Emerging Developments in Antiepileptic Drug Therapy

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Abstract
Nearly two out of five patients with epilepsy continue to have seizures despite treatment with antiepileptic drugs or surgery. This dismal record has prompted the reevaluation of current therapies in underserved special populations, such as children with epileptic disorders, and the identification of new antiepileptic compounds with novel mechanisms of action and a tolerable side-effect profile. At the 64th Annual Meeting of the American Academy of Neurology, researchers presented data from the CATZ study, a recently completed phase III, double-blind, placebo-controlled trial evaluating the safety and efficacy of zonisamide in pediatric patients with partial-onset seizures. Other presenters described the results of three separate phase III randomized clinical trials exploring the clinical benefits and tolerability of perampanel as adjunctive therapy in adult patients with refractory focal or partial-onset seizures.

The past few decades have produced several exciting developments in our understanding and management of epilepsy, including renewed enthusiasm for surgery, trials of new therapeutic neurostimulation devices, and several new antiepileptic drugs (AEDs). This research effort is providing practitioners with an expanding array of therapeutic choices, allowing them to tailor medication regimens according to patient response and side-effect profiles. However, these advances have so far produced little improvement in patients achieving seizure freedom. Nearly 40% of patients with epilepsy remain refractory to AEDs. At best, current surgical treatment offers long-term seizure freedom in 60%–70% of selected ideal patients.

For many other individuals with epilepsy, however, surgery is not an option, and neurostimulation offers little more than a palliative option. Contemporary research is focusing on identifying novel therapeutic targets or mechanisms of action for antiepileptic therapy and developing new preclinical evaluation methods to pinpoint more effective treatments that reduce or prevent epileptogenesis. Additional emphasis is being placed on reevaluating current therapies in special populations, improving the design and efficacy of neurostimulation devices, treating common comorbidities associated with epilepsy, and refining clinical trial designs.

Zonisamide efficacy in Pediatric Patients
Based on a presentation by Anna Rosati, MD, PhD, Paediatric Neurology Unit, Children’s Hospital Anna Meyer, University of Florence, Florence, Italy

Zonisamide, which was approved by the FDA in 2000 for the adjunctive treatment of partial seizures in adults, has several mechanisms of action. It acts as a sodium-channel antagonist; reduces inward T-type calcium-channel currents; and inhibits neurotransmitters primarily by affecting γ-aminobutyric acid, serotonin, and dopamine levels.

Epilepsy treatments generally remain underinvestigated in the pediatric population. Several AEDs, including zonisamide, have been tested in phase II clinical trials to establish a pharmacokinetic profile and determine the adverse effects of adjunctive therapy when these drugs are used in pediatric patients. However, their efficacy has not been studied in a young population.

Data from the CATZ trial, a recently completed, phase III, double-blind, placebo-controlled, multicenter study,
were presented at the 2012 Annual Meeting of American Academy of Neurology (AAN) by Rosati et al. The investigators assessed the efficacy and safety of zonisamide in 207 young patients aged 6–17 years old with partial-onset seizures who were being treated with one or two AEDs. The patients were randomized to receive either placebo (n = 100) or zonisamide (n = 107); the zonisamide dosage was titrated from 1 mg/kg/d to 8 mg/kg/d over a period of 8 weeks. Patients were then maintained on that dosage for 12 weeks and subsequently either continued taking 8 mg/kg/d of the drug as part of an extension study or were gradually withdrawn from zonisamide therapy.

Endpoints were ≥ 50% seizure frequency reduction and median percent change from baseline in 28-day seizure frequency during the 12-week maintenance period and the entire double-blind period (ie, titration plus maintenance). A total of 95 patients treated with zonisamide and 93 patients receiving placebo completed the study.

The results are summarized in Table 1. A ≥ 50% reduction in seizure frequency was achieved in 50.5% of patients given 8 mg/kg/d of zonisamide and 31.0% of those given placebo. The secondary endpoint, the median percent change in baseline 28-day seizure frequency, was −50.0% for the zonisamide group and −24.5% for the placebo group during the maintenance phase (between-group difference, 25.2%) and −42.2% for zonisamide and −20.4% for the placebo group during the entire double-blind period (between-group difference, 25.3%).

Adverse effects (most commonly, headache, decreased appetite, nasopharyngitis, and upper abdominal pain) were reported in 55.1% of patients receiving zonisamide and 50.0% of those given placebo. Adverse effects that were associated with zonisamide therapy to a significantly greater extent than with placebo use included decreased appetite, weight loss, somnolence, vomiting, and diarrhea. Severe adverse effects and those leading to withdrawal from the study occurred more often among patients using placebo than among those using zonisamide, whereas serious adverse effects were seen in four patients treated with zonisamide and two using placebo.

This study demonstrated that zonisamide is an effective adjunctive treatment for partial-onset seizures in children ≥ 6 years of age when compared with placebo. Further, use of zonisamide in this pediatric population was not associated with serious or new adverse effects or safety concerns.

**TABLE 1**

Improvement in 50% Responder Rate and 28-Day Seizure Rate with Zonisamide vs Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zonisamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% Reduction in seizures</td>
<td>50.5%</td>
<td>31.0%</td>
</tr>
<tr>
<td>Median 28-day seizure rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind phase</td>
<td>−42.2%</td>
<td>−20.4%</td>
</tr>
<tr>
<td>Maintenance phase</td>
<td>−50.0%</td>
<td>−24.5%</td>
</tr>
</tbody>
</table>

Source: Rosati et al.12

**Perampanel effectively reduced seizure frequency when given as adjunctive therapy to patients with refractory partial-onset epilepsy.**

**Perampanel Establishes Efficacy in Stage III Clinical Trials**

Based on presentations by Gregory Krauss, MD, Associate Professor and Director, Adult Epilepsy Clinic, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; Antonio Laurenza, MD, Executive Director, Eisai Medical Research, Woodcliff Lake, New Jersey; Jacqueline French, MD, Professor of Neurology and Co-Director of Epilepsy Research and Epilepsy Clinical Trials, New York University Comprehensive Epilepsy Center, New York, New York; Ziad Hussein, PhD, Senior Director of Modelling and Simulation, Eisai Ltd, Hatfield, Hertfordshire, United Kingdom; and Lynn Kramer, MD, FAAN, President of Eisai Neuroscience Product Creation Unit, Ridgefield Park, New Jersey.

Perampanel, a noncompetitive α-aminoo-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist, is a novel investigational compound being developed to treat patients with epilepsy. Glutamate, the predominant excitatory chemical neurotransmitter, has been long studied for its role in acute seizures and epilepsy. Until recently, clinical investigators focused on the link between N-methyl-D-aspartate receptors and glutamate. More recently, studies have been directed toward AMPA receptors, which transmit the majority of fast glutamaterig signaling and may play a central role in seizure generation and spread.13

Following promising preclinical and early clinical studies, phase III trials of perampanel have been completed. The drug effectively reduced seizure frequency when given as adjunctive therapy to patients with refractory partial-onset epilepsy. During the 2012 annual AAN meeting, several investigators summarized data from three multicenter, double-blind, parallel-group phase III trials (studies 304, 305, and 306), which were performed in three phases: prerandomization (baseline period), a double-blind phase, and a follow-up period.14–18

**Patient Population and Treatment Schema**

A total of 1,478 patients (age ≥ 12 years) with uncontrolled focal or partial-onset seizures while taking up to three AEDs were randomized to receive adjunctive therapy with 8 or 12 mg/d of perampanel or placebo (studies 304 and 305) or 2, 4, or 8 mg/d of perampanel or placebo (study 306) over 6 weeks. The dosage was titrated upward by 2 mg/wk until the target dose was reached; patients then continued on maintenance therapy for 13 weeks. Patients with primary generalized epilepsy, Lennox-Gastaut syndrome, or a history of status epilepticus within the previous year were excluded from the study. Seizures were recorded daily in a patient diary and normalized to 28 days for analysis.
To determine the dependency of response rate on perampanel dosage, Krauss et al14 evaluated 50%, 75%, and 100% responder rates in patients given 2, 4, 8, or 12 mg/d of perampanel. Data were pooled from previously described phase III trials with a 6-week titration period and 13-week maintenance period (n = 442). Latin-American patients were excluded due to a regional effect that resulted in a high placebo response. Responder rates were defined as the proportion of patients having a lower seizure frequency as compared with the 28-day baseline seizure rate (median, 10.2–18.9).

Responder rates and last medication dose determined during the maintenance period (Table 2)14 suggested that use of 4–12 mg/d of perampanel significantly increased 50% and 75% responder rates in a dose-dependent manner. Additionally, a trend toward seizure freedom with increasing perampanel exposure was observed.

Time to Seizure Recurrence

Laurenza et al15 employed a novel study design, measuring median and individualized “time to event,” which was intended to reduce baseline variability and to allow patients to complete studies with less exposure to the drug. Endpoints were median time to 1st, 3rd, 6th, 9th, and 12th seizure; the individualized temporal endpoint was the median time for patients to reach their baseline 28-day seizure rate (Nth seizure).

Data were pooled from the phase III studies 304, 305, and 306 and excluded patients from Central and South America. Adjunctive therapy with perampanel prolonged the median times to baseline, 28-day seizure rate (Table 3)15; median time to next seizure over baseline (Table 4)15; and median times to 6th, 9th, and 12th seizure events.

These results suggested that administration of 4–12 mg/d of perampanel effectively prolonged the 28-day seizure rate and time to next seizure. In addition, they supported the outcomes of previous investigations, showing that 4–12 mg/d of perampanel is effective as adjunctive therapy of partial-onset seizures. The lack of seizure-rate prolongation with the 12-mg/d dose was attributed to most patients reaching a 12th seizure before receiving the full 12-mg daily dose.

These results supported the use of an individualized “time to event” in future studies. Additionally, the investigators suggested that adequate evaluation of later or higher drug exposure would be better reflected by endpoints involving long titration periods and/or high baseline event frequency.

Efficacy with Concomitant AEDs

French et al16 analyzed the effect of concomitant AED administration on perampanel efficacy via assessment of seizure frequency and responder rate. This study included 1,478 pooled phase III trial participants. After randomization, 180 patients were given 2 mg/d of perampanel, 172 were given 4 mg/d of perampanel, 431 were given 8 mg/d of perampanel, 254 were given 12 mg/d of perampanel, and 441 were given placebo. Endpoints were median percent change in 28-day seizure frequency (Table 5)16 and 50% responder rate (Table 6).16 Patients used an average of 2.2 concomitant AEDs, most commonly carbamazepine (n = 491), valproate (n = 478), lamotrigine (n = 457), and valproate (n = 478), lamotrigine (n = 457),...
and levetiracetam (n = 435).

The findings suggested that 4–12 mg/d of perampanel is an effective adjuvant therapy for reducing seizure frequency and increasing responder rates. Further, the efficacy of this drug was not influenced by the concomitant use of other AEDs.

**Effect of Concomitant AEDs on Perampanel Pharmacokinetics and Pharmacodynamics**

Hussein and colleagues\(^\text{17}\) studied the pharmacokinetic and pharmacodynamic effects of perampanel as they related to demographic factors and concomitant AED administration. In addition, the authors performed an analysis of predicted exposure/efficacy with the last dose achieved in a model.

Patients in studies 304, 305, and 306 were randomized and treated with perampanel as described previously. Of the 1,478 participants in the phase III trials, 1,109 patients were included in the pooled pharmacokinetic/pharmacodynamic study (770 patients in the pharmacokinetic study alone, including 745 in the last-dose analysis). Investigators compared blood samples taken at baseline with those obtained during the double-blind treatment phases, maintenance therapy periods, and at the end of the follow-up phases or upon discontinuation of perampanel therapy. Perampanel levels were determined via liquid chromatography and mass spectroscopy.

Investigators reported that 12 concomitant AEDs (carbamazepine, lamotrigine, valproate, levetiracetam, topiramate, oxcarbazepine, clobazam, zonisamide, phenytoin, clonazepam, pregabalin, and phenobarbital) were used by at least 50 patients in the pharmacokinetic/pharmacodynamic population analysis. Furthermore, 71% of patients were prescribed at least one perampanel inducer (Table 7).\(^\text{17}\)

Mean plasma perampanel concentrations remained linear over the dose range, regardless of concomitant AED use. The pharmacokinetic/pharmacodynamic analysis demonstrated that seizure frequency decreased and 50% responder rate increased in a linear fashion with increasing perampanel serum level at steady state, regardless of the presence of a concomitant perampanel inducer.

Adverse effects (Table 7)\(^\text{17}\) increased with greater perampanel exposure and were not affected by demographic factors or use of concomitant AEDs, including perampanel inducers. No change in appetite or headaches related to perampanel concentration was seen. Demographic factors (age, sex, body mass, and race) did not affect the exposure/efficacy relationship, the probability of response to perampanel, or the occurrence of adverse effects.

**Dose-Response Analysis**

Kramer and others\(^\text{18}\) assessed 28-day seizure frequency and 50% responder rate from patients enrolled in the three pooled phase III trials (studies 304–306) and an open-label extension study (OLE 307). This research involved 209 patients who completed double-blind phase III trials involving 8 mg/d of perampanel to start and then 12 mg/d during the conversion period of the OLE study. Another analysis was performed on patients randomized to receive 12 mg/d of perampanel by the conversion period. Latin-American patients were excluded from the analysis due to a regional placebo effect.

The findings suggested that improved perampanel efficacy via reduced seizure frequency and increased responder rate can be achieved with doses increased to 12 mg/d from 8 mg/d (Table 8).\(^\text{18}\)

### CONCLUSION

The relatively recent proliferation of new AEDs and treatments for intractable epilepsy has not had a significant impact on patients achieving seizure freedom. A critical shift in the development and assessment of therapies, however, has produced novel AEDs; this movement is leading to a reevaluation of current therapies for different target populations. Whether this new emphasis will improve the static efficacy facing current therapies is yet to be seen. Both zonisamide and perampanel have demonstrated promising efficacy in pediatric and adult patients, respectively, with refractory partial-onset seizures in medically refractory patients, with the potential to improve the current level of AED efficacy and provide new options for the treatment of epilepsy in these populations.

### REFERENCES


### TABLE 7

<table>
<thead>
<tr>
<th>Perampanel Inducers</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Gait disturbances</td>
</tr>
<tr>
<td>Topiramate (mild)</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
</tr>
<tr>
<td></td>
<td>Euphoric mood</td>
</tr>
</tbody>
</table>

*Adverse effects are listed in decreasing order of occurrence.

Source: Hussein et al\(^\text{17}\)

### TABLE 8

Median Percent Change in 28-Day Seizure Frequency and 50% Responder Rate with Perampanel Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>8 mg/d</th>
<th>8 mg/d + 12 mg/d*</th>
<th>12 mg/d*</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day seizure frequency</td>
<td>−32.4%</td>
<td>−43.3%</td>
<td>−42.1%</td>
</tr>
<tr>
<td>50% Responder rate</td>
<td>37.8%</td>
<td>43.5%</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

*Patients completing maintenance therapy with 8 mg/d of perampanel and then increased to 12 mg/d

*Patients randomized to and then maintained on 12 mg/d of perampanel

Source: Kramer et al\(^\text{18}\)
Society Basic Science Committee; The International League Against Epilepsy Working Group on Recommendations for Preclinical Epilepsy Drug Discovery. 


