### Background and Overview

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<tr>
<td>Funding Source</td>
<td>Supported by grants from the National Institutes of Health (NIH)</td>
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#### Introduction/Brief Background
- Absence seizures are classified as a generalized seizure, meaning that there may be a focal point of origination, however, the seizure activity spreads over the entire brain
- Absence seizures are the most common type of seizure disorder in children and adolescents
- With this type of seizure, there is a sudden, brief lapse of consciousness with no loss of postural control. There is also no post-ictal confusion associated with absence seizures (the main differentiating factor with complex, partial seizures)
- There are many medications available to treat absence seizures. For this reason, it can be difficult to pick one antiepileptic medication to begin empirically in new onset absence seizures.
- Three commonly used medications for empiric therapy include ethosuximide, valproic acid, and lamotrigine.
- This study evaluates these three medications to help clinicians make better therapy recommendations.

#### Objective
To perform a double-blind, randomized trial to assess the efficacy, tolerability, and neurophysiological effect of three commonly used antiepileptic medications to determine the optimal empirical monotherapy for children with childhood absence epilepsy

#### Methods

##### Study Design
- Double-blind, randomized trial
- Patients were randomized to receive study medications in a 1:1:1 ratio utilizing a computer-generated randomization schedule
- 16 weeks in length
- N=453 (E 156, L 149, and V 148) at study commencement
  - Ethosuximide 250mg capsules or 250mg/5mL syrup
  - Valproic acid 25mg capsules or 125mg sprinkles
  - Lamotrigine 5mg and 25mg chewable tablets or 25mg tablets
- Study medications were prepared at a central pharmacy
- Blinding of medications: use of a double-dummy approach or over-encapsulation
- Dose titrations were made every 1-2 weeks until freedom from seizures or side effect limitations
- Baseline neuropsychological testing was performed using CPT-II to assess attention, verbal and nonverbal intelligence, vocabulary, memory, learning skills, visuomotor integration, executive function, and academic achievement.
- Study visits were performed every four weeks
- Seizure assessments were performed to indicated if the child was seizure free or if a seizure could still be induced (hyperventilation, EEG, etc)
- At 16 weeks, if patients were not receiving the maximum dose of a medication and were still experiencing seizures, one more titration could be utilized (20 week total)
- Open-label phase: only an option for those patients who met one of the qualifications defined as treatment failure. They would be randomly assigned to one of the other two groups for therapy.

#### Selection and Enrollment
**Inclusion Criteria:** Must be 2.5 to 13 years old; have new onset childhood absence epilepsy that was clinically diagnosed; have bilateral synchronous and symmetric spike waves on an EEG with at least one lasting three seconds or more; weight at least 10kg; have a BMI below the 99th percentile; have normal CBC, ALT, AST, and bilirubin levels; girls have to be premenarchal.
**Exclusion Criteria:** The patient received anti-seizure medication for more than seven days before randomization; history of non-febrile seizures other than absence; history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy; history of severe dermatological reaction to any medication; history of psychiatric disease, autistic-spectrum disorder, or any clinically significant medical condition.

### Statistical Analysis
- Power was calculated to be 80% and was met.
- P-value determined to be 0.05.
- Baseline characteristics were compared using either an exact chi-squared test or a two-way ANOVA test depending on the characteristic (no significant differences).
- All subjects who received at least one dose of a study drug were included in the safety analysis.
- Primary and secondary outcomes were evaluated with the use of a Fisher’s exact test for pairwise comparisons (p=0.017).
- Odds ratios were calculated at a 95% confidence interval.
- Kaplan-Meier curves were constructed to show the time to treatment failure.

### Primary and Secondary outcomes
*Including subgroup analysis, also include both efficacy and safety parameters, if appropriate*

#### Primary Outcome: Freedom-from-failure rate
- **N=451** for safety analysis (two patients never received medication) and **N=446** for efficacy analysis (two patients never received medication and five patients were ineligible upon central review).
- Overall, 209 patients were free from treatment failure at 16 (20) weeks.
- Ethosuximide: 53% freedom from failure.
- Valproic Acid: 58% freedom from failure.
- Lamotrigine: 29% freedom from failure.
- V vs. E: OR 1.26, 95% CI 0.8-1.98, p=0.35.
- E vs. L: OR 2.66, 95% CI 1.65-4.28, p<0.0001.
- V vs L: OR 3.34, 95% CI 2.06-5.42, p<0.0001.

#### Secondary Outcome: Evidence of attention dysfunction
- A confidence index of 0.6 or higher on the CPT-II test was indicative of an attention deficit disorder.
- Baseline testing indicated that cognition was within normal range for all subjects.
- CPT-II testing was elevated (>0.6) in 112 patients (of the 316 that could be tested).
- Ethosuximide: 33%.
- Valproic Acid: 49%.
- Lamotrigine: 25%.
- V vs. E: OR 1.95, 95% CI 1.12-3.41, p=0.03.
- E vs. L: OR 1.56, 95% CI 0.85-2.85, p=0.17.
- V vs. L: OR 3.04, 95% CI 1.69-5.49, p<0.0001.

- Relatively well tolerated in regards to adverse effects.
- In eight patients, treatment was discontinued due to tonic-clonic seizures.
- Seventeen types of adverse events were reported, only eight subjects had events requiring hospitalization.
- Thirteen patients ceased treatment due to the development of a severe rash (non SJS).

### Conclusion
- For children with childhood absence epilepsy, ethosuximide and valproic acid were significantly more effective than lamotrigine in controlling seizures (primary outcome).
- Ethosuximide had a significantly smaller negative effect on attention measures than valproic acid (secondary outcome).
- There were no significant differences among the three groups in regard to discontinuation of treatment due to intolerable side effects.
- Ethosuximide is the optimal choice in for empirical monotherapy for childhood absence epilepsy.
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<th>Student’s Discussion &amp; Conclusion</th>
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| **Strengths**                     | • RCT is the gold standard for testing a hypothesis  
|                                  | • Similar treatment groups in regards to demographics  
|                                  | • Appropriate primary and secondary outcomes to help clinicians make a more appropriate choice in regards to empirical monotherapy  
|                                  | • Utilized appropriate dosing as per clinical recommendations  
|                                  | • Allowed for an open-label phase for those patients not adequately controlled on a certain medication after 20 weeks  |
| **Limitations**                  | • Patients who received at least one dose of medication were included in safety study  
|                                  | • Only short term effectiveness was evaluated while treatment often lasts for 2-5 years  
|                                  | • In regards to the CPT-II test, 0.6 is not a definite diagnosis for attention disorders (though it is utilized most commonly in clinical practice)  |
| **Clinical Applications**        | Absence epilepsy is the most common form of epilepsy in children. There are many different medications available to treat this disorder. This study looked at three common treatment modalities for their effectiveness as well as their tolerability. Evaluating this topic is extremely important in helping clinicians make proper recommendations to begin treatment in a naïve patient. Often times, doses will be titrated to a maximum tolerable dose and medication regimens are converted; however, having a relatively reliable starting medication is beneficial to the patient.  |
| **Recommendations**             | I feel that this study was a well designed, randomized trial and feel comfortable recommending ethosuximide as the optimal choice for empiric treatment in childhood absence epilepsy. While there are certain side effects associated with this medication, they are usually transient over time and do not hinder therapy. Ethosuximide is also an older medication, allowing it to be available generically as well as established in the clinical setting.  |
| **Level of Evidence**            | Delfini Grade B: High quality in design, execution with non-lethal threats to validity, and sufficiently useful information to aid in clinical decision-making leading to reasonable certainty in drawing conclusion  |