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Perampanel: A Selective AMPA Antagonist for Treating Seizures

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Perampanel is a selective, noncompetitive AMPA receptor antagonist that has recently been approved for treating localization-related epilepsy. This article reviews the pharmacology, clinical development, efficacy, and safety/tolerability of perampanel.

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 dihydropyridin-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

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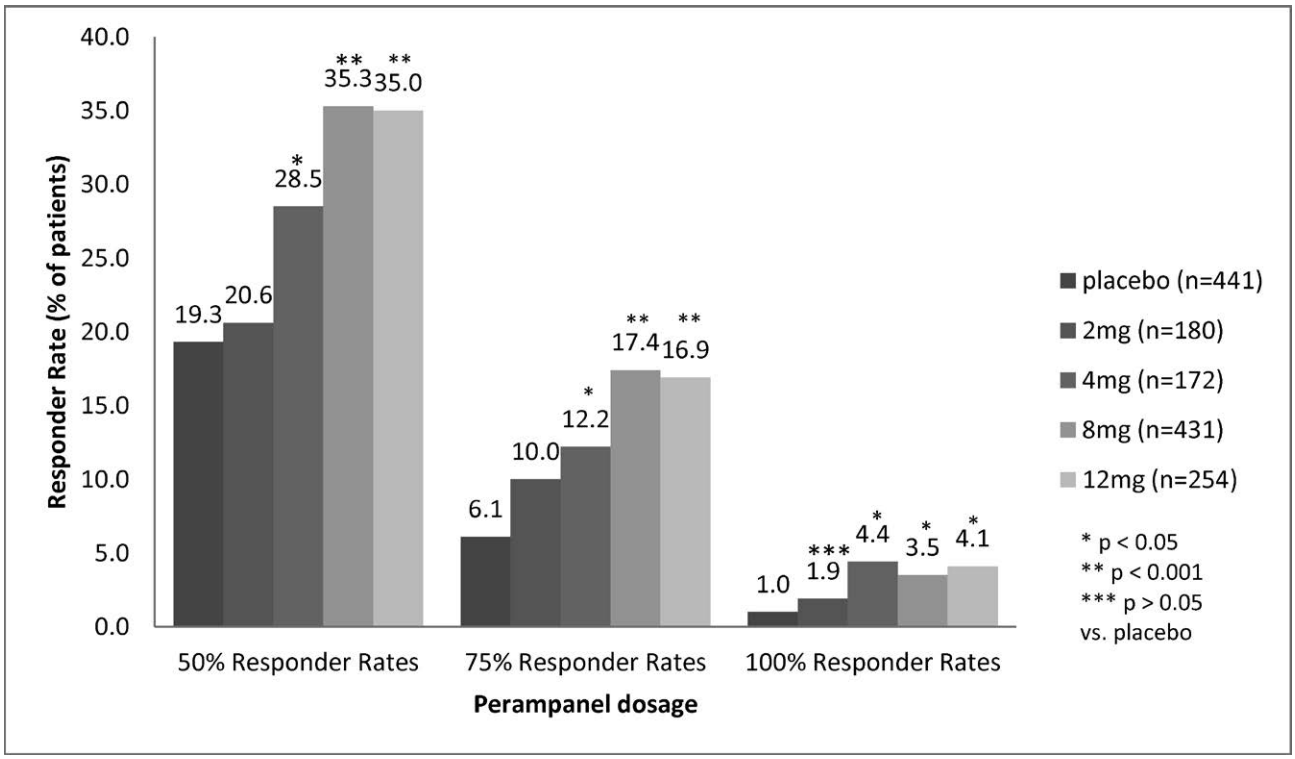

FIGURE. Efficacy of perampanel: proportions of 50%, 75%, and 100% responders (Intent-to-Treat analysis of pooled data for all partial seizure types) (Adapted from Steinhoff et al. (12)).

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

TABLE. ***Incidence of Common Side Effects (>5% of patients) During Adjunctive Perampanel Treatment: Pooled Analysis Adapted from Steinhoff et al. (12)***

		Perampanel Treatment Groups			
Adverse Event, *n* (%)	**Placebo (*n* = 442)**	**2 mg (*n* = 180)**	**4 mg (*n* = 172)**	**8 mg (*n* = 431)**	**12 mg (*n* = 255)**
Any treatment-emergent adverse event	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

Data were derived from Steinhoff et al. (12).

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.

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