalized seizures:
  - Rapidly affect extensive neuronal networks on both cerebral hemispheres.
When to start AED therapy

- After the second seizure because this indicates that the patient has an increased risk for additional seizures.

- Three high-risk features for seizure recurrence:
  - Remote symptomatic cause, (e.g., brain tumor, brain malformation)
  - Epileptiform abnormalities on EEG
  - Abnormal neurologic examination, (focal findings and intellectual disability)

Kim LG, Johnson TL, Marson AG, Chadwick DW, MRC MESS Study group; Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial.; Lancet Neurol. 2006;5(4):317.
Choosing an AED

- Drug effectiveness for the seizure type or types
- Potential adverse effects of the drug
- Interactions with other medications
- Comorbid medical conditions
- Age and gender, including childbearing plans
- Lifestyle and patient preferences
- Cost
When to stop AED therapy

• After 2-4 years seizure-free

• Reasons for stopping AED
  • Offers patients a sense of being “cured”
  • Adverse effects associated with chronic therapy may take years to become evident
  • Cognitive and behavioral side effects of AEDs may not be fully recognized until drugs are discontinued
  • Newer AEDs are expensive
  • Special circumstances, such as pregnancy or serious coexisting medical conditions
Antiepileptics
First generation

- Carbamazepine
- Ethosuximide
- Phenobarbital
- Phenytoin
- Fosphenytoin
- Valproic acid
Carbamazepine

- Used for partial and generalized seizure
- Other uses: Bipolar disorders, trigeminal neuralgia

Rose FC, Johnson FN; Carbamazepine in the treatment of non-seizure disorders: trigeminal neuralgia, other painful disorders, and affective disorders; Rev Contemp Pharmacother. 1997; 8:123.
Carbamazepine (Cnt’d)

- **Mechanism of action:**
  - Slowing the rate of reactivation of voltage-dependent sodium channels after depolarization

- **Side effects:**
  - Common: Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus; drowsiness, dizziness, blurred or double vision, lethargy, headache
  - Rare: Agranulocytosis, SJS, aplastic anemia, hepatic failure, panreatitis, lupus syndrome
Carbamazepine (Cnt’d)

- Pharmacokinetics

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme induction/inhibition</th>
<th>Protein binding</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>•&gt;90 % by CYP 3A4 and 2C8 (minor) to active (epoxide) &amp; inactive</td>
<td>•Potent &amp; broad-spectrum inducer of CYP &amp; P-gp</td>
<td>•75%</td>
<td>•25-65 hrs (initial use, enzyme inducing naive patient)</td>
</tr>
<tr>
<td>•Dose adjustment severe renal or hepatic insufficiency</td>
<td></td>
<td></td>
<td>•8-22hrs (after several weeks due to auto induction)</td>
</tr>
</tbody>
</table>

www.uptodate.com/contents/image?imageKey=NEURO%2F60182&topicKey=NEURO%2F2220&rank=3~150&source=see _link&search=seizure+preampenel&utdPopup=true
Ethosuximide

- For the treatment of absence seizure
- No activity against generalized tonic-clonic and partial seizure

Oliver L. Hung, MD*, Richard D. Shih, MD; Antiepileptic drugs: The old and the new
Ethosuximide (Cnt’d)

- **Mechanism of action:**
  - Diminishes T-type calcium currents in thalamic neurons, which are further reduced as membrane potentials become more hyperpolarized

- **Side effects:**
  - Common: Nausea, vomiting, sleep disturbance, drowsiness, hyperactivity
  - Rare: Agranulocytosis, SJS, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness
Ethosuximide (Cnt’d)

- Pharmacokinetics

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme Induction/Inhibition</th>
<th>Protein binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>~80 percent metabolized by CYP 3A4 and non-CYP transformations to inactive metabolites</td>
<td>None</td>
<td>&lt; 5%</td>
<td>40-60 hours</td>
</tr>
</tbody>
</table>
Phenobarbital

- The oldest AED
- Used for generalized and partial seizure
- As effective as phenytoin and carbamazepine in preventing seizures → yet it is considered a second-line AED
- Significant CNS side effects, including excessive fatigue in adults and hyperactivity and aggression in children

Oliver L. Hung, MD*, Richard D. Shih, MD; Antiepileptic drugs: The old and the new
Phenobarbital (Cnt’d)

- **Mechanism of action:**
  - Potentiation of GABA receptor → directly increasing the duration for which the chloride channels remain open

- **Side effects:**
  - Common: Nausea, rash, alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, tolerance, dependence
  
  - Rare: Agranulocytosis, Stevens-Johnson syndrome, hepatic failure, dermatitis/rash
Phenobarbital (Cnt’d)

**Pharmacokinetics:**

<table>
<thead>
<tr>
<th>Metabolism/Clearance</th>
<th>Enzyme Inhibition/Induction</th>
<th>Protein binding</th>
<th>Half life</th>
</tr>
</thead>
</table>
| • 75% metabolized by CYP 2C19; 2C9 and 2E1 (minor) to inactive  
• 25% excreted renally as unchanged drug  
• Dose adjustment in severe renal or hepatic insufficiency | • Potent inducer of CYP and glucuronidation | • 45% | • 75-110 hours |
Phenytoin

- Introduced nearly 60 years ago for use in epilepsy
- Still widely prescribed for partial and generalized seizures

Merritt HH, Putnam TJ; Sodium diphenyl hydantoinate in the treatment of convulsive disorders; JAMA. 1938;111:1068.
Phenytoin (Cnt’d)

- **Mechanism of action:**
  - Blocks voltage-dependent neuronal Na channels*

- **Side effects**: 
  - Common: Gingival hypertrophy, rash, confusion, slurred speech, double vision, ataxia, IV formulation → hypotension
  - Rare: Agranulocytosis, SJS, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, neuropathy, ataxia, lupus-syndrome, hirsutism


#www.uptodate.com/contents/image?imageKey=NEURO/78896&topicKey=NEURO%2F2221&source=outline_link&search=antiepileptic+drugs
Phenytoin (Cnt’d)

- **Pharmacokinetics:**

<table>
<thead>
<tr>
<th>Metabolism/Clearance</th>
<th>Enzyme Inhibition/Induction</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90% by CYP 2C9, 2C19 and 3A4 (minor) and non-CYP to inactive</td>
<td>Potent inducer of CYP and glucuronidation</td>
<td>90-95%</td>
<td>9- &gt;42hours (dose dependent)</td>
</tr>
</tbody>
</table>
Phenytoin Vs. fosphenytoin

- Same pharmacologic activity
- However,
  - Fosphenytoin is more water soluble → does not require alcohol and propylene glycol → it lacks the serious side effects of phenytoin such as hypotension, cardiac arrhythmias, and infusion site reaction
  - Fosphenytoin rate of infusion = 150 mg/min Vs. phenytoin = 50 mg/min
  - Fosphenytoin available IM
Valproic acid

- Used alone and in combination of generalized and partial onset seizures
- Mechanism of action:
  - It prolongs the recovery of voltage-activated sodium channels from inactivation
  - VA stimulates GABA synthesis by activating glutamic acid decarboxylase and inhibiting GABA degradation enzymes
  - VA acts against T-type calcium currents (weaker than ethosuximide)
Valproic acid (Cnt’d)

- Side effects:
  - Common: Weight gain, nausea, vomiting, hair loss, easy bruising, tremor, dizziness
  - Rare: Agranulocytosis, Stevens-Johnson syndrome, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, pancreatitis, polycystic ovary syndrome
Valproic acid (Cnt’d)

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme Inhibition/Induction</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
</table>
| •>95 % CYP 2C9, 2C19, 2A6, glucuronidation and non-CYP metabolism  
•Dose adjustment in hepatic insufficiency | •Moderate broad spectrum inhibitor including CYP 2A6, 2B6, 2C9, 2C19, 2E1 and glucuronidation | •80-95% | •7-16 hours |
Second generation

- Ezogabine
- Felbamate
- Gabapentin
- Levetiracetam
- Topiramate
- Tiagabine
- Zonisamide
- Lacosamide
- Lamotrigine
- Oxcarbazepine
- Rufinamide
- Vigabtrin
Ezogabine

- Add-on for partial seizures in adults
- Mechanism of action:
  - Opening KCNQ2/3 voltage-gated potassium channels
  - Activating M-current, which regulates neuronal excitability and suppresses epileptic activity

Ezogabine (Cnt’d)

- Side effects:
  - Common: dizziness and vertigo, fatigue and weakness, confusion, somnolence, tremor, ataxia, blurred or double vision, dysarthria, inattention, and memory impairment
  - Ezogabine can also cause urinary retention, usually, but not always, within the first six months of initiation
Ezogabine (Cnt’d)

- **Pharmacokinetics**

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme induction/Inhibition</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Liver and kidney</td>
<td>None</td>
<td>80%</td>
<td>• 8 hours</td>
</tr>
<tr>
<td>• Not metabolized by the cytochrome P450</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• N-glucuronidation and N-acetylation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ minimal drug interactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Felbamate

- Used for partial seizure and Lennox-Gastaut
- Mechanism of action:
  - Not well understood
  - Blocks the channel at the (NMDA) excitatory amino acid receptor and augments GABA function

Rho JM, Donevan SD, Rogawski MA; Mechanism of action of the anticonvulsant felbamate: opposing effects on N-methyl-D-aspartate and gamma-aminobutyric acidA receptors; Ann Neurol. 1994;35(2):229.
Felbamate (Cnt’d)

- Side effects:
  - Common: Nausea, vomiting, anorexia, weight loss, Insomnia, dizziness, headache, ataxia
  - Rare: Aplastic anemia, liver failure
## Felbamate (Cnt’d)

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Metabolism / clearance</th>
<th>Enzyme inhibitor/ inducer</th>
<th>Protein binding</th>
<th>Half life</th>
</tr>
</thead>
</table>
| •60 % by CYP 3A4 and 2E1 (minor)  
•~30 % renally excreted as unchanged drug  
•Dose adjustment in renal insufficiency | •Induces CYP 3A4 (moderate)  
•Inhibits CYP 2C19 (minor) | •25 | •13-22 (prolonged in renal insufficiency) |
Gabapentin

- Add-on for partial seizures +/- secondary generalized tonic-clonic seizures
- Also for painful neuropathies and postherpetic neuralgia

Investigational uses:
- Monotherapy of refractory partial seizure
- Treatment of spasticity in multiple sclerosis
- Treatment of tremor
Gabapentin (Cnt’d)

- **Side effects:**
  - Somnolence, dizziness, ataxia

- **Pharmacokinetics**

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme induction/inhibition</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>•&gt;95 % renally excreted as unchanged drug •Dose adjustment in renal insufficiency</td>
<td>•None</td>
<td>•&lt;5 %</td>
<td>•5-7 (prolonged in renal insufficiency; &gt;130 hours in anuria)</td>
</tr>
</tbody>
</table>
### Second generation

<table>
<thead>
<tr>
<th></th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam</td>
<td>Unknown</td>
<td>Fatigue, somnolence, dizziness, agitation, anxiety, irritability, depression</td>
</tr>
</tbody>
</table>
| Topiramate          | • Enhances the inhibitory effect of GABA  
• Blocks sodium channels  
• Antagonizes kainate/AMPA receptors | Weight loss, paresthesias, Rare: Glaucoma, kidney stones                      |
| Tiagabine           | • Inhibits the reuptake of GABA by binding to recognition sites associated with the GABA uptake carrier | Abdominal pain, dizziness, lack of energy, somnolence, nausea, nervousness, tremor, difficulty concentrating Rare: nonconvulsive status epilepticus |
Second generation (Cnt’d)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism /clearance</th>
<th>Enzyme induction/Inhibition</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam</td>
<td>&gt;65 renally excreted as unchanged drug; 24 percent metabolized by non-CYP Dose adjustment in renal insufficiency</td>
<td>None</td>
<td>&lt;10</td>
<td>6-8</td>
</tr>
<tr>
<td>Topiramate</td>
<td>&gt;65 % excreted renally unchanged &lt;30% by non-CYP Dose adjustment in moderate and severe renal or hepatic</td>
<td>Inhibits 2C19 (minor) Induces CYP 3A4 (minor)</td>
<td></td>
<td>9-17</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>&gt;90 % metabolized by CYP 3A4 and non-CYP</td>
<td>None</td>
<td>95</td>
<td>7-9</td>
</tr>
</tbody>
</table>
## Second generation (Cnt’d)

<table>
<thead>
<tr>
<th></th>
<th>Metabolism /clearance</th>
<th>Enzyme induction/Inhibition</th>
<th>Protein binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zonisamide</strong></td>
<td>&gt;70 % metabolized by CYP 3A4, 2C19 (minor) and non-CYP</td>
<td>None</td>
<td>40</td>
<td>63 hrs</td>
</tr>
<tr>
<td></td>
<td>Not recommended moderate or severe renal insufficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>&gt;90 % metabolized by non-CYP</td>
<td>May induce its own metabolism</td>
<td>55</td>
<td>12-62 hrs</td>
</tr>
<tr>
<td></td>
<td>Dose adjustment: moderate-severe renal / hepatic insufficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oxcarbazepine</strong></td>
<td>&gt;90% metabolized by non-CYP active and inactive</td>
<td>Induces CYP 3A4 (moderate to severe) and glucuronidation</td>
<td>40</td>
<td>9 hrs</td>
</tr>
<tr>
<td></td>
<td>Dose adjustment in severe renal insufficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lacosamide

- Approved as an adjunctive therapy for partial-onset seizures in patients aged 17 years and older
- Mechanism of action:
  - Selectively enhances slow inactivation of voltage-dependent Na channels

Lacosamide (Cnt’d)

- Side effects:
  - Nausea, vomiting, fatigue, Ataxia, dizziness, headache, diplopia

- Pharmacokinetics:

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme induction/Inhibition</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 40% renally excreted as unaltered drug;</td>
<td>Inhibits 2C19 (minor)</td>
<td>&lt;15</td>
<td>13 hrs</td>
</tr>
<tr>
<td>• 30% metabolized by non-CYP transformations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dose adjustment in renal insufficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rufinamide

- Approved as an adjunctive treatment for seizures associated with Lennox Gastaut syndrome

- Mechanism of action:
  - Modulates the activity of Na channels, prolonging the inactive state
Rufinamide (Cnt’d)

- Side effects:
  - Nausea, vomiting, fatigue, dizziness, somnolence, headache

- Pharmacokinetics

<table>
<thead>
<tr>
<th>Metabolism/ clearance</th>
<th>Enzyme induction/ Inhibition</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90 % metabolized by non-CYP</td>
<td>Induces CYP 3A4 (minor)</td>
<td>35</td>
<td>6-10 hrs</td>
</tr>
<tr>
<td></td>
<td>Inhibits CYP 2E1 (minor)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vigabatrin

- Used as an add-on agent in patients with refractory partial seizures

- Mechanism of action:
  - Irreversible inhibitor of GABA-transaminase that raises the concentration of GABA in the CNS
Vigabatrin (Cnt’d)

- **Side effects:**
  - Vision loss, drowsiness, fatigue, dizziness,
  - Rare: MRI abnormalities, depression, weight gain

- **Pharmacokinetics:**

<table>
<thead>
<tr>
<th>Metabolism/clearance</th>
<th>Enzyme induction/Inhibition</th>
<th>Protein Binding</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70% excreted renally as unchanged drug</td>
<td>Induces CYP 2C9</td>
<td>0</td>
<td>5-13 hrs</td>
</tr>
<tr>
<td>Dose adjustment in renal insufficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Concurrent illnesses

- Medical comorbidities are important to consider when selecting an AED

- Some comorbidities can be problematic → potential drug side effects or interaction

- Other → an opportunity to choose an AED that has efficacy in both conditions
Concurrent illnesses (Cnt’d)

- Renal disease
  - Renally excreted: gabapentin, topiramate, lacosamide, levetiracetm, and pregabalin
  - Topiramate and zonisamide are associated with nephrolithiasis
Concurrent illnesses (Cnt’d)

- Hepatic disease
  - Valproate and felbamate, and to a lesser extent, phenytoin and carbamazepine $\rightarrow$ hepatotoxicity
  - Many other are metabolized in the liver and require dose adjustment:
    - Carbamazepine, lamotrigine, phenytoin, phenobarbital
Concurrent illnesses (Cnt’d)

- Psychiatric disorders
  - Persons with epilepsy have a higher than expected prevalence of comorbid psychiatric disorders
  - Some AEDs (valproate, lamotrigine, carbamazapine, oxcarbazapine) have mood stabilizing properties (Bipolar disorders, anxiety and depression)
Concurrent illnesses (Cnt’d)

- In contrast, some AEDs, (phenobarbital, tiagabine, vigabatrin, topiramate) → cause or exacerbate a depressed mood

- Similarly, (levetiracetam, topiramate, vigabatrin, zonisamide, and ethosuximide) → psychosis

- Drug interactions:
  - Enzyme-inducing AEDs can decrease the plasma concentration of many antidepressants and benzodiazepines
Concurrent illnesses (Cnt’d)

- Migraine
  - Valproate, gabapentin, and topiramate → efficacy in migraine prevention
Concurrent illnesses (Cnt’d)

- Osteoporosis
  - AEDs in chronic use have been associated with bone loss
  - The evidence strongest for phenytoin
  - There is insufficient data to recommend avoiding or choosing any other specific AED

- Monitoring (chronic AED)
  - bone density, routine supplementation of calcium and vitamin D, and a consistent exercise regimen
Concurrent illnesses (Cnt’d)

- Diabetes
  - Valproate associated with weight gain, insulin resistance, the metabolic syndrome, and polycystic ovarian syndrome

- Carbamazepine, vigabatrin, gabapentin, and pregabalin are also, but less frequently, associated with weight gain

- Some AEDs (gabapentin, pregabalin, and possibly carbamazepine and topiramate) have efficacy in treating pain associated with diabetic neuropathy
Perampanel

- FDA approved → October 2012
- Add-on for partial seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
Perampanel (Cnt’d)

- Orally active
- Noncompetitive AMPA-type glutamate receptor antagonist
- It appears to inhibit AMPA-induced increases in intracellular calcium, reducing neuronal excitability
Perampanel (Cnt’d)

- Glutamate receptors:
  - NMDA receptor (N-methyl D-aspartic acid)
  - AMPA receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor)
Glutamate receptors Physiology

- http://www.sumanasinc.com/webcontent/animations/content/receptors.html
Glutamate receptors Physiology

Glutamate receptors Physiology

Glutamate receptors Physiology

Glutamate receptors Physiology

Glutamate receptors Physiology

Glutamate receptors Physiology

Glutamate receptors Physiology

Dosing

- **Not** receiving enzyme-inducing AED:
  - Initial: 2 mg qd at bedtime
  - Recommended dose: 8-12 mg qd at bedtime

- Receiving enzyme-inducing AED:
  - Initial: 4 mg qd at bedtime
  - Recommended dose: 8-12 mg once daily at bedtime

- May increase daily dose by 2 mg at weekly intervals based on response and tolerability (for both)
# Dose adjustment

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild impairment</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Severe impairment:</td>
<td>Use not recommended (has not been studied)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Use not recommended (has not been studied)</td>
</tr>
</tbody>
</table>
## Dose adjustment (Cnt’d)

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild impairment</td>
<td>Initial 2 mg qd; May increase daily dose by 2 mg every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Maximum: 6 mg qd</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>Initial 2 mg once daily; May increase daily dose by 2 mg every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Maximum: 4 mg qd</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>Use not recommended (has not been studied)</td>
</tr>
</tbody>
</table>
Black Box Warning

- Dose-related **serious and/or life-threatening neuropsychiatric events** (including aggression, anger, homicidal thoughts, hostility, and irritability)
  
- Most often occurring in first 6 weeks of therapy in patients with or without pre-existing psychiatric disease
  
- Monitor patients during dosage adjustments and when receiving higher doses
- Adjust dose or immediately discontinue use if severe or worsening symptoms
## Side effects

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>Central nervous system: Dizziness, somnolence, headache, fatigue, irritability</td>
</tr>
<tr>
<td>1% to 10%:</td>
<td>Cardiovascular: Peripheral edema</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous: Head injury</td>
</tr>
<tr>
<td></td>
<td>Central nervous system: Ataxia, vertigo, balance impaired, gait disturbance,</td>
</tr>
<tr>
<td></td>
<td>anxiety</td>
</tr>
<tr>
<td></td>
<td>Dermatologic: Bruising, skin laceration</td>
</tr>
<tr>
<td></td>
<td>Endocrine &amp; metabolic: Hyponatremia</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: Weight gain, nausea, vomiting, constipation</td>
</tr>
</tbody>
</table>
Clinical Trials
Study 304

Title: “Adjunctive perampanel for refractory partial-onset seizures”

Objective: To assess efficacy and safety of once daily 8 or 12 mg perampanel, a noncompetitive AMPA receptor antagonist, when added to concomitant AEDs in the treatment of drug resistant partial-onset seizure
Study 304 (Cnt’d)

- Multicenter, double-blind, placebo-controlled trial

- Inclusion Criteria:
  - ≥12 years, with ongoing seizure despite 1-3 AEDs

- 388 patients were randomized in 1:1:1 ratio to once daily perampanel 8mg, 12mg, or placebo
Study 304 (Cnt’d)

- Duration:
  - Total 19-week
  - 6-week titration (2mg/week increments to target dose)
  - Followed by 13 week maintenance period

- Primary endpoint $\rightarrow$ Percent change in seizure frequency
Figure 1  Patient flow

Subjects enrolled\(^a\)  N=534

Subjects randomized  n=390\(^b\)

Not treated  n=2

Screen failure  (n=147)
Reason:
- INC/EXC criteria  (n=126)
- Adverse event  (n=2)
- Subject choice  (n=13)
- Lost to follow-up  (n=4)
- Admin/other  (n=2)

Safety analysis set  n=388

ITT analysis set  n=387

Placebo  n=121
- Completed - 106 (88%)
- Discontinued - 15 (12%)
- Reason for discontinuation:
  - Adverse event - 7 (6%)
  - Subject choice - 3 (3%)
  - Lost to follow-up - 0
  - Inadequate therapeutic effect - 2 (2%)
  - Admin/other - 3 (3%)

Perampanel 8 mg  n=133
- Completed - 114 (86%)
- Discontinued - 19 (14%)
- Reason for discontinuation:
  - Adverse event - 9 (7%)
  - Subject choice - 7 (5%)
  - Lost to follow-up - 2 (2%)
  - Inadequate therapeutic effect - 0
  - Admin/other - 1 (<1%)

Perampanel 12 mg  n=133\(^c\)
- Completed - 100 (75%)
- Discontinued - 34 (25%)
- Reason for discontinuation:
  - Adverse event - 24 (18%)
  - Subject choice - 4 (3%)
  - Lost to follow-up - 0
  - Inadequate therapeutic effect - 2 (2%)
  - Admin/other - 4 (3%)
Study 304(Cnt’d)

- Results

<table>
<thead>
<tr>
<th></th>
<th>Reduction in seizure frequency</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-21%</td>
<td></td>
</tr>
<tr>
<td>Perampanel 8mg</td>
<td>-26.3%</td>
<td>0.0261</td>
</tr>
<tr>
<td>Perampanel 12mg</td>
<td>-34.5%</td>
<td>0.0158</td>
</tr>
</tbody>
</table>

- 68 patients (17.5%) discontinued perampanel due to adverse effects
- Adverse effects: dizziness, somnolence, irritability, headache, fall, and ataxia
Conclusions: This trial demonstrated that once-daily, adjunctive perampanel at doses of 8 or 12 mg improved seizure control in patients with uncontrolled partial-onset seizures. Doses of perampanel 8 and 12 mg were safe, and tolerability was acceptable.
<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To assess the efficacy and safety of once daily doses of perampanel 8 and 12 mg when added to 1-3 concomitantly administered, approved (AEDs) in patients with uncontrolled partial-onset seizures</th>
</tr>
</thead>
</table>
| **Methods** | Multicenter, double blind, placebo-controlled trial  
Randomized to 8mg, 12 mg or placebo  
Duration 19 weeks  
Primary endpoint → responder rate and % change in seizure frequency  
Secondary endpoint → % change in the frequency of complex partial plus secondarily generalized seizures |
| **Results** | 50% responder rate: 14.7%, 33.3%(p value 0.002) and 33.9%(p value <0.001) respectively for placebo, 8mg, 12 mg  
% change in frequency: -9.7; -30.5(p value <0.001); -17.6 (p value 0.011) |
Studies 306, 307

- Studies 306 and 307 demonstrated consistent results with the previous trials
Thank you

Questions/comments