Perampanel is the first selective noncompetitive AMPA receptor antagonist to be successfully developed to treat epilepsy. The drug was recently approved in the United States and Europe to treat localization-related seizures in patients ≥12 years old (1, 2). In the past, glutamate receptor antagonists were evaluated to treat a variety of neurologic disorders, including hypoxic injury, amyotrophic lateral sclerosis, Parkinson disease, and epilepsy. NMDA receptor antagonists, however, produced unacceptable CNS depression and talampanel, a selective noncompetitive AMPA antagonist, was not developed after an initial promising epilepsy trial and limited effects in ALS and glioma trials (3).

Perampanel—2-(2-oxo-1-phenyl-5-pyridin-2-yl)-1,2-dihydropripyridin-3-yl)benzonitrile hydrate (4:3) or benzonitrile, 2-(1',6'-dihydro-6'-oxo-1'-phenyl[2,3'-bipyridin]-5'-yl)—was discovered and developed by Eisai Laboratories (4–6). It was not effective in treating multiple sclerosis, Parkinson disease, or migraine prophylaxis, but was tested at low 0.5- to 4-mg/d doses. A subsequent “maximum tolerated dose” (MTD) trial showed that nearly all patients with epilepsy tolerated 4-mg/d doses; a dose-escalation trial then showed that the majority of patients tolerated doses of 6 to 12 mg/d (7). Epilepsy trials subsequently evaluated perampanel doses of 2 to 12 mg/d (compared with placebo), with the largest number treated with 8-mg/d doses. A major feature of perampanel development is that its long half-life, approximately 105 hours (24 hours in the presence of perampanel metabolism inducer antiepileptic drugs [AEDs]), permits it to be dosed at bedtime, which alleviates its most common adverse event of postdose sedation.

The efficacy, and safety and tolerability of perampanel were demonstrated in three large global trials and in several extension studies (Figure) (8–12). Treatment with perampanel 4 mg/d, but not 2 mg/d, was effective and established the lower effective dose range. Doses of 8 and 12 mg/d were effective compared with placebo, with only small increases in efficacy with 12 mg/d compared with 8 mg/d. Responder rates (>50% seizure reduction) in pooled trial data were 28.5% for 4-mg/d, 35.3% for 8-mg/d, and 35.0% for 12-mg/d doses (compared with placebo 19.3%) (12). Reductions in median seizure frequency were 23.3% for 4-mg, 28.8% for 8-mg, and 27.2% for 12-mg dose groups. One clinical trial included several study sites in Latin America with unusually high placebo responses (9). These data were included in the primary efficacy analysis but were removed for several of the sensitivity analyses. Perampanel was tested in a large number of countries, including many patients in China; with similar treatment responses across various regions and ethnicities.

Important secondary efficacy endpoints showed benefits of 8- to 12-mg/d doses. The proportion of patients with ≥75% reduction in seizure frequency was 12.2%, 17.4%, and 16.9% for 4-mg, 8-mg, and 12-mg/d doses, respectively. The proportion of seizure-free patients for study completers was 4.4%, 3.5%, and 4.1% for 4-, 8-, and 12-mg doses, respectively, compared with 1% for placebo in the pooled data (12). Secondary generalized seizures (for patients with this seizure type) decreased by 62.9% during treatment with 8 mg/d and 53.3% with 12 mg/d (12). Patients’ treatment responses appeared to be sustained during 1 to 4 years of open treatment (11). Early postmarketing experience using perampanel in Germany has shown similar responses (13).

Pharmacology
Perampanel is rapidly absorbed after oral administration with a long half-life of approximately 105 hours in uninduced patients (approximately 24 hours in induced patients). The drug is 95% protein bound. Perampanel is oxidized into a dihydrodiol metabolite and an N-acetyl cysteine conjugate by CYP3A4 and CYP3A5 and is then excreted as glucuronidated metabolites; about 50% of perampanel is excreted unchanged (14). Cytochrome induction by carbamazepine reduces the half-life and plasma concentrations of perampanel by approximately 70%, phenytoin, and oxcarbazepine reduces these by approximately 50%. Pooled pharmacokinetic sampling showed expected reductions in perampanel concentrations across its dosing range in clinical trials (15). Perampanel has few other drug interactions—topiramate concentrations increased by...
Perampanel: A Selective AMPA Antagonist

20%, and oxcarbazepine concentrations increased by 35% in pooled PK samples (15). Perampanel 12 mg/d decreased levonorgestrel concentrations by 40%, and patients may require additional nonhormonal forms of contraception while taking perampanel. Therapeutic plasma concentrations have not been established for perampanel, though the effective dose range of 4- to 12-mg/d was associated with a range in plasma concentrations of approximately 200 to 800 ng/mL (15).

Tolerability and Safety of Perampanel

Plasma concentrations for perampanel peak 0.5 to 2 hours after dosing (T_{max}) and may be associated with sedation; this was successfully alleviated in clinical trials by bedtime dosing with the once-a-day medication. In adjunctive treatment trials, the most common adverse events were CNS-related symptoms similar to other AEDs—dizziness, drowsiness, blurred vision, and imbalance. These symptoms were more common at higher doses (e.g., dizziness was reported by 16% with 4-mg/d compared with 32% with 8-mg/d and 43% during 12-mg/d treatment) (12). These symptoms were often transient during dose titration; most patients successfully tolerated forced titration to 8- to 12-mg/d doses during conversion to open treatment in extension trials (11, 16).

Special adverse events reported during clinical trials were unexplained falling, particularly in the elderly, and psychiatric symptoms. Perampanel labeling includes a warning for possible psychiatric symptoms: aggression, hostility, unusual changes in mood, personality, or behavior, and other behavioral symptoms such as homicidal ideation and threats. Homicidal ideation or threat were exhibited in 0.1% of 4,368 perampanel treated patients in controlled and open label studies, including non-epilepsy studies (2). In patients with epilepsy, these symptoms were usually associated with lethargy and somnolence, and most patients had prior histories of homicidal thoughts, mood or behavioral disorders. Systemic complications of perampanel treatment were rare and not increased compared with placebo. Patients experienced a small increase in weight (mean 1.1 kg compared with 0.3 kg with placebo treatment); though, 46% of all patients were overweight or obese at study entry. No unusual laboratory changes or safety concerns were observed during 1 to 4 years of exposure in extension trials (11, 16).

Rashes were rare, occurring in 2.2% of patients treated with perampanel compared with 1.6% for placebo, with no definite cases of severe cutaneous reactions (17).

Perampanel studies evaluated patients aged 12 to 77 years; only 28 patients were aged >65 years (1, 14). Patients from a large number of regions and ethnicities were exposed with similar efficacy and safety findings during treatment.

Starting and Adjusting Treatment With Perampanel

Perampanel is approved in Europe and the United States for treating localization-related epilepsy in patients ≥12 years old. Perampanel can be initiated at 2 mg qHS and increased 2 mg every 1 to 2 weeks, usually to 8- to 12-mg/d doses. During blinded titration in extension studies, most patients

![Graph](image-url)
achieved doses of 8- to 12-mg/d (median, 10.6 mg/d) (11, 16). Carbamazepine, phenytoin, and oxcarbazepine may induce perampanel metabolism, and higher perampanel doses may be required. Patients stopping AEDs, which induce perampanel metabolism, need to be monitored for “de-induction” effects on perampanel concentrations. Patients should usually discontinue perampanel slowly to avoid rapidly “unmasking” of a treatment effect; however, because of the long half-life of perampanel, it can be discontinued abruptly if necessary (14).

Conclusion
Perampanel is a first-in-class selective noncompetitive AMPA receptor antagonist shown to be effective as adjunctive treatment for partial-onset seizures. Future studies will be needed to examine perampanel’s long-term safety, efficacy for treating children, and effectiveness for treating other seizure types, particularly the generalized epilepsies.

References


American Epilepsy Society

Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
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Section #1 Identifying Information

1. Today’s Date: 7/30/13

2. First Name  Last Name  Degree
   Gregory Krauss  MD

3. Are you the Main Assigned Author?  Yes  No

If no, enter your name as co-author:

4. Manuscript/Article Title:

5. Journal Issue you are submitting for:

Section #2 The Work Under Consideration for Publication
Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
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<th>Type</th>
<th>No</th>
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* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
**Section #3 Relevant financial activities outside the submitted work.**
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**
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