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REVIEW ARTICLE

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Perampanel, an AMPA receptor antagonist: From clinical research to practice in clinical settings

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Abstract

Epileptic seizures are refractory to treatment in approximately one-third of patients despite the recent introduction of many newer antiepileptic drugs (AEDs). Development of novel AEDs therefore remains a high priority. Perampanel is a first-in-class non-competitive selective AMPA receptor antagonist with a unique mechanism of action. Clinical efficacy and safety of perampanel as adjunctive treatment for focal seizures with/without secondary generalization (±SG) and primary generalized tonic-clonic (PGTC) seizures have been established in five phase 3 randomized controlled trials (RCTs), and a long-term extension study, and perampanel is approved as monotherapy for focal seizures ±SG in the USA. In patients with focal seizures ±SG, add-on perampanel resulted in median percent reduction in seizure frequency 23.3%-34.5% and ≥50% responder rate 28.5%-37.6%; in PGTC seizures, these results were 76.5% and 64.2%, respectively. Efficacy among adolescents (reduction in seizure frequency 34.8%-35.6%; ≥50% responder rate 40.9%-45.0%) and elderly people (reduction in seizure frequency 12.5%-16.9%; ≥50% responder rate 22.2%-42.9%) is similar to those in adults, and results remain comparable between Asian (reduction in seizure frequency 17.3%-38.0%) and global populations. Perampanel has been extensively studied in real-world clinical practice, with similar efficacy and safety results to the RCTs (≥50% responder rate 12.8%-75.0%; adverse events of somnolence/sedation, dizziness, ataxia, and behavioral changes). Real-world observational studies suggest that perampanel tolerability can be improved by slow titration (2 mg every 2-4 weeks), and bedtime administration can mitigate somnolence and dizziness. Counseling about the potential for behavioral changes and close monitoring are recommended.

KEYWORDS

AMPA receptors, clinical trial, focal seizures, generalized tonic-clonic seizures, perampanel

1 | INTRODUCTION

The ultimate goal of epilepsy therapy remains complete freedom from seizures with minimal adverse events (AEs). Despite the introduction of numerous new antiepileptic drugs (AEDs) over the past two decades, epileptic seizures remain refractory in approximately one-third of patients,[1,2] highlighting the need for effective novel therapies.

Monotherapy is the gold standard for newly diagnosed epilepsy, with a second choice of monotherapy if the first treatment is not successful.[3] The therapeutic choice may depend on the epileptic syndrome (etiology), seizure type (focal or generalized), and patient factors (sex, age, and comorbidity) as well as the characteristics of a drug (efficacy, safety, tolerability, pharmacodynamics, and pharmacokinetics).[3,4] Ultimately, polytherapy may be needed to control seizures in drug-resistant epilepsy, and thus, the potential for both pharmacodynamic synergistic effects and pharmacokinetic drug interactions must be considered.[3]

The intention of "rational polytherapy" is to improve efficacy by combining AEDs with different mechanisms of action (MoAs) that

act on multiple drug targets, and reduce AEs by avoiding AED combinations with similar MoAs that can induce or exacerbate AEs, particularly older drugs with less favorable pharmacokinetic profiles.[3-7] In the laboratory, the combination of zonisamide, which modulates voltage-sensitive sodium channels and T-type calcium currents, and perampanel, a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist, has resulted in a marked synergistic anticonvulsant effect in a rat amygdala kindling model of chronic epilepsy, suggesting the potential for increased efficacy.[8] Exploration of the interactions between perampanel and other commonly administered AEDs was done in a drug-resistant amygdala kindling model.[9] When administered alone, low-dose perampanel, levetiracetam, lamotrigine, carbamazepine, and valproic acid did not demonstrate efficacy. However, when similar low-dose perampanel was combined with each of the individual AEDs, there were significant reductions in all seizure parameters tested. Thus, the synergic effect on seizure control to the other AEDs of perampanel add-on might be the result of pharmacodynamic synergism between the different MoAs, although the plasma concentration of perampanel was reduced pharmacokinetically by concomitant carbamazepine (18.2%) or valproic acid (31.4%) one enzyme-inducing AED and one enzyme-inhibiting AED. In contrast, the plasma concentration of perampanel was increased with concomitant levetiracetam (17.2%) or lamotrigine (8.2%), suggesting a complicated and unresolved pharmacodynamic and pharmacokinetic relationship between the different drug levels of perampanel and combination with either levetiracetam or lamotrigine.[9]

In clinical practice, when administered by MoA (sodium channel blocker, gamma-aminobutyric acid analog, synaptic vesicle protein 2A binding, and multiple mechanisms), AED combinations with different MoAs resulted in significantly better outcomes for treatment effectiveness (longer mean and median persistence) and healthcare resource use (lower risk for inpatient admissions and emergency department visits) than those with the same MoAs.[5] It is likely that clinicians prescribe AED combinations with different MoAs in clinical practice, whether consciously or not.

In a study to ascertain the efficacy of substitution or add-on therapy in patients for whom monotherapy was unsuccessful, a second drug was substituted for patients with intolerable AEs or added for patients who experienced lack of efficacy with the first drug.[10] Overall, seizure freedom and incidence of intolerable AEs were similar for both groups, but significantly more patients prescribed a sodium channel blocker with a drug with multiple mechanisms of action became seizure-free than those treated with other combinations (36% vs 7%; $P = .05$), suggesting a role for rational polytherapy.

Perampanel has been studied in the presence or absence of enzyme-inducing AEDs (EIAEDs), sodium channel blockers, and non-sodium channel blockers among 1480 patients receiving 2 or more concomitant AEDs at baseline. Despite the known interaction between perampanel and EIAEDs (reduction in perampanel plasma concentration), addition of perampanel improved efficacy outcomes regardless of the type of concomitant AEDs.[11] Data from a phase 3 trial show that perampanel efficacy was maintained when co-administered with carbamazepine, valproic acid, lamotrigine, and levetiracetam.[12]

Among other combination therapy studies, eslicarbazepine with carbamazepine has been shown to achieve similar seizure reduction to eslicarbazepine with a non-carbamazepine AED, suggesting that the efficacy of adjunctive eslicarbazepine is independent of concomitant carbamazepine.[13,14] However, there was a higher incidence of AEs with the carbamazepine regimen and at higher carbamazepine doses suggesting an additive effect on AEs.

A trial of lacosamide with traditional sodium channel blockers or non-sodium channel blockers showed significant reductions in seizure frequency and responder rates compared with placebo regardless of the presence of traditional sodium channel blockers in an AED regimen.[15] Tolerability appeared to be worse for patients taking a sodium channel blocker regimen, evidenced by the lacosamide dose-dependent discontinuations in this group compared with those taking a non-sodium channel blocker regimen.

There appears to be some therapeutic synergy between lamotrigine and sodium valproate, evidenced by the better response seen for lamotrigine plus valproate than for lamotrigine plus either carbamazepine or phenytoin.[16]

A study of combination therapy according to MoA suggested that AED combinations with different MoAs have greater effectiveness (measured by treatment persistence and lower risks for hospitalization and emergency department visits)[5] and provide an optimal strategy for achieving rational combination therapy for partial-onset seizures (POS; also known as focal seizures). The evidence of the impact of perampanel on healthcare resource utilization, in terms of hospitalization and outpatient visits, has recently been reported.[17] Notably, hospitalizations for status epilepticus were significantly reduced after perampanel initiation.

Perampanel is the first AMPA receptor antagonist to receive regulatory approval.[18] Perampanel has been licensed as monotherapy for POS with or without secondary generalization (±SG) in the USA, and as adjunctive therapy for POS ±SG in patients aged 12 years and older in more than 55 countries to date, including Australia, Canada, the USA, Europe, Asia, and Russia. Perampanel has also been licensed for primary generalized tonic-clonic (PGTC) seizures in Canada, the USA, Europe, Asia, and Russia in patients aged 12 years and older.

Clinical efficacy and safety of perampanel as adjunctive treatment for POS ±SG have been established in four phase 3 randomized controlled trials (RCTs),[19-21] and one phase 3 RCT has shown the efficacy and safety of perampanel in PGTC seizures.[22] To date, more than 100 000 patients have been treated with perampanel. Clinical studies designed for regulatory purposes are performed under controlled conditions that do not reflect real life, with strict inclusion and exclusion criteria, dosing schedules, and titration strategies (that do not reflect real life).[23] However, real-world observational studies reflect drug use according to individual dosing, comedications, comorbidities, and different epileptic syndromes in a pragmatic clinic setting, and provide clinical efficacy and tolerability data accordingly.

The aim of this study was to review the phase 3 evidence of perampanel efficacy and to demonstrate the use of perampanel in real-world clinical situations, with recommendations for mitigating AEs thereby enhancing retention.

2 | PERAMPANEL: A NON-COMPETITIVE SELECTIVE AMPA RECEPTOR ANTAGONIST

Glutamate is one of the major excitatory amino acids involved in neuronal processes playing a key role in generating and spreading epileptic activity.[24] The glutamate receptors involved in neurotransmission are classed as ionotropic and metabotropic. Ionotropic receptors are classified according to their affinity to specific agonists such as N-methyl-D-aspartic acid (NMDA), kainic acid, and AMPA, which allow sodium, potassium, and calcium flux upon binding with glutamate.[24]

NMDA receptors are thought to be important in seizure generation, and AMPA receptors are important in generating and spreading epileptic activity. Clinical studies of NMDA receptor antagonists have not been promising, and they have worsened seizures in some patients.[25] Consequently, this has prompted interest in AMPA receptors as possible therapeutic targets.[25] Perampanel was identified from high-throughput screening, and has undergone extensive preclinical testing in animal models to ascertain its potential antiseizure effects. This novel compound has exhibited broad-spectrum efficacy and high potency in several acute and chronic seizure models, including models of generalized seizures.[18,26,27] Although the precise mechanism by which perampanel exerts its anticonvulsant effects is not fully understood, it is believed to inhibit excitatory neurotransmission.[26]

3 | CLINICAL PHARMACOLOGY OF PERAMPANEL

Perampanel is administered orally at doses of 2 to 12 mg. The half-life of perampanel is approximately 105 hours, with steady-state concentration being reached within 2 to 3 weeks. The area under the concentration-time curve increases in a dose-proportional manner,[26,28] and steady-state plasma concentrations of ≥70 ng/mL are likely to result in a positive therapeutic response.[29] After oral administration, absorption is rapid and complete with negligible first-pass metabolism.[26] Under fasting conditions, median time to maximum plasma concentration (T_{max}) of perampanel 6 mg is 0.5 to 2.0 hours. Food slows the rate of absorption and, under fed conditions, the maximum plasma concentration of perampanel 6 mg is decreased by 28%-40% and the T_{max} delayed by 2-3 hours.[30] There is a linear reduction in seizure frequency with increasing perampanel exposure that remains consistent regardless of concomitant AED administration, age, sex, race, study, or region.[29]

Perampanel is primarily metabolized in the liver by cytochrome P450 (CYP) 3A4. Thus, its clearance is enhanced by other CYP3A4 inducers (EIAEDs), including phenytoin, carbamazepine, and oxcarbazepine.[31] Carbamazepine, oxcarbazepine, phenytoin, and topiramate increased perampanel clearance, while clobazam, clonazepam, lamotrigine, levetiracetam, valproic acid, and zonisamide did not appear to influence perampanel clearance.[31] Importantly, concomitant EIAEDs do not appear to affect the response to perampanel by plasma concentration,[29] although increased dosages and faster titration of perampanel might be needed for patients receiving a concomitant EIAED, if tolerated.[32]

In the phase 3 studies, the most frequently reported AEs included dizziness, somnolence, fatigue, irritability, gait disturbance, headache, weight increase, and dysarthria, while AEs of special interest included decreased appetite, increased appetite, and euphoric mood.[29] The predicted probability of euphoric mood, dysarthria, weight increase, gait disturbance, irritability, fatigue, somnolence, and dizziness increased with higher perampanel plasma concentrations, while the predicted probability of headache and increased or decreased appetite was not affected by increased perampanel plasma concentrations. Demographic variables and region did not affect the probability of experiencing these AEs, although concomitant levetiracetam increased the risk for fatigue, concomitant phenobarbital increased the risk for irritability, and concomitant oxcarbazepine or primidone increased the risk for decreased appetite. The relationship between perampanel dose, plasma concentration, and expected response should help clinicians in tailoring individual patient therapy, thus optimizing treatment.

4 | PHASE 3 RCTS OF PATIENTS WITH REFRACTORY POS

4.1 | Partial-onset seizures with or without secondary generalization

Three multicenter, double-blind, phase 3 RCTs—studies 304,[19] 305,[20] and 306[21]—were performed to assess the efficacy and safety of adjunctive once-daily perampanel at doses up to 12 mg in adolescents and adults with uncontrolled POS despite current treatment with 1-3 AEDs.

The three studies each included a 6-week baseline period and a double-blind treatment phase comprising a 6-week titration phase and 13-week maintenance phase. The primary endpoints were median percent change in POS frequency per 28 days and percentage of patients achieving ≥50% reduction in seizure frequency both compared for the maintenance phase vs baseline (response rate was a secondary endpoint in the USA, but a primary endpoint in the EU). The studies showed a significant benefit for perampanel 4, 8, and 12 mg over placebo (Table 1). Studies 304, 305, and 306 provided class I evidence that perampanel is effective in reducing uncontrolled POS. A pooled analysis of the data from studies 304, 305, and 306 supports the efficacy of perampanel as an adjunctive treatment for refractory POS (Table 1).[12]

Among patients in the three studies receiving 1-3 of the most commonly prescribed AEDs, such as carbamazepine, valproic acid, lamotrigine, or levetiracetam, perampanel consistently provided greater reductions in seizure frequency and greater 50% responder rates than placebo.[12] Efficacy was lower with carbamazepine (an EIAED) than with valproic acid, lamotrigine, or levetiracetam for both endpoints. Perampanel plasma concentration is reduced in patients receiving EIAEDS such as phenytoin, carbamazepine, and oxcarbazepine, so they may need higher perampanel doses (and a higher starting dose of 4 mg) in the presence of these EIAEDs and

TABLE 1 Results of the randomized controlled trials of perampanel vs placebo in patients with partial-onset seizures with or without secondary generalization

Parameter	Study 304[19]	Study 305[20]	Study 306[21]	Pooled analysis[12]
No of patients (intent-to-treat)	387	386	705	1478
Study drug	Perampanel 8 or 12 mg vs placebo	Perampanel 8 or 12 mg vs placebo	Perampanel 2, 4, or 8 mg vs placebo	Perampanel 2, 4, 8 or 12 mg vs placebo
Primary efficacy endpoints				
Median % change in seizure frequency				
Placebo	−21.0	−9.7	−10.7	−12.8
2 mg	–	–	−13.6	−13.6
4 mg	–	–	−23.3 (P = .0026)	−23.3 (P < .01)
8 mg	−26.3(P = .0261	−30.5 (P < .001)	−30.8 (P < .0001)	−28.8 (P < .01)
12 mg	−34.5 (P = .0158)	−17.6 (P = .011)	–	−27.2 (P < .01)
≥50% responder rate, %				
Placebo	26.4	14.7	17.9	19.3
2 mg	–	–	20.6	20.6
4 mg	–	–	28.5 (P = .0132)	28.5 (P < .05)
8 mg	37.6 (P = .0760)	33.3 (P = .002)	34.9 (P = .0003)	35.3 (P < .001)
12 mg	36.1 (P = .0914)	33.9 (P < .001)	–	35.0 (P < .001)
Secondary efficacy endpoint				
Median % change in frequency of CP plus SG seizures				
Placebo	−17.9	−8.1	−17.6	−13.9
2 mg	–	–	−20.5	−20.5
4 mg	–	–	−31.2 (P = .007)	−31.2 (P < .001)
8 mg	−33.0 (P = .0020)	−32.7 (P < .001)	−38.7 (P < .001)	−35.6 (P < .001)
12 mg	−33.1 (P = .0081)	−21.9 (P = .005)	–	−28.6 (P < .001)

CP, complex partial; SG secondarily generalized.
All P values vs placebo.

dose reductions if stopping a concomitant EIAED. Overall, perampanel was efficacious and well tolerated in these groups of patients with refractory epilepsy.

4.2 | Secondarily generalized seizures

Patients with POS with secondary generalization frequently do not have an adequate response to AEDs, with almost one-third being resistant to treatment.[25] There is a paucity of data on the effects of AEDs in patients with secondarily generalized seizures. A subanalysis of patients with secondarily generalized seizures in the three phase 3 trials was conducted to evaluate the efficacy of perampanel in this population.[33] This is clinically important as secondarily generalized seizures are harder to treat than simple POS.

At baseline, 71.9% of placebo-treated and 68.4% of perampanel-treated patients (69.5% overall) had a history of secondarily generalized seizures. In the phase 3 studies, results from the pooled analysis were consistent with the results of the individual trials (Table 2). Except for study 306, which did not include the 12 mg dose, perampanel 8 and 12 mg significantly reduced the median percent change in seizure frequency of secondarily generalized seizures and improved ≥50% responder rates compared with placebo. Additionally, perampanel 8 and 12 mg provided significant improvement in 75% responder rates (46.5% [P < .001] and 38.9% [P < .05], respectively) and seizure freedom (28.9% [P < .01] and 27.0% [P < .05], respectively) vs placebo.

At baseline, most patients (86%) were taking 2 or 3 concomitant AEDs. The reduction in seizure frequency and improved 50% responder rates with perampanel tended to be lower with concomitant carbamazepine than with valproic acid, lamotrigine, or levetiracetam, but improvements in seizure frequency and 50% responder rates were retained at the 4, 8, and 12 mg doses with each of these AEDs.[33]

In a meta-analysis of RCTs of adjunctive AEDs in patients with secondarily generalized seizures, perampanel was one of only three of seven drugs (along with lacosamide and topiramate) to demonstrate significantly greater efficacy than placebo.[34] In this analysis, responder rates were significantly greater for secondarily generalized seizures than for all seizure types.

4.3 | Long-term extension trial

Patients completing the three phase 3 RCTs were enrolled in a long-term open-label extension trial (study 307) to evaluate the long-term safety,

TABLE 2 Results of the randomized trials of perampanel vs placebo in patients with secondarily generalized seizures

Parameter	Study 304[19]	Study 305[20]	Study 306[21]	Pooled analysis[33]
No of patients (intent-to-treat)	159	135	270	564
Median % change in SG seizure frequency				
Placebo	−14.2	−6.7	−35.8	−19.4
2 mg	–	–	−28.0	−28.0
4 mg	–	–	−48.6	−48.6
8 mg	−61.1 ($P < .001$)	−52.0 ($P < .001$)	−69.2	−62.9 ($P < .001$)
12 mg	−75.4 ($P < .001$)	−47.4 ($P < .05$)	–	−53.3 ($P < .001$)
≥50% responder rate, %				
Placebo	37.5	25.0	44.9	37.0
2 mg	–	–	44.1	44.1
4 mg	–	–	49.3	49.3
8 mg	66.7 ($P < .01$)	50.0 ($P < .01$)	62.9	60.5 ($P < .001$)
12 mg	59.6 ($P < .05$)	46.5	–	53.7 ($P < .01$)

SG, secondarily generalized.
All *P* values vs placebo.

tolerability, and retention of perampanel.[35] Among the 1216 patients, the median exposure time was 1.5 years (range, 1 week to 3.3 years) for 1803 patient-years; more than 300 patients were treated for >2 years. Treatment retention was 58.5% at the cutoff point (3 years after the first patients were enrolled in the extension study). The responder rate and median percent change from baseline in seizure frequency were 46% for both measures among 980 patients with ≥9 months' perampanel exposure, and 58% and 60%, respectively, among 337 patients with 2 years' exposure. Median percentage reduction in secondarily generalized seizures was 77% of 422 patients at 9 months and 90% of 141 patients at 2 years. One-year seizure freedom was achieved by 5.3% of 694 patients with maintenance data for ≥1 year.

The greater reduction in secondarily generalized seizure frequency in the phase 3 trials was sustained in the long-term extension study.[33,35] The greatest reductions in secondarily generalized seizures were observed during the first 26 weeks, and reached 90% among patients who continued treatment for ≥104 weeks.

5 | PHASE 3 RCT OF PGTC SEIZURES

A multicenter, double-blind RCT assessed the efficacy of adjunctive perampanel in patients with refractory PGTC seizures in idiopathic generalized epilepsy. All diagnoses were confirmed by independent reviewers from the Epilepsy Study Consortium. Patients aged 12 years or older were randomized to placebo (n = 81) or perampanel titrated to 8 mg/d or the highest tolerated dose (n = 81).[22] Compared with placebo, perampanel resulted in significantly greater median percent reduction in PGTC seizure frequency per 28 days and ≥50% PGTC seizure responder rate (Table 3). Perampanel also resulted in greater PGTC seizure freedom than placebo. This study provides class I evidence that adjunctive perampanel is efficacious in reducing the frequency of refractory PGTC seizures.

6 | PERAMPANEL AS MONOTHERAPY

In July 2017, the US Food and Drug Administration approved a supplemental New Drug Application for perampanel as monotherapy to treat POS ±SG in patients with epilepsy aged 12 years and older. The approval was given on the basis of extrapolation of efficacy and safety data from the clinical trials of perampanel as adjunctive therapy to its use as monotherapy. This enables more patients to have the option of a single-agent AED.[36]

7 | SAFETY AND TOLERABILITY

In the three pivotal phase 3 studies, perampanel 2 to 12 mg generally had an acceptable safety profile and was well tolerated.[19-21] Most AEs were mild or moderate in intensity. According to the pooled analysis, treatment-emergent AEs (TEAEs) occurred in 294 patients (66.5%) in the placebo group and 799 (77%) in patients receiving any dose of perampanel. The most frequently reported TEAEs were dizziness, somnolence, headache, fatigue, and irritability.[12] In the phase 3 trials, falls were more frequent with perampanel.[37]

Analysis of TEAEs was performed using broad and narrow Standardized Medical Dictionary for Regulatory Activities Queries (SMQs). SMQs are used to monitor drug safety during clinical development. The terms are hierarchical, with broad SMQ terms identifying all possible cases regardless of relevance and narrow terms being more likely to represent the condition of interest.[38] Hostility/aggression TEAEs by narrow SMQ terms occurred in 2.8%, and 6.3% of patients receiving perampanel 8 and 12 mg (all doses 3.0%), respectively, and in 0.7% of those receiving placebo. By narrow-and-broad SMQ terms, hostility/aggression TEAEs occurred in 12.3% and 20.4% of patients receiving perampanel 8 and 12 mg, respectively, and in 11.8% of patients receiving all doses compared with 5.7% receiving placebo.

TABLE 3 Results of the randomized trial of perampanel vs placebo in patients with PGTC seizures

Parameter	Study 332[22]
No of patients (full analysis set)	162
Design	
Baseline	4 or 8 wk[a]
Titration	4 wk
Maintenance	13 wk
Study drug	Perampanel 8 mg vs placebo
Median % change in PGTC seizure frequency per 28 d	
Placebo	−38.5
Perampanel 8 mg	−76.5 ($P < .0001$)
50% responder rate, %	
Placebo	39.5
Perampanel 8 mg	64.2 ($P = .0019$)
Median % change in all seizure frequency per 28 d	
Placebo	−22.9
Perampanel 8 mg	−43.4 ($P = .0018$)
Freedom from PGTC seizures, %	
Placebo	12.3
Perampanel 8 mg	30.9
Freedom from all seizures, %	
Placebo	4.9
Perampanel 8 mg	23.5

PGTC, primary generalized tonic-clonic.
[a]Depending on the accuracy of diary-documented seizures during screening.
All *P* values vs placebo.

Serious TEAEs by narrow-and-broad SMQ terms were observed in seven patients (0.7%) receiving perampanel and one (0.2%) in the placebo group.[12] Aggression was the most common serious psychiatric TEAE, occurring among three patients (0.3%) receiving perampanel. According to the narrow-and-broad SMQ terms, for concomitant use of medications, including AEDs, that have been associated with hostility/aggression AEs, there were no differences between the perampanel and placebo groups. Among the patients in the phase 3 trials, less than half of the patients with psychiatric serious AEs (SAEs) had a prior history of psychiatric problems (43% in study 307).[35,38]

Most TEAEs reported in patients with PGTC seizures were mild to moderate in intensity.[22] The most frequent TEAEs with perampanel were dizziness (32.1% vs 6.1% for placebo), fatigue (14.8% vs 6.1%), headache (12.3% vs 9.8%), somnolence (11.1% vs 3.7%), and irritability (11.1% vs 2.4%). The numbers of SAEs were similar in the placebo (n = 7; 8.5%) and perampanel (n = 6; 7.4%) groups. Psychiatric TEAEs occurring more frequently in the perampanel group included those related to alertness and cognition, hostility/aggression, and psychosis and psychotic disorders.

In the long-term extension trial (study 307), the most common AEs (reported in ≥10% of patients) were dizziness, somnolence, headache, fatigue, irritability, and weight increase.[35] Dizziness and irritability led to discontinuation in >1% of patients (3.9% and 1.3%, respectively). However, most AEs were mild or moderate. Of 1216 patients in the safety analysis, 47 (3.9%) had at least one psychiatric SAE, 20 of whom had a prior psychiatric disorder. Twelve patients (1.0%) had an SAE of aggression and six (0.5%) each had SAEs of psychotic disorder or suicidal ideation. Overall, there were no significant laboratory abnormalities in any of the phase 3 trials or the long-term extension study (up to 4 years of perampanel exposure).

8 | CLINICAL EFFECTS IN SPECIAL POPULATIONS

8.1 | Adolescents

Subgroup analysis of the adolescent patients (age 12-17 years; n = 143) in the three phase 3 RCTs found that perampanel 4, 8, and 12 mg also had greater efficacy than placebo in this patient population.[39] Median percent reduction in seizure frequency were 34.8% and 35.6% for perampanel 8 and 12 mg, respectively, and 18.0% for placebo; 50% responder rates were 40.9% and 45.0%, respectively, and 22.2% for placebo. In the long-term extension study, adolescent patients maintained improvements in seizure control compared with baseline. The most common TEAEs were dizziness, somnolence, and aggression; aggression was reported more frequently among the adolescent patients (8.2%) than in the overall population (1.6%). Thus, awareness of the potential for aggressive behavior among this group and monitoring during dose titration and at higher doses is important.[39,40]

Study 235 assessed the efficacy of perampanel among adolescents (n = 133) with inadequately controlled POS and investigated its effects on cognition and growth.[41] The median percent reduction in seizure frequency per 28 days was 58% for perampanel and 24% for placebo. The 50% responder rate was also greater for perampanel than placebo (59% vs 37%). The safety profile of perampanel for adolescents in study 235 was similar to that for adolescents in the phase 3 RCTs.

There was no difference between perampanel and placebo on the Cognitive Drug Research (CDR) System Global Cognition Score, Quality of Working Memory, or Power of Attention, but there were small differences in the domains of Quality of Episodic Memory (improved), Continuity of Attention (worsened), and Speed of Memory (worsened). Differences between perampanel and placebo in letter and category fluency scores, and Lafayette Grooved Pegboard Test were not significant.[42] There were no short-term effects on growth and development compared with placebo, and no clinically significant changes in vital signs or laboratory values related to growth or important changes in bone age. Sexual development was not compromised.[43]

8.2 | Elderly patients

Elderly patients are often excluded from RCTs, so clinical data for this population are limited.[44] The efficacy and safety of perampanel have been investigated in a subanalysis of elderly patients (age ≥ 65 years) who participated in the three phase 3 RCTs. In this group

(n = 28; 1.9%), median percent reductions in seizure frequency per 28 days were 16.9% and 12.5% for perampanel 8 and 12 mg, respectively, and 6.8% for placebo; 50% responder rates were 22.2% and 42.9%, respectively, and 25% for placebo. These efficacy results were considered to be consistent with those of the adult population (≥18-<65 years).[44] TEAEs were also largely similar to those of the adult population, with some exceptions. Falls, dizziness, and fatigue occurred more frequently in the elderly group, so careful titration of perampanel in patients aged 65 years or older is recommended, especially at higher doses.

More recently, pooled data from European observational studies have become available.[45] A total of 2396 patients from 48 sites in 7 countries were included. Older age at perampanel initiation (≥65 years) was associated with a greater chance of seizure freedom. After 12 months, 67 of 134 patients (50%) were continuing with perampanel and, of 46 patients with evaluable seizure data, 13 (28.3%) had achieved seizure freedom for at least the previous 6 months. The most common AEs (>10%) were dizziness/vertigo, somnolence/sleepiness, and psychiatric AEs. The rate of AEs was similar to the overall population except for dizziness/vertigo (25%) and falls/unsteadiness/ataxia (5.6%), which were more common in the elderly population. However, there were no new or unexpected AEs in this group of older patients.

8.3 | Women of childbearing age

Perampanel clearance is lower (17%) in women than in men conferring slightly greater efficacy for women.[46] There are currently no data on perampanel in pregnancy, so contraception is recommended for women of childbearing age who are taking perampanel.[32] At the highest dose, perampanel lowers serum concentrations of progestogen so may reduce the efficacy of oral contraceptives. Therefore, for women taking perampanel 12 mg, non-hormonal contraception is recommended. Although perampanel was excreted into breastmilk in animal studies, there are no data on perampanel specific to breastfeeding women.[47]

8.4 | Other populations

Perampanel can be prescribed to patients with mild (maximum dose 6 mg) or moderate (maximum dose 4 mg) hepatic impairment, but it is not recommended for patients with severe hepatic impairment.[32] Patients with moderate renal impairment can be prescribed perampanel, with close monitoring, but it is not recommended for those with severe renal impairment. Slow titration is advised for patients with hepatic or renal impairment (minimum every 2 weeks).

8.5 | Asia-Pacific populations

Subgroup analyses of patients in the phase 3 RCTs were performed to evaluate perampanel in patients from the Asia-Pacific region.[48] Median percent reduction in POS frequency per 28 days and 50% responder rates were significantly greater with perampanel 8 mg ($P = .0043$ and $P = .0049$, respectively) than with placebo. In one analysis of Asian patients in the phase 3 trials, the median percent change in seizure frequency per 28 days (30.6% and 38.0% reduction; $P < .0001$) and the 50% responder rate (39.1% and 43.6%; $P < .0001$) were significantly greater than placebo for perampanel 8 and 12 mg, respectively.[49] The most frequent TEAEs were dizziness and somnolence. These results suggest that outcomes with perampanel are similar in Asia-Pacific patients to those in Western patients.[48]

A RCT of patients from the Asia-Pacific region with POS also found significantly greater median percent changes in seizure frequency per 28 days for perampanel 8 and 12 mg compared with placebo ($P = .0003$ and $P < .0001$, respectively) and 50% responder rates ($P = .0005$ and $P < .0001$, respectively).[50] Median percent reductions in complex partial plus secondarily generalized seizure frequency and secondarily generalized seizure frequency were also greater with perampanel than with placebo. The most frequently reported TEAEs were dizziness, somnolence, and nasopharyngitis. Perampanel demonstrated a positive risk-benefit balance in patients from the Asia-Pacific region.

In a 2017 update of the Hong Kong Epilepsy Guideline, the consensus group suggested Level A evidence for perampanel based on literature review on the clinical use of AEDs as adjunctive therapy.[51]

9 | REAL-WORLD CLINICAL EXPERIENCE

9.1 | Adults (Table 4)

Several observational studies of adjunctive perampanel in a real-world clinical practice setting have been reported (Table 4). The real-world studies generally support the efficacy, tolerability, and safety profile of adjunctive perampanel in refractory POS that was demonstrated in the phase 3 RCTs.

An observational study of consecutive adult patients with severe refractory focal epilepsy at the Danish Epilepsy Centre[52] revealed a retention rate of 54.5%. The responder rate was 27.2%, including 9.1% who were seizure-free for at least 3 months at 12 months after starting perampanel. The mean perampanel dose for responders was 8 mg (range 4-10 mg). AEs were reported by 59.1% of patients. AEs were less common in patients with the slowest titration rates of 2 mg every 4 weeks. The authors suggest that slow uptitration of perampanel may reduce the risk of AEs (Table 5).

Brodie et al.[53] conducted a prospective audit among adult patients with focal seizures. Data show that 5.6% achieved seizure freedom for at least 6 months, 14.8% attained ≥50% reduction in seizures, 31.5% achieved <50% seizure reduction but wished to continue taking perampanel, and 48.1% stopped taking perampanel. The median perampanel dose was 8 mg (range 4-14 mg). Six patients reported depression, increased irritability, or aggression that resulted in discontinuation of perampanel. However, AEs could be managed by careful dose titration and patient selection, including caution for patients with a history of psychiatric symptoms or anger management issues.

An observational study of patients aged 12 years or older treated at nine centers in Germany and Austria[54] showed a retention rate at

TABLE 4 Summary of real-world clinical experience

Study	N	Response	Seizure freedom (%)	Most frequent adverse events
Adults				
Juhl[52]	22	50% responder rate: 27.2%	9.1% (previous 3 mo)	Tiredness, behavioral changes (aggression), dizziness
Brodie[53]	54	50% responder rate at 6 mo: 14.8%	5.6% (previous 6 mo)	Nausea, vomiting, ataxia, dizziness, and somnolence
Steinhoff[54]	281	50% responder rate: All seizures: 50% Complex partial seizures: 48% Generalized tonic-clonic seizures: 57%	All seizures: 15% (previous 3 mo) Complex partial seizures: 14.5% Generalized tonic-clonic seizures: 32%	Somnolence, dizziness, ataxia, aggression, nausea, irritability
Shah[55]	310	50% responder rate at 3 mo: Tonic-clonic seizures: 36.4% Complex partial seizures: 47.5% Simple partial seizures: 39.3% 50% responder rate at final follow-up: Tonic-clonic seizures: 57.5% Complex partial seizures: 57.4% Simple partial seizures: 43.8%	3.5% (previous 3 mo)	Sedation, behavior/mood disturbance, dizziness, unsteadiness
Villanueva[56]	464	50% responder rate at 1 y: 26.8% Median % seizure reduction at 1 y: All seizures: 33.3% Simple partial seizures: 58.3% Complex partial seizures: 33.3% Secondarily generalized seizures: 75.0%	7.2% at 1 y	Dizziness, somnolence, and irritability
Ryan[57]	70	Overall response Complex partial seizures: 21.4% Secondary generalized tonic-clonic seizures: 12.8% At 4 mo <50% response: 32.8% ≥50% response: 14.2% At 6 mo <50% response: 20.0% ≥50% response: 12.8%	Not achieved	Behavioral disturbance, sedation, and dizziness
Wehner[58]	376	50% responder rate at 6 mo: 20% Retention 1 y: 60.4% 2 y: 48.3% 3 y: 42.7%	5% at ≥6 mo	Drowsiness, dizziness, unsteadiness, mood changes, increased irritability, and challenging behavior
Children				
Biró[61]	58	50% responder rate: 31%	9% at 3 mo	Reduced vigilance/fatigue, behavioral changes (aggressiveness), dizziness or gait instability, and change in appetite
De Liso[62]	62	50% responder rate: 50%	5%	Behavioral disturbance (irritability/aggressiveness), dizziness, sedation, and fatigue
Heyman[63]	24	50% responder rate: 42%	12.5%	Nervousness, restlessness, behavioral deterioration, insomnia, violence, psychosis, and unsteadiness
Datta[64]	24	50% responder rate: 42%	Not achieved	Dizziness, unsteadiness, mood swings/irritability, verbal/physical aggression

(Continues)

TABLE 4 (Continued)

Study	N	Response	Seizure freedom (%)	Most frequent adverse events
Adults and children				
Singh[69]	101 (16 pediatric)	Median seizure frequency reduction: 33% in adults 50% in children 50% responder rate 49% in adults 63% in children	6% (all adults) at >6 mo	Sleepiness/fatigue, dizziness/falls, and behavioral problems—aggression, irritability, and mood changes

TABLE 5 Summary of experience of perampanel use in real-world clinical practice

Factor	Experience
Overall results	The efficacy, tolerability, and safety results in real-world studies are similar to the results of the phase 3 clinical trials
Special populations	Efficacy is similar in children and adolescents (≤17 y) and elderly patients ≥65 y) to that in adults
AEs	The main AEs are central nervous system related • AEs are associated with higher doses and fast titration • Slow initiation and titration (2 mg every other day for 2 wk or 2 mg every 2-4 wk) reduces AEs, particularly dizziness and falls • Nighttime administration improves tolerability, but must be balanced against the potential for falls at night, especially for elderly people • Patients with prior psychiatric comorbidity are more likely to experience psychiatric AEs than those with no prior psychiatric comorbidity, particularly for hyperactivity or personality disorders • The potential for neuropsychiatric AEs should be discussed before initiation of perampanel • Monitoring of psychiatric AEs is recommended for patients with psychiatric comorbidity • Slow titration may reduce the occurrence of psychiatric AEs
Concomitant EIAEDs	Dose increase may be needed when prescribed with concomitant EIAEDs, but this needs to be individually titrated in small, slow increments

AE, adverse event; EIAED, enzyme-inducing antiepileptic drug.

6 months of 60% and 3-month seizure freedom of 15%. The mean perampanel dose was 7.7 mg (range 4-15 mg). The overall incidence of AEs was 52.0%, with patients taking three or more concomitant AEDs being more likely to experience AEs. Administration at bedtime was recommended to reduce somnolence and dizziness (Table 5). A few patients responded well to perampanel at low doses, although the reason is unclear. Patients taking EIAEDs may require dose increment.

A chart review of adult patients with refractory epilepsy conducted at 18 centers in the UK and Ireland[55] resulted in 3.5% of patients being seizure-free for ≥3 months at final follow-up. The retention rate was 71% after 6 months and 47.6% after 1 year, with a mean duration of treatment of 6.9 months (range, 1 day to 22.3 months). AEs were experienced by 67.4% of patients; 18.1% experienced irritability or aggression, 7.7% experienced mood changes or anxiety, and 1.3% reported suicidal ideation. It is unclear why there were higher rates of behavior and mood AEs in this study, but monitoring for neuropsychiatric AEs is recommended. This study suggested that fast titration increased the severity of AEs (Table 5).

The FYDATA (Follow-up of 1 Year Data of paTients on perAmpanel) study was a multicenter 1-year observational study in patients aged 12 years or older.[56] The retention rate was 60.6% at 1 year. The median percentage reduction in all seizures was 33.3% and 7.2% of patients achieved seizure freedom at 1 year. Patients taking non-EIAEDs were more likely to be seizure-free than those taking EIAEDs. Other factors contributing to a better clinical response were older age, vascular etiology, and fewer prior AEDs. At 12 months, 62.9% of patients had experienced AEs, with dizziness, somnolence, and irritability being the most frequent. Most AEs were mild or moderate in severity.

A retrospective audit of perampanel in Ireland using the national epilepsy electronic patient record enrolled 70 patients from 2 regional centers.[57] The best responses were seen in patients with complex partial seizures (21.4%) and secondarily generalized tonic-clonic seizures (12.8%). Overall, the <50% responder rate at 6 months was 20.0% and the ≥50% responder rate was 12.8%. AEs were experienced by 67.1% of patients, with behavioral disturbance, sedation, and dizziness being the most common AEs. AEs resulting in reduction or termination of treatment were most apparent at doses of 8 mg or higher. Behavioral change was most evident among patients with intellectual disability, and observation for emotional changes is recommended when treating with perampanel. Interestingly, this audit found that the number and type of concomitant AEDs impacted the AEs. Perampanel was poorly tolerated when taken with carbamazepine, but was better tolerated when taken with lamotrigine or levetiracetam. It is also known that

concomitant carbamazepine can lower perampanel plasma concentrations, which may result in reduced perampanel efficacy.[12,21]

An observational study at a large UK tertiary epilepsy study analyzed 376 patients treated with perampanel.[58] The >50% responder rate for ≥6 months was 20% and 5% attained seizure freedom for ≥6 months. Patients reporting longer periods of seizure freedom (≥6 months) had taken fewer previous or current AEDs (mean 7.4 compared with 10.1 for patients without seizure freedom). Five patients discontinued all other AEDs and took perampanel as monotherapy. The retention rate at 1 year was 60.4% and 42.7% at 3 years. Interestingly, perampanel retention was positively impacted by concomitant pregabalin and negatively impacted by concomitant zonisamide, although no pharmacodynamic or pharmacokinetic interactions between these AEDs have been reported. These efficacy results and AEs (drowsiness, dizziness, unsteadiness, mood changes and irritability/behavioral changes) were considered similar to the results reported in the perampanel phase 3 clinical trials, and the retention rates were similar to those achieved with lacosamide.[59]

One patient, a 13-year-old girl developed a drug reaction with eosinophilia and systemic symptoms 5 weeks after introduction of perampanel as adjunctive therapy to lamotrigine and valproic acid. Perampanel was suspected to be the causative agent, although all three AEDs were discontinued and methylprednisolone was given.[60] She was discharged with levetiracetam.

Overall, the results of the real-world studies show similar efficacy and safety profiles to those observed in the phase 3 RCTs. AEs did not seem to be clearly related to the dosage of perampanel, but to a fast titration schedule. These studies suggest that tolerability can be improved by slow titration to reduce the severity of AEs. It is recommended that perampanel is taken once daily at bedtime to mitigate somnolence and dizziness.[53]

Caution should be exercised when treating patients with psychiatric comorbidities (Table 5), as those with prior psychiatric comorbidity are more likely to experience psychiatric AEs than those with no prior psychiatric comorbidity, particularly for hyperactivity or personality disorders.[56] The potential for neuropsychiatric AEs should be discussed before initiation of perampanel and patients should be monitored carefully for these AEs.[54,55,58] Slow titration may reduce the occurrence of psychiatric AEs.

9.2 | Pediatric patients (Table 4)

The first report of real-world clinical experience with perampanel in a pediatric population with refractory epilepsy came from a multicenter retrospective survey in Europe.[61] A total of 58 patients aged 2-17 years (mean age 10.5 years) with various epilepsies were enrolled. The response rate of ≥50% seizure reduction was 31% after 3 months, and seizure freedom was attained by five patients (9%). Children aged 6 years and older tended to show a better response than younger children. Aggravation of seizures occurred in five patients (9%). AEs occurred in 48% of patients, which is less than in the clinical trials (77.0% for perampanel patients in the pooled analysis of the phase 3 studies).[12] Reduced vigilance/fatigue, behavioral changes (aggressiveness), dizziness or gait instability, and change in appetite were the most frequent AEs. Titration rates varied between centers and between individual patients, but were slower for children younger than 12 years (1 mg/2 wk or 2 mg/3-4 wk).

A retrospective study of perampanel was performed among 62 children and adolescents (age range 6-18 years) with refractory epilepsy treated in 16 pediatric epilepsy centers in Italy.[62] The retention rate was 77.4% after an average follow-up of 6.6 months (range 5-13 months). The response rate was 50%, 16% of patients achieved ≥75% seizure frequency reduction, and 5% became seizure-free. However, seizure aggravation occurred in 9.7% of patients. The most common AEs were behavior disturbance (irritability/aggressiveness), dizziness, sedation, and fatigue. Age (<12 years vs ≥12 years) did not affect the AE rate. The AE rate of 30.6% was considerably lower than that of some other studies, including the phase 3 clinical trials.

A review of perampanel in a pediatric neurology clinic in Israel enrolled 24 patients aged 18 months to 17 years.[63] Ten patients (42%) had a ≥50% seizure reduction, and three (12.5%) achieved seizure freedom. Additionally, 2 children were treated with perampanel as monotherapy, and one became seizure-free. Sixteen children (67%) experienced AEs, which were predominantly behavioral. AEs occurred more frequently in children older than 12 years, but there was no difference between groups for seizure outcome.

A retrospective review of perampanel was performed at a single Canadian epilepsy center among 24 pediatric patients aged 12-18 years with highly refractory epilepsy.[64] The ≥50% responder rate was 42%, which is comparable to previous studies, while 17% of patients had a <50% reduction in seizures. The median duration of treatment was 59 weeks. A total of 17 patients (71%) experienced adverse events; seven had serious adverse events (homicidal ideation, aggression, self-harm, and oculogyric crisis) and five of them discontinued treatment. Overall, 12 patients (50%) had behavioral AEs causing perampanel withdrawal, although 58% of them had behavioral comorbidity (compared with 22% who continued perampanel). The authors concluded that preexisting behavioral problems and a history of behavioral problems with other AEDs might be risk factors for behavioral AEs with perampanel, and recommended counseling all patients and their families.

Overall, the use of perampanel in pediatric patients has an acceptable risk-benefit profile, with the advantages of ease of titration and once-daily dosing, although there is a risk of seizure aggravation and behavioral AEs.[61]

9.3 | Comparison with lacosamide

A retrospective analysis compared first use of perampanel with that of lacosamide in 70 patients with refractory epilepsy (mean 7.3-8.7 previous AEDs) treated in a German epilepsy center.[65] At 6 months, the 50% responder rate for all seizures was 48.6% for perampanel and 28.6% for lacosamide, seizure freedom was 14.3% and 4.3%, respectively, and the retention rate was 67.1% and 65.1%, respectively. There were 51 AEs in the perampanel group, with the most common

being somnolence/tiredness (41.4%), and 32 in the lacosamide group, with the most common being dizziness (22.9%). This trial suggests clinical benefits from newer AEDs for some patients even in the presence of highly refractory epilepsy.

9.4 | Monotherapy

In a retrospective study conducted in the EU and Russia (study 504), perampanel monotherapy (primary or secondary) was evaluated in routine clinical practice.[66] Perampanel monotherapy was maintained for a median of 6.1 months, and 41 patients (68.3%) were receiving perampanel at the study cutoff date, most of whom had improvements in seizure outcomes (median reduction in seizure frequency per 28 days of 81.7% and 50% responder rate of 80.0% during the first 3 months of perampanel monotherapy). The safety profile was similar to that in the phase 3 clinical trials of perampanel as adjunctive therapy. Thus, perampanel monotherapy may be a feasible option in the real-world clinical setting. This is important, as monotherapy in epilepsy has many advantages,[67] including ease of use, better tolerability, improved compliance, reduced risk of pharmacodynamic and pharmacokinetic interactions, reduced costs, and reduced perception of disease. Newly administered AED therapy is effective in approximately 60% of patients with the first AED.[68]

10 | BROAD-SPECTRUM USE

10.1 | All ages with various epilepsy syndromes (Table 4)

A single-center retrospective analysis was conducted to assess the efficacy, safety, and tolerability of adjunctive perampanel in patients with various treatment-resistant epilepsy syndromes.[69] Of 101 patients ranging in age from 1 to 66 years, 16 were in the pediatric age group (0-18 years), eight of whom were younger than 12 years (perampanel is currently approved for patients aged 12 years and older). The mean treatment duration was 8.2 months, and the mean perampanel dose was 6.5 ± 3.1 mg (median 6.0 mg); ≥50% responder rates were 51% overall, 63% in children, and 49% in adults. Responder rates by seizure type were 60% for patients with focal seizures, 43% for secondarily generalized seizures, 53% for PGTC seizures, and 56% for other seizure types. The seizure freedom rate was 6%. Median seizure frequency reduction was 33% for focal seizures ($P < .0001$), 44% for PGTC seizures ($P = .0008$), and 33% for secondarily generalized seizures ($P = .0002$).[69] Perampanel can therefore be considered as an adjunctive treatment option for refractory PGTC seizures, along with lacosamide, lamotrigine, topiramate, and levetiracetam.[63] Perampanel had greater efficacy at higher doses and in children vs adults (all children younger than 12 years had a ≥50% reduction in seizures), but efficacy was not affected by seizure type.[70]

In the first study, AEs were reported by 48% of patients. The most common AEs were somnolence/fatigue (18%), dizziness/falls (18%), and behavioral problems (15%), although the AEs that were more likely to lead to discontinuation were cognitive impairment, headaches, weight gain, and allergies.[69] The AE rate was not affected by age, but was related to higher doses (7.3 mg vs 5.5 mg).[70] Overall, there were fewer AEs in this group than in other reports (48% vs 65-89%), which may have been in part because of slower titration than in the clinical studies (2 mg every 2-3 weeks vs 2 mg every week).

10.2 | Special epilepsy syndromes

Perampanel is among the newer drugs considered suitable for treating Lafora disease, which is a progressive myoclonus epilepsy.[71,72] In a study of 10 patients with Lafora disease, addition of perampanel (mean dose 6.7 mg/d) resulted in a significant reduction in seizures of ≥74% from baseline for four patients and an improvement of myoclonus for seven patients (from 7.01 at baseline to 5.67 and 5.18 at 2-3 and 9-10 months, respectively).[71] Two single case reports have noted that perampanel reduced seizures and myoclonus in Lafora disease,[73,74] while 2 have reported improvement in post-hypoxic myoclonus with perampanel.[75,76] Two small studies have found perampanel to be effective in terminating some episodes of status epilepticus.[77,78]

Perampanel has blocked myoclonus and the photoparoxysmal response in a patient with progressive myoclonus epilepsy. [Tayard Desudchit. Personal Communication. 2017] Furthermore, the AMPA kainate glutamate receptor antagonist BGG492 (selurampanel) has been effective in reducing the photoparoxysmal response in patients with photosensitive epilepsy.[79] These encouraging results suggest that perampanel could potentially become an important broad-spectrum new AED.

11 | FUTURE DIRECTIONS

A multicenter study designed to evaluate the pharmacokinetics, efficacy, and safety of perampanel oral suspension on seizure frequency in pediatric patients (age 2-11 years) maintained on 1-3 stable AEDs has recently been completed (ClinicalTrials.gov Identifier: NCT01527006). An open-label extension to study 332 to evaluate the safety and tolerability of perampanel administered as adjunctive therapy in patients with PGTC seizures is ongoing (ClinicalTrials.gov Identifier: NCT02427607). A study of perampanel as adjunctive treatment for inadequately controlled seizures associated with Lennox-Gastaut syndrome is currently recruiting participants (ClinicalTrials.gov Identifier: NCT02834793). Further research into the strategy for initiation and dose escalation based on the clinical pharmacology characteristics of perampanel may be meaningful to reduce the occurrence of TEAEs.

12 | SUMMARY

Perampanel, with a novel mechanism of action, is a potent and selective AMPA receptor antagonist, showing a broad spectrum of anticonvulsant activity, which makes it a high-priority option for rational polytherapy. In the pivotal phase 3 RCTs in patients with POS ±SG or PGTC seizures despite treatment with 1–3 AEDs, adjunctive

perampanel provided significant reductions in seizure frequency and was associated with an acceptable tolerability and safety profile. Reductions in seizure frequency and improvements in responder rate were maintained with perampanel in the long term. Evidence from the use of perampanel in different populations and in the real-world clinical setting supports the phase 3 study findings.

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CONFLICT OF INTEREST

J.J. Tsai has received honoraria from Eisai for educational presentations and has received investigator fees from Eisai for participation in the clinical trials. T. Wu has received honoraria from Eisai for educational presentations and has received investigator fees from Eisai for participation in the clinical trials. H. Leung has received investigator fees from Eisai for participation in the clinical trials. T. Desudchit has received honoraria from Eisai for educational presentations. He has received investigator fees from Eisai for participation in the clinical trials. S. Tiamkao has received honoraria from Eisai for educational presentations. K.S. Lim has received honoraria from Eisai for educational presentations. A. Dash is an employee of Eisai Singapore Pte. Ltd., Singapore.

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