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Original Article

Preliminary Asian experience of using perampanel in clinical practice

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ABSTRACT

Background: To analyze the efficacy and safety of perampanel over a 3-month period in a sample of Asian people with epilepsy.
Methods: The efficacy and safety of perampanel as an adjunctive therapy for patients with epilepsy were retrospectively reviewed and analyzed. Patients were categorized according to seizure type, concomitant antiepileptic drug usage, and perampanel dosage.
Results: A total of 210 patients were included in the study and 131 patients completed 3 months of perampanel treatment. The average dosage of perampanel was 5.31 mg/day, and the 50% responder rate (≥50% seizure frequency reduction) in all patients was 45.8%, with a 27.5% seizure-free rate. For focal seizures, focal to bilateral tonic-clonic seizures, and primary generalized seizures, the 50% responder rates were respectively 29.4%, 49.5%, and 36.4%. In total, 39.5% of patients experienced adverse events within 3 months of observation period, and the rate of drug withdrawal due to adverse events was 8.6%. Dizziness, ataxia, irritability/aggression were the most common adverse events.
Conclusions: The efficacy and safety of perampanel in a real-world setting with Asian patients is comparable to that in clinical trials that have included fewer Asian patients.

Uncontrolled seizures reduce patients' quality of life [1] and increase mortality [2]. Although several antiepileptic drugs (AEDs) have been developed in the past 20 years, the proportion of patients that have achieved seizure-free status is suboptimal, and high drug resistance rates persist. Among the newest AEDs, perampanel (PER) is a new chemical entity that employs a new mechanism of action through noncompetitive antagonism of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor of glutamate on postsynaptic neurons [3,4]; it has been approved for use as an adjunctive therapy for the partial-onset seizure with or without secondarily generalized seizures in patients with epilepsy aged ≥12 years. Furthermore, the U.S. Food and Drug Administration (FDA) approved an expanded indication for PER as an adjunctive treatment for primary generalized tonic–clonic seizures in patients with epilepsy [5] in 2015; in the

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At a glance commentary

Scientific background on the subject

Perampanel is a new antiepileptic drug (AMPA antagonist) used as adjuvant therapy for refractory epilepsy. The efficacy for seizure control and its safety profile has been demonstrated in three phase-III core studies and post-marketing studies in Europe and North American.

What this study adds to the field

This is the first study using perampanel in Asian population for patients with epilepsy, which revealed the 50% responder rate (45.8%) and treatment emergency adverse event (39.5%) similar to the studies of Europe and North American.

same year, the Taiwan FDA approved the use of PER for partial onset seizures with or without secondarily generalized seizures and primary generalized seizures.

The efficacy and safety of PER have been demonstrated in three phase-III core studies [6–8] and a long-term extension of these studies [9]. Adjunctive PER at 4–12 mg/day was associated with reductions in the frequency of focal seizures, and subsequent data analyses showed higher responder rates (>50% seizure reduction) than the placebo [10]. Additionally, no major safety problems have been detected, and dizziness, somnolence, and fatigue are the most frequently reported dose-related adverse events (AEs) [11,12].

However, clinical data on the efficacy and safety of PER are scarce in real-world clinical settings involving Asian patients. Such data are crucial because the results of randomized controlled trials cannot predict outcomes in everyday clinical practice [13]. When a new drug is introduced, drug safety is the greatest concern, especially when the drug is administered to patients of different ethnic groups. Thus, the current study was aimed at reporting the postmarketing clinical experience of PER use in a single epilepsy center in Taiwan, with emphasis on its safety in early therapeutic schedules.

Material and methods

Patients and study design

This retrospective observational study enrolled 210 epilepsy patients who were administered PER from March to December 2016. Inclusion criteria were ≥12 years of age and receiving treatment with PER as an adjunctive therapy according to conventional clinical practice. Exclusion criteria were inaccurate or unreliable clinical records. The institutional review board of the hospital approved this study (E2007-M065-411).

The efficacy endpoints were the proportion of patients who were seizure-free and the proportion of 50% responders (patients with a reduction of ≥50% in seizure frequency from baseline) after 3 months of treatment. Seizure freedom was defined as having no seizures for more than 1 month at the time of the last visit. Seizure reduction measures were based on a frequency of one seizure every 4 weeks. Analysis of efficacy outcomes included all patients who fulfilled the inclusion and exclusion criteria and received PER for the entire 3-month follow-up period.

The safety population included all patients who fulfilled the inclusion and exclusion criteria and had received at least one dose of PER. The safety endpoint included the proportion of patients with AEs during 3-months treatment and the proportion of patients with AEs that led to a PER dose reduction or discontinuation of PER during the 3-month treatment. The AEs identified from the clinical records were considered to be related to the prescription of PER by attending physicians.

Data collection

Data were gathered from patients' clinical records. The following data were collected at baseline: demographics, age at seizure onset, duration of epilepsy, seizure type, etiology of seizure, seizure frequency per month, previous and concomitant AEDs, treatment emergency AEs (TEAEs), and psychiatric comorbidity (present when PER treatment began). Concomitant AEDs were classified as enzyme-inducing AEDs (EIAEDs; oxcarbazepine, carbamazepine and phenytoin) and non-EIAEDs (any other AED). The usual dosage schedule for PER was 2 mg/day in the first 2 weeks and 4 mg/d in the next 2 weeks. If a patient presented with an AE, the dosage of PER remained the same or was reduced to the previous dosage; patients stopped PER treatment when severe AEs were noted. The initial starting dose was typically 2 mg/day and then titrated up with increments varied between 2 mg/2 weeks and 2 mg/6 weeks according to the judgments of the clinician for improved seizure control. The dosage was kept constant for patients who were seizure-free. The minimal dosage was 2 mg/day and maximal dosage was 12 mg/day.

The following information was collected from clinical charts at every visit: seizure frequency, AEs, and PER dose. AEs transcribed in the charts after patient complaints or caregiver inquiries were included.

Statistical analysis

SPSS version 21 (SPSS Inc., Chicago, IL, USA) was used for the data analysis, and the chi-square test was used to compare the categorical variables. Quantitative variables are summarized as the frequency, arithmetic mean, standard deviation, median, minimum, and maximum. Efficacy was evaluated by comparing the seizure frequency at baseline and in the third month of PER treatment.

Results

Patient disposition

Of the 210 patients who received at least one dose of PER enrolled in the study database, fifty-one patients who continued to receive PER had less than 3 months of observation period and twenty-eight patients stopped PER due to either AEs (n = 18) or a lack of efficacy (n = 10). The safety

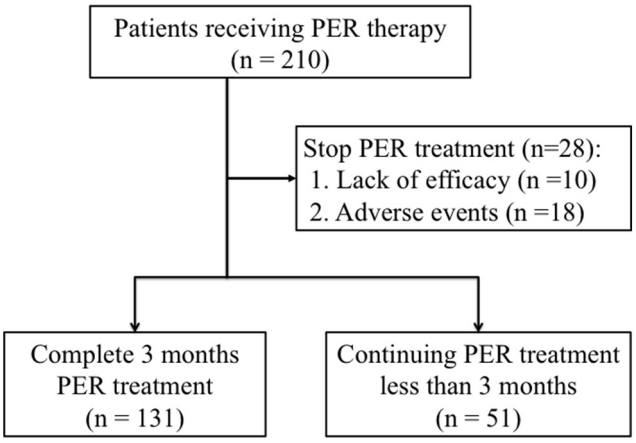

Fig. 1 Patient flow chart from baseline to 3 months follow-up. Abbreviation: PER: perampanel.

population comprised 210 patients, and a total of 131 patients completed 3 months of follow-up (completer population). The patient's flow chart from baseline to 3 months follow-up was shown in Fig. 1. The mean dose of PER at the end was 5.31 mg/d (range: 2–12 mg/d) in all patients and 4.17 mg/d (range 2–8 mg/d) in the seizure-free patients. Table 1 provides their baseline demographic and disease characteristics. Most of the patients had focal to bilateral tonic-clonic seizures (81.8%); 10.7% had focal seizures only and 7.6% had primary generalized seizures. Most patients (94.8%) received ≥2 concomitant AEDs prior to PER initiation.

Table 1 Demographics and clinical characteristics of the patients.

Category	N = 159 (%)
Mean age (SD), Year	38.1 (12.6)
Age range, Year	16–75
Female, n (%)	73 (47.4)
Age at epilepsy onset (SD), years	18.0 (12.9)
Duration of epilepsy, mean (SD), years	20.1 (12.0)
Seizure type, n (%)	
Focal seizures only	17 (10.7)
Focal to bilateral tonic-clonic seizures	130 (81.8)
Primary generalized seizures	12 (7.6)
Etiological classification of epilepsy	
Idiopathic epilepsy	16 (10.1)
Cryptogenic epilepsy	90 (56.6)
Symptomatic epilepsy, acquired causation	
Cerebral trauma	20 (12.6)
Cerebral tumor	4 (2.5)
Cerebral infection	14 (8.8)
Cerebrovascular disorders	3 (1.9)
Cerebral immunologic disorders	2 (1.3)
Hippocampal sclerosis	5 (3.1)
Symptomatic epilepsy, genetic or developmental causation	5 (3.1)
Seizure frequency per 28 days before PER, n (max, min)	11.6 (420, 0.3)
Medium Seizure frequency per 28 days	2
Number of concomitant AEDs at baseline, n (%)	
1	8 (5.2)
2	37 (23.3)
3	61 (38.4)
4	43 (27.0)
5	6 (4.8)
6 and more than 6	4 (2.5)
Enzyme-inducing AED, n (%)	111 (69.8)
Carbamazepine	41 (25.8)
Phenytoin	15 (9.4)
Oxcarbazepine	58 (36.5)
Non enzyme-inducing AED, n (%)	48 (30.2)

Abbreviations: SD: standard deviation; AED: antiepileptic drug.

Efficacy

At 3 months, 45.8% of patients were 50% responders; 13.7% exhibited 50–74% improvement, 4.6% exhibited 75–99% improvement, and 27.5% were seizure free. In addition, 29 patients (22.1%) had <50% seizure reduction (Fig. 2). Overall, most of the patients (n = 48; 36.6%) received 4 mg/day of PER as a maintenance dose, followed by 6 mg/day (n = 28; 21.4%), 2 mg/day (n = 23; 17.6%), 8 mg/day (n = 22; 16.8%), and 10 and 12 mg/day (n = 5 each; 3.8%), respectively. Fig. 3 demonstrates the seizure reduction rate at the end of 3 months' treatment with different PER dosages.

Fig. 4 shows the seizure 50% responder rates in various subgroups. A 50% responder rate was observed in 29.4% (5/17) of patients with focal seizures, 49.5% (51/103) with focal to bilateral tonic-clonic seizures, and 36.4% (4/11) with primary generalized seizures, and PER efficacy did not differ across seizure types (p = 0.246). When patients were classified into two subgroups at baseline, namely those who were receiving PER with concomitant EIAEDs and those who were not (non-EIAEDs), no significant differences were observed in the responder rates (p = 0.165).

Safety

The AEs of PER are summarized in Table 2. Overall, 83 out of 210 patients (39.5%) experienced at least one AE, of which dizziness was the most common (n = 36; 17.1%); followed by ataxia (n = 13; 6.2%), irritability/aggression (n = 11; 5.2%), malaise/fatigue (n = 10; 4.8%) and somnolence (n = 9; 4.3%). A total of 18 patients (8.6%) withdrew from PER treatment because of AEs (some with more than one AE), and 15 patients (7.1%) reduced their PER doses to decrease the likelihood of AEs.

Psychiatric or behavioral AEs include aggression (2/12), irritability (9/12) and depression (1/12); one suicide ideation related to PER was noted in this study. The details of patients with psychiatric or behavioral AEs are summarized in Table 3. Six patients experiencing psychiatric AEs had preexisting psychiatric or behavioral disorders. Two patients discontinued PER because of severe psychiatric AEs when using 2 mg of PER, and the other four patients discontinued PER when using 6–8 mg of PER. Five patients were able to self-alleviate side effects without the need to adjust their PER doses. Fig. 5 shows the proportion of psychiatric or behavioral AEs in patients with psychiatric comorbidities and without psychiatric comorbidities. Patients with pre-existing psychiatric comorbidities have higher proportion of psychiatric or behavioral AEs (n = 6; 14.0%) than patients without pre-existing psychiatric comorbidities ($p = 0.018$).

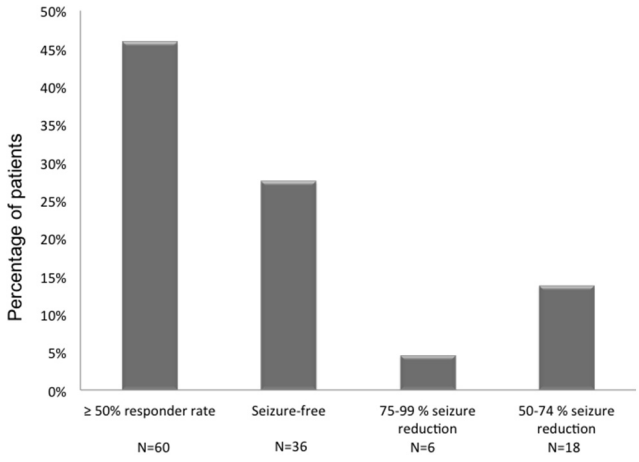

Fig. 2 Seizure reduction rate in 131 patients receiving 3 months of perampanel treatment.

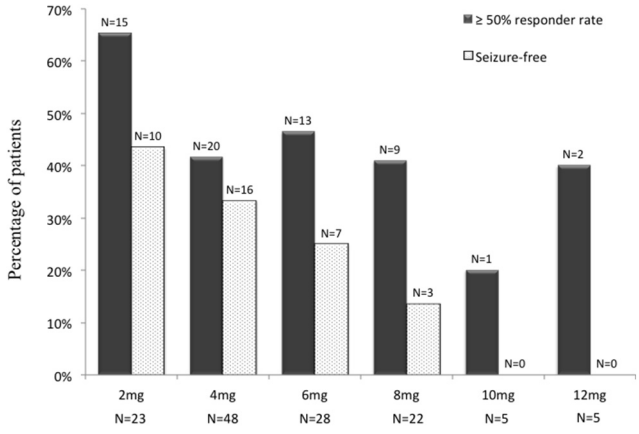

Fig. 3 Seizure reduction rate after 3 months of treatment with different perampanel dosages.

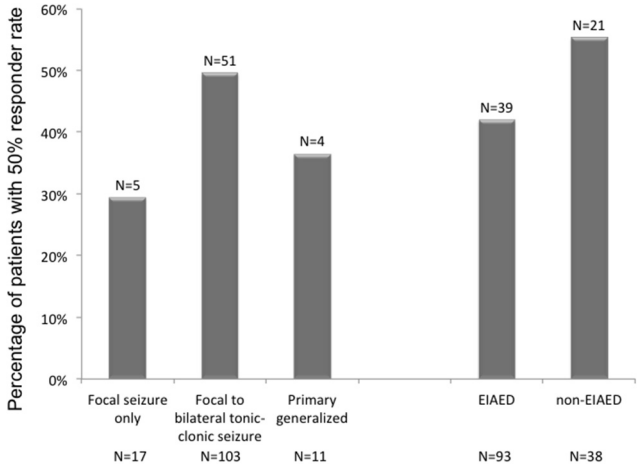

Fig. 4 Seizure and EIAED subgroups' 50% responder rates.

Discussion

This study illustrates real-world efficacy outcomes and safety among 210 patients treated with PER for 3 months. The sample of patients reported here are a highly refractory group, as observable from the long durations of epilepsy and high concomitant usage rates of AEDs. In our series, 45.8% (60/131) of patients experienced a seizure reduction of more than 50%, and 27.5% (36/131) became seizure free.

The overall 50% responder rate (45.8%) in our study was higher than in a randomized controlled trial (33.3–37.6%) [6–8]. Clinical data on PER usage after marketing has indicated similar responder rates of 48.0% in Germany [14], 51% in the United States [15], 43.8–57.5% in the United Kingdom and Ireland [16], 41.8% in Austria [17], 41.6% in France [18], and 50.0% in Italy [19]. An exception was the 26.8–32.7% rate observed in Spain [20]. The seizure-free rate was 27.5%, which was similar to data from the Austrian study (27.0%) [17]. This was significant higher than that of the randomized controlled trial (1.9–4.8%). The difference maybe related to the current study patient population was different to the randomized controlled trial. The inclusion and exclusion criteria in the randomized controlled trial tend to recruit patients with much more seizure burden. This is common phenomenon observed after the new AEDs were formally on the market. Other real-world observations of seizure-free rates in past studies have included 8.1–15% in 6 months of observation [14,20,21] and 5.9% in 3 months of observation. In addition to the usage of PER for focal seizures, the retrospective nature and large cohort of the current study also provided opportunities to evaluate the effectiveness of PER for primary generalized seizures [22]. Overall, there was no major difference in efficacy between the focal seizure and primary generalized subgroups. These findings support existing research on PER efficacy in focal seizures, focal to bilateral tonic-clonic seizures, and primary generalized seizures [6,10].

An open-label trial after the randomized controlled trials reported that almost all long-term continuations of PER required dosages of 8 or 12 mg [11]. The current study observed that some patients continued to take lower dosages of PER due to slow titration for patients with AEs. Only 8% of patients received 10–12 mg/day of PER, whereas approximately 54% of patients received 2–4 mg/day. By contrast, a number of patients were seizure free in lower doses (43.5% at 2 mg/day and 33.3% at 4 mg/d) due to the shorter period of observation or achievement of more than 50% seizure reduction (65.2% at 2 mg/d and 41.7% at 4 mg/d) even at these doses. This differs from the results of another postmarketing study [15], which showed that higher dosages were correlated with higher seizure responder rates. The longer follow-up duration of the cohort in the current study explains this difference. A previous phase-III study [8] revealed that the 50% responder rate was 28.5% for doses of 4 mg/d, and another review article [23] demonstrated a statistically significant percent change in seizure frequency for 4-, 8-, and 12-mg doses of PER compared with the placebo group. This difference may be related to the use of fixed-dose titration up to 8 or 12 mg/day in the randomized controlled trial, while the dose was determined according the clinical response and increased dose as needed in

Table 2 TEAEs in 210 patients taking PER.

PER dosage (mg/day)	2	4	6	8	10	12	Total
Number of any TEAE (%)	26 (31.3)	45 (84.9)	5 (6.0)	4 (4.8)	1 (1.2)	2 (2.4)	83 (39.5)
TEAEs leading to PER adjustment, n							
Dose reduction		13	1			1	15 (7.1)
Discontinuation	10	5		3			18 (8.6)
Incidence of individual TEAE occurring ≥5% of overall population, n							
Dizziness	10	22	4				36 (17.1)
Ataxia	1	8	2	1		1	13 (6.2)
Irritability/aggression	3	2	1	5			11 (5.2)
Incidence of individual TEAE occurring <5% of overall population, n							
Depression			1				1 (0.5)
Suicide ideation	1						1 (0.5)
Malaise/fatigue	3	7					10 (4.8)
Somnolence	2	7					9 (4.3)
Asthenia	2	1					3 (1.4)
Nausea	1	1					2 (1.0)
Body weight gain	1	4			1		6 (2.9)
Appetite increase	1					1	2 (1.0)
Headache	1	2					3 (1.4)
Itching no eczema	1	1					2 (1.0)
Blur vision	1						1 (0.5)
Tinnitus	1						1 (0.5)
Numbness	2						2 (1.0)
Memory impairment	1						1 (0.5)

Abbreviations: AE: adverse events; PER: perampanel; TEAE: treatment emergent adverse event.

the real clinical practice. Further study of the long-term efficacy of low-dose PER is warranted. More patients with titrations of 8–12 mg/d should be included in these future analyses. More experience in PER usage after a longer period and more patients usage will further delineate whether ethnic difference contribute to the dosage difference.

The 3-month retention rate in this study was 82.4%, as compared with the 88% and 73% rates observed in two post-marketing studies [18,20]. A total of 28 patients withdrew, 18 due to TEAEs and 10 due to poor efficacy. One patient reported increased seizure frequency. A total of 15 patients (7.1%) had dose reductions due to AEs; all of these patients continued to use PER for seizure control. No serious AEs significantly associated with PER treatment were observed in our study. In a previous pooled analysis of phase-III core studies [10], most AEs were mild to moderate, just 8.9% of patients experienced severe AEs, and 5.5% of patients experienced serious AEs. These findings demonstrate the safety of PER usage in Asian patients.

The most common AE was dizziness (17.1%) in trial studies and some postmarketing studies. Other significant AEs in our data on an Asian population were ataxia (6.2%), psychiatric or behavioral problems (irritability/aggression 5.2%, depression 0.5%), and malaise and fatigue (4.8%). Somnolence (4.3%) was also common, especially in postmarketing studies. PER-related TEAEs were mostly observed in the low-dosage groups (2 and 4 mg/day), and most of the patients who dropped out did so in the initial 4 weeks. In both clinical trials and some real-world studies, most discontinuation of PER treatment occurs in the first 1–2 months, often due to TEAEs such as dizziness, somnolence, and ataxia [17,20,24]. During the trial period, several studies reported higher AEs of 69.9–80.6%. The postmarketing studies had lower incidences of AEs (45.0–67.4%) [14,15,17,20]. AEs occurred in 40.9% of patients in the current cohort, which was similar to the result of a previous 3-month study (45%) [20] and the other studies of different durations (47.0–67.4%) [14,16,17,25]. This difference might be related to the faster fixed titration scheme in previous three phase III studies (from 2 to 8–12 mg/day in 6 weeks in 304, 305 and from 2 to 4–8 mg/d in 306) [6–8], which differed from the flexible dosage increase found in conventional clinical practices. In addition, a previous study indicated that slow-dose titration could minimize AEs [26]. The dosage of PER most commonly used in the current cohort was 2–6 mg/d, contrasting with the dosage of 8–12 mg/d most commonly used in clinical trials. The most common side effects of PER are dose-related [10,12,27]. More TEAEs were observed in a previous study if the observation period was longer (45% at 3 months, 57.8% at 6 months, and 62.9% at 12 months in Spain study) [20], and most of the TEAEs appeared within the first 6 months of treatment [20].

Like many other AEDs, PER can contribute to or produce comorbid psychiatric disorders. This is exacerbated by the propensity of many patients with epilepsy to develop these problems before and after receiving a diagnosis of epilepsy [28]. These concerns have been highlighted in other outcome studies with PER [14,29] and psychiatric or behavioral AEs, including irritability, aggression, depression, and suicidal ideations, are important to monitor given the potential role of glutamate in psychiatric problems such as aggressive behavior [30]. In the current study, 8.2% of patients had psychiatric or behavioral AEs at 3 months follow-up and the proportion was lower than the 15.3% observed in a previous post-phase-III pooled study [31]. Psychiatric or behavioral AEs tend to be dose-related (9.4% at 2 mg/d, 6.4% at 4 mg/d, 17.2% at 8 mg/d, and 22.4% at 12 mg/d) and were demonstrated to

Table 3 Clinical characteristics of the patients with psychiatric or behavioral adverse events.

Age/gender	Onset age	Preexisting psychiatric or behavioral condition	Severity; psychiatric or behavioral AEs	Management
27/M	17	Psychosis	Severe; Irritability when PER was titrated to 8 mg in 1 month	Stop PER
31/M	14	No	Mild; Irritability when PER was titrated to 4 mg	Spontaneous subsided without PER adjustment
24/M	4	Autism, hyperactive	Severe; irritability when PER was titrated to 8 mg	Stop PER
24/M	10	No	Mild; irritability when PER was titrated to 8 mg	Spontaneous subsided without PER adjustment
29/F	21	Depression	Severe; worse of depression when PER was titrated to 6 mg	Stop PER
38/M	26	No	Severe; aggression when PER 2 mg	Stop PER
33/M	5	Irritability	Mild; aggression when PER 2 mg was used	Spontaneous subsided without PER adjustment
59/F	43	No	Moderate; irritability when PER was titrated to 4 mg	Reduced PER dose
34/M	9	No	Severe; irritability when PER was titrated to 8 mg	Stop PER
29/M	7	No	Mild; irritability when PER titrate up to 6 mg	Spontaneous subsided without PER adjustment
19/M	0	Irritability	Mild; worse of irritability when PER titrate up to 8 mg	Spontaneous subsided without PER adjustment
35/F	22	Depression	Severe; irritability and suicide ideation after PER 2 mg	Stop PER

Abbreviations: PER: perampanel; FTLE: frontotemporal lobe epilepsy; FLE: frontal lobe epilepsy; IGE: idiopathic generalized epilepsy; JME: juvenile myoclonic epilepsy; MTLE: mesial temporal lobe epilepsy.

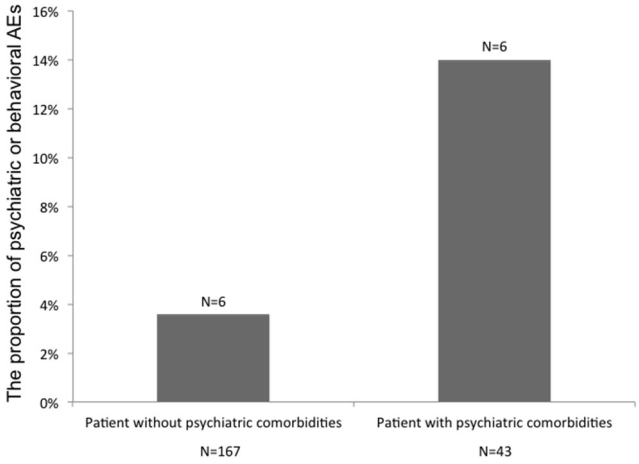

Fig. 5 The proportion of psychiatric or behavioral AEs in patients with and without psychiatric comorbidities ($p = 0.018$).

occur during the first 6 weeks of treatment with PER up to 12 mg/d in a post-phase-III pooled study [31] and a post-marketing study [16]. Six of the 12 patients with psychiatric AEs (50%) had preexisting psychiatric or behavioral conditions at baseline, and 14.0% patient with psychiatric comorbidities suffer from psychiatric AEs after receiving PER treatment compared with 3.6% patients without psychiatric comorbidities ($p = 0.018$). This finding was similar to a previous retrospective study [20]. That retrospective study demonstrated that patients with psychiatric comorbidities at baseline, specifically personality disorders and hyperactivity, were more likely to develop a psychiatric AE while receiving PER. As such, increased caution should be employed when treating patients with PER, especially patients with psychiatric comorbidities.

We acknowledge that current study had some limitations. The retrospective design of current study may have resulted in unstandardized evaluation of AE and the lack of control or comparison patients in this study type meant that was difficult to ascertain the true background risks for psychiatric symptoms and other AEs. Beside, our study had limitations in addition to the use of a single-center patient population. Additionally, few patients were titrated to the upper 10–12 mg/day dose range and this limitation was related to dosing determined by individual physicians and short observation period. We emphasize that an observation period of 3 months is a relatively short period to judge the effects of an adjunctive AED on patients with epilepsy. Because the PER was released later in the market in Asia than in Europe and North America, where previous studies were conducted, the follow-up period was limited. Further information of efficacy and AE in patients receiving PER therapy will be available in this continuing study cohort, and the total patients number is expanded to reach 500 in one year. Both anticonvulsant efficacy and AEs occurred in some subjects at relatively low dosages. Reasons for this aside from PER usage may have been differences in seizure frequency or the number of previously failed AEDs, neither of which were assessed in this study. However, the strengths of current study include large Asian

sample size, in a real-world setting, analyzing some patients who could not have been included in the randomized controlled trial. Finally, adjunctive PER therapy has comparable efficacy and acceptable AE as an add-on AED in Asian people.

Conclusion

The current study adds to the accumulating body of real-world data on PER. The efficacy and safety of PER in a real-world setting is comparable with the findings of clinical trials with far fewer Asian participants. However, for those patients with preexisting psychiatric symptoms, regular monitoring of these symptom and signs is warranted after initiation of PER use.

Conflicts of interest

The authors declare no conflicts of interest.

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