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ORIGINAL COMMUNICATION

Efficacy and safety of adjunctive perampanel treatment in pediatric patients with epilepsy aged 4–12 years: a real-world study

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Abstract

Objective To determine the efficacy and safety of perampanel (PER) as an adjunctive therapy in children aged 4–12 years with epilepsy.

Methods We performed a non-randomized, open-label, placebo-uncontrolled, real-world self-controlled study that included 216 young children (aged 4–12 years) with epilepsy who received PER as adjunctive therapy at the children's hospital affiliated with Chongqing Medical University from July 4, 2020, to September 20, 2023.

Results (1) The efficacy rates of adjunctive PER therapy at 3, 6, 9, and 12 months were 62.8%, 67.8%, 65.3%, and 61.2%, respectively. PER showed efficacy in alleviating focal seizures, generalized tonic–clonic seizures, myoclonic seizures, and absence seizures. The efficacy rates for variants of self-limited epilepsy with centrotemporal spikes (SeLECTS) and Lennox-Gastaut syndrome (LGS) were 89.5% and 66.7%, respectively. (2) Focal non-motor onset seizures with or without impaired awareness, focal to bilateral tonic–clonic seizures (FBTCS), LGS, variants of SeLECTS, the number of concomitant antiseizure medications (ASMs), a family history of epilepsy, and focal lesions on cranial magnetic resonance imaging were independent factors affecting efficacy. The order of PER addition did not affect efficacy. The retention rates at 3, 6, 9, and 12 months were 90.7%, 84.7%, 74.7%, 64.9%, respectively. (3) Adverse reactions occurred in 45 patients (45/216, 20.8%), with irritability/aggressive behavior (18/216, 8.3%) and somnolence (14/216, 6.5%) being the most common. Twelve patients (12/216, 5.6%) withdrew from the study because of adverse reactions.

Conclusion In young Chinese children with epilepsy, PER is effective, safe, and well-tolerated as an adjunctive therapy, making it a viable option for use with broad-spectrum ASMs.

Keywords Young children · Epilepsy · Perampanel · Adjunctive therapy · Real-world study

Introduction

Perampanel (PER) is a novel third-generation antiseizure medication (ASM) that is a noncompetitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor on postsynaptic neurons [1]. The AMPA receptor is the primary postsynaptic glutamate receptor mediating rapid excitatory synaptic transmission and excitatory postsynaptic potentials. PER works by binding to the extracellular domain of the channel protein subunits of the AMPA receptor, inducing a conformational change, thereby inhibiting the binding of glutamate to the receptor, reducing the activity of rapid excitatory neurotransmitters, and exerting an antiepileptic effect [2]. In 2012, PER was only approved for the treatment of focal seizures in patients aged 12 years and older. In 2017, the Food and Drug Administration of the United States authorized its use for focal

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seizures in individuals aged 4 years and older, as well as for primary generalized tonic–clonic seizures in patients aged 12 years and older [3]. In 2021, the National Medical Products Administration of China approved PER for the treatment of focal seizures (with or without secondary generalization) in children aged 4 years and above. In 2022, Chinese experts consensus recommended that PER be used in pediatric patients with epilepsy for various etiologies and seizure types, including specific epileptic syndromes such as Dravet syndrome and Lennox-Gastaut syndrome (LGS) [35]. This difference in timelines has led to varying levels of awareness among researchers regarding the use of PER in these age groups, with a consequent variation in the volume of literature reports on this topic. Evidence on the efficacy and safety of PER in young children (aged 4–12 years) with epilepsy is limited. There are currently numerous challenges associated with the treatment of pediatric epilepsy, particularly because of the constraints on clinical drug trials and research in young children with epilepsy. Real-world studies have become an important complement to clinical research on epilepsy among young children.

This study included 216 children with epilepsy, aged 4 to 12 years, who received adjunctive therapy with PER at Chongqing Medical University Children's Hospital from July 4, 2020, to September 20, 2023. This a non-randomized, open-label, placebo-uncontrolled, real-world self-controlled study aimed to analyze the efficacy and safety of PER as an adjunctive treatment in young children with epilepsy, and to elucidate the factors influencing its efficacy, thereby providing evidence to guide the clinical application of PER in the treatment of pediatric epilepsy.

Materials and methods

Study participants

Inclusion criteria

(1) Dates of consultation: Between July 4, 2020, and September 20, 2023.
(2) Aged between 4 and 12 years.
(3) Diagnosis of epilepsy according to the 2017 International League Against Epilepsy (ILAE) criteria.
(4) Previous conventional use of one or more ASMs, with at least one clinical seizure episode within 3 months before starting PER treatment.

The study was approved by the Medical Ethics Committee of the Children's Hospital affiliated with Chongqing Medical University [Ethical Approval Number: (2023) Lun-Shen (Yan) No. 473].

Prior to administration, detailed discussions were held with the caregivers, and informed consent was obtained from the caregivers and from patients who were capable of understanding the form and providing consent. For all uses of PER outside the indications approved by the National Medical Products Administration of China, caregivers were informed about off-label use in the consent forms, including potential efficacy and adverse effects.

Exclusion Criteria

Poor compliance and patients who could not provide an accurate medical history.

Research methodology

PER (Eisai Co., Ltd., Kawashima Factory, Registration Certificate No. H20190053) was administered as adjunctive therapy without altering the patients' existing ASM regimen or substituting any of the ASMs. All patients received PER treatment once daily at bedtime. The initial dose was stratified according to weight ranges: patients weighing < 20 kg started at 0.5 mg/day; those weighing 20–30 kg at 1 mg/day; and those weighing > 30 kg at 2 mg/day. Dose adjustments were made by increasing the dose by one initial dose every 1–2 weeks, with the target maintenance dose individually adjusted based on therapeutic efficacy and patient tolerance.

The average number of seizures per month in the three months before PER treatment was defined as the baseline seizure frequency ("times/month"). The seizure reduction rate = (baseline seizure frequency − post-treatment seizure frequency)/baseline seizure frequency × 100%. Clinical efficacy evaluation was categorized into complete control, marked effect, effective, and ineffective as follows: [4] (1) Complete control: control of seizures, with no clinical seizures; (2) Marked effect: reduction of seizure frequency by $\geq 75\%$; (3) Effective: reduction of seizure frequency by $\geq 50\%$; (4) Ineffective: reduction of seizure frequency by $< 50\%$. Clinical effectiveness rate = [(complete control + marked effect + effective cases)/total treated cases] × 100%. An exacerbation of epilepsy was defined as an increase in the frequency of all countable types of epileptic seizures by $> 25\%$ compared with the baseline frequency [5].

This non-randomized, open-label, placebo-uncontrolled, self-controlled observational study was conducted under real-world clinical practice conditions. It comprised a retrospective phase (up to 35 months) and a prospective phase (up to 6 months) (Fig. 1). The observation period ended on December 21, 2023. The primary endpoint was the efficacy rate of PER treatment at 3, 6, 9, and 12 months after initial PER administration. Secondary endpoints included drug retention rates for the entire study cohort and the safety of PER treatment. Patients

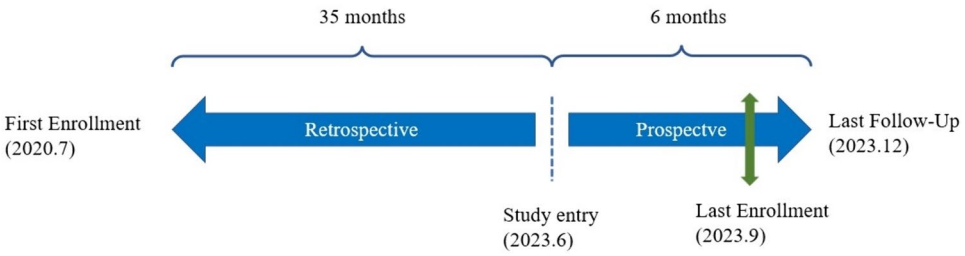

Fig. 1 Study design

who received additional treatments [including ketogenic diet, epilepsy surgery, vagus nerve stimulation (VNS)] or changed ASMs during the study were excluded from efficacy observations but included in the safety assessment.

Refractory epilepsy was defined according to the ILAE criteria as epilepsy that remains uncontrolled after the administration of ≥ 2 tolerable ASMs at adequate doses and durations, reaching effective concentrations in the body [6].

Statistical analysis

Continuous variables are represented by medians with interquartile ranges (IQRs), and categorical variables are represented as frequencies (%). Drug retention rates were evaluated through Kaplan–Meier survival analysis. Missing clinical data, assumed to be missing at random, were handled using multiple imputation techniques. Specifically, the random forest method was chosen for continuous variables, while polynomial regression was used for categorical variables with multiple ordered or unordered categories. Non-random missingness due to deaths, discontinuations, changes in treatment plans, or insufficient follow-up (< 12 months) was addressed using the worst observed value imputation. A mixed model for repeated measures (MMRM) analysis was used for sensitivity analysis on the impact of missing data imputation and adjustments for concomitant ASM doses on the outcomes. Models included Toeplitz and diagonal covariance structures.

Lasso-Cox regression was used for variable selection of baseline characteristics with $p < 0.1$, and multifactorial Cox regression analysis was used to assess the independent risk factors for efficacy.

A p-value of < 0.05 (two-sided) was considered statistically significant. Data analysis was performed using R software version 4.3.2, incorporating the glmnet, survival, mice, mmrm packages.

Results

Baseline clinical characteristics

This study included 216 pediatric patients with epilepsy, aged 4–12 years, who received PER as adjunctive therapy at the Children's hospital affiliated with Chongqing Medical University from July 4, 2020, to September 20, 2023 (Table 1; Fig. 2).

Efficacy analysis

Patients were followed up at 3, 6, 9, and 12 months after initiation of PER treatment (Fig. 3-1). MMRM models were constructed, using the Toeplitz covariance structure before and after imputation of missing data. The results indicated that the average seizure reduction rate in the original dataset with missing data was approximately 3.7% higher (95% CI = – 0.9 to 8.3, p = 0.179) than that in the dataset after imputation, suggesting that imputation of missing data had no significant effect on the results. To assess the impact of adjusting concomitant ASM dose during the study, a sensitivity analysis was conducted on the primary variables using an MMRM model with a diagonal covariance structure. The seizure reduction rate in the group with adjusted concomitant ASM doses was approximately 12.2% lower (95% CI = – 27.6 to 3.2, p = 0.119) than that in the group without concomitant ASM dose adjustments, indicating that dose adjustments during the study had no significant impact on the outcomes.

The efficacy of adjunctive PER therapy across different time periods was therefore calculated using the post-imputation dataset (Fig. 3-2). The efficacy rates at 3, 6, 9, and 12 months were 62.8%, 67.8%, 65.3%, and 61.2%, respectively, and the average seizure reduction rates at the same time points were 50.1% (95% CI = 46.7–53.6), 59.0% (95% CI = 54.7–63.3), 56.6% (95% CI = 51.3–61.9), and 52.7% (95% CI = 46.0–59.4; P < 0.001), respectively. The seizure-free rates at 3, 6, 9, and 12 months were 33.7% (66/196), 43.9% (86/196), 38.8% (76/196), and 34.7% (68/196), respectively. After introducing PER, the initial efficacy rate in patients receiving PER as their first adjunctive therapy was 78.1%, with a seizure-free rate of 53.1%; for patients who were refractory to ≥ 5 ASMs, the efficacy and seizure-free rates dropped to 50.0% and 13.6% (Fig. 3-3). The impact of PER adjunctive therapy on different seizure types and epilepsy syndromes is shown in Fig. 3-4 and -5. Focal non-motor onset seizures with or without impaired awareness and focal to bilateral tonic–clonic seizures (FBTCS) with

Table 1 Risk factors affecting the efficacy of PER adjuvant therapy for treating epileptic seizures in young children

Characteristics	Total n = 216	[a]HR, 95% CI n = 196	[a]p-value n = 196	[b]HR, 95% CI n = 196	[b]p-value n = 196
Sex, female	92 (42.6%)	1.0, 0.8–1.1	0.596		
PER initiation age, y	8.1 [6.5–10.5]	1.0	0.668		
Duration of epilepsy prior to PER, y	3.4 [1.5–5.8]	1.0	0.343		
Age at seizure onset, y	4.4 [1.3–6.6]	1.0	0.166		
Family history of epilepsy	28 (13.0%)	1.6, 1.3–2.1	< 0.001	1.5, 1.1–1.9	0.003
Perinatal high-risk factors	23 (10.6%)	0.7, 0.5–0.9	0.012	0.8, 0.5–1.2	0.216
Epileptic seizure type					
Focal seizures	123 (56.9%)	1.4, 0.8–2.5	0.258		
Focal motor onset seizures with or without impaired awareness	61 (28.2%)				
Focal non-motor onset seizures with or without impaired awareness	8 (3.7%)	0.4, 0.2–0.7	0.004	0.4, 0.3–0.9	0.017
Focal to bilateral tonic–clonic seizures	54 (25.0%)	0.6, 0.5–0.8	< 0.001	0.7, 0.6–0.9	0.014
Generalized seizures	86 (39.4%)	1.4, 0.8–2.5	0.259		
Generalized tonic–clonic seizures	35 (16.2%)	1.0, 0.7–1.2	0.731	1.0, 0.8–1.3	0.959
Absence seizures	31 (14.8%)	0.7, 0.5–0.9	0.010	0.7, 0.5–1.1	0.098
Typical absence seizures	21 (9.7%)	1.2, 0.9–1.6	0.182		
Atypical absence seizures	10 (4.6%)	0.3, 0.2–0.6	0.001		
Myoclonic seizures	14 (6.5%)	0.8, 0.6–1.2	0.294	0.9, 0.6–1.4	0.568
Atonic seizures	3 (1.4%)	0.3, 0.1–0.8	0.024	0.5, 0.1–1.5	0.214
Tonic seizures	3 (1.4%)	0.4, 0.1–1.0	0.044	0.4, 0.2–1.2	0.109
Epileptic spasm	6 (2.8%)	0.6, 0.3–1.0	0.053	0.6, 0.3–1.1	0.092
Epileptic syndromes	73 (33.8%)				
IGE syndromes	13 (6.0%)	1.1, 0.8–1.6	0.487		
Childhood absence epilepsy	5 (2.3%)	0.6, 0.3–1.3	0.191	0.6, 0.3–1.3	0.219
Juvenile absence epilepsy	5 (2.3%)	1.3, 0.7–2.1	0.407	1.2, 0.7–2.3	0.484
Juvenile myoclonic epilepsy	1 (0.5%)	2.0, 0.7–5.3	0.172	1.5, 0.5–4.4	0.491
GTCA	2 (0.9%)	2.0, 1.0–4.0	0.055	1.0, 0.5–2.1	0.993
DEE	59 (27.3%)	1.3, 1.1–1.6	0.002		
variants of SeLECTS	24 (11.1%)	1.8, 1.4–2.3	< 0.001	1.4, 1.0–1.8	0.043
LGS	13 (6.0%)	1.3, 0.9–1.8	0.205	1.5, 1.0–2.3	0.040
West syndrome	12 (5.6%)	1.1, 0.8–1.6	0.619	1.2, 0.8–1.8	0.403
Dravet syndrome	2 (0.9%)	< 0.001	0.993	0	0.993
Rasmussen syndrome	3 (1.4%)	1.0, 0.4–2.5	0.946	0.9, 0.3–2.8	0.914
SHE	1 (0.5%)	2.0, 0.7–5.3	0.172	1.1, 0.4–3.1	0.894
GLUT1DS	1 (0.5%)	2.0, 0.7–5.3	0.172	0	0.993
HHE	1 (0.5%)	2.0, 0.7–5.3	0.172	2.4, 0.8–7.6	0.125
MTLE-HS	1 (0.5%)	< 0.001	0.993	0	0.993
FIRES	1 (0.5%)				
Etiology					
Structural	56 (25.9)	0.9, 0.7–1.1	0.196	1.1, 0.9–1.5	0.380
Genetic	27 (12.5%)	0.7, 0.5–0.9	0.016	0.7, 0.5–1.0	0.092
CNS infection	17 (7.9%)	0.5, 0.3–0.8	0.001	0.6, 0.4–1.1	0.080
Autoimmune	9 (4.2%)	0.8, 0.5–1.3	0.404	1.3, 0.7–2.4	0.470
Metabolic	2 (0.9%)	0.6, 0.2–1.7	0.389	0	0.993
Unknown	105 (48.6%)				
Cranial MRI					
Normal	84 (38.9%)				
Focal	52 (24.1%)	0.8, 0.6–0.9	0.015	0.8, 0.6–1.0	0.036

Table 1 (continued)

Characteristics	Total n = 216	[a]HR, 95% CI n = 196	[a]p-value n = 196	[b]HR, 95% CI n = 196	[b]p-value n = 196
Multifocal	49 (22.7%)	0.7, 0.6–0.9	0.003	0.9, 0.7–1.3	0.619
Diffuse	31 (14.4%)	0.6, 0.5–0.9	0.003	0.8, 0.6–1.2	0.381
EEG					
Focal	49 (24.4%)	0.9, 0.5–1.4	0.563		
Multifocal	104 (51.0%)	0.7, 0.4–1.1	0.147		
Extensive	47 (23.0%)	0.8, 0.5–1.3	0.333		
Normal	4 (2.0%)				
EEG background slow activity	76 (37.3%)	0.7, 0.6–0.9	0.002	0.9, 0.7–1.1	0.375
Comorbidities					
Global developmental delay	53 (24.5%)	0.7, 0.6–0.9	0.008		
ADHD	10 (4.6%)	1.1, 0.8–1.6	0.529		
Autism spectrum disorder	1 (0.5%)	1.7, 0.6–4.6	0.288		
Status epilepticus	19 (8.8%)	0.7, 0.5–1.0	0.053	0.9, 0.6–1.4	0.666
The number of previous ASMs	3 [2–4]	0.9, 0.9–1.0	0.002		
The number of concomitant ASMs	2 [1–2]	0.8, 0.7–0.8	< 0.001	0.8, 0.7–0.9	0.004
Previous ketogenic diet	27 (12.5%)	0.8, 0.6–1.1	0.153		
Concomitant ketogenic diet	5 (2.3%)	1.8, 1.0–3.2	0.039	1.9, 0.9–4.0	0.108
Concomitant VNS	8 (3.7%)	0.6, 0.3–1.1	0.095	0.6, 0.3–1.3	0.212
Initial dose of PER, mg/d	1 [1–1]	1.0, 0.8–1.2	0.658		
Maximum dose of PER, mg/d	4 [3–6]	1.0, 1.0–1.1	0.288		
Maintenance dose of PER, mg/d	4 [3–6]	1.0, 1.0–1.1	0.282		

Note: Continuous variables are represented by the median [interquartile range], and categorical variables are represented by n (%). 'a' represents univariate COX analysis, and 'b' represents multivariate COX analysis. Missing data: 2 cases of onset age, 2 cases of duration of epilepsy before PER, 1 case of type of epileptic seizure, 12 cases of EEG

Abbreviations: *CI* confidence interval, *HR* hazard ratio, *PER* perampanel, *IGE* idiopathic generalized epilepsy, *GTCA* epilepsy with generalized tonic clonic seizures alone, *DEE* developmental epileptic encephalopathy, *SeLECTS* self-limited epilepsy with centrotemporal spikes, *LGS* Lennox-Gastaut syndrome, *SHE* sleep-related hypermotor/hyperkinetic epilepsy, *GLUT1DS* glucose transporter 1 deficiency syndrome, *HHE* hemiconvulsion–hemiplegia–epilepsy syndrome, *MTLE-HS* mesial temporal lobe epilepsy with hippocampal sclerosis, *FIRES* febrile infection-related epilepsy syndrome, *CNS* central nervous system, *MRI* magnetic resonance imaging, *EEG* electroencephalogram, *ADHD* attention deficit hyperactivity disorder, *ASMs* antiseizure medications, *VNS* vagus nerve stimulation

effectiveness rates of 28.6% and 55.1%, respectively, which are lower than those for absence seizures (50.0%) and generalized tonic–clonic seizures (GTCS) (76.5%). The efficacy and seizure-free rates for adjunctive treatment of LGS were 66.7% and 33.3%, respectively; for variants of self-limited epilepsy with centrotemporal spikes (SeLECTS), they were 89.5% and 63.2%, respectively.

A univariate Cox analysis with seizure reduction rate ≥ 50% as the dependent variable and baseline clinical characteristics as independent variables was performed (Table 1). Age at seizure onset, duration of epilepsy before PER treatment, maximum and maintenance doses of PER, epileptic seizure types, epilepsy syndromes 1 [developmental and epileptic encephalopathy (DEE), idiopathic generalized epilepsy syndromes (IGEs)] and 2 [childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, generalized tonic–clonic seizures alone (GTCA), variants of SeLECTS, LGS, West syndrome, Dravet syndrome, Rasmussen syndrome, sleep-related hypermotor/hyperkinetic epilepsy (SHE), glucose transporter 1 deficiency syndrome (GLUT1DS), hemiconvulsion–hemiplegia–epilepsy syndrome (HHE), mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), febrile infection-related epilepsy syndrome (FIRES)], cranial magnetic resonance imaging (MRI), and etiology showed strong linear correlations (Fig. 3-6). To avoid multicollinearity issues, variables with $p < 0.1$ in the Cox univariate analysis were included, and a Lasso-Cox regression was applied to penalize the absolute values of their regression coefficients. With increasing penalty factor (lambda), the factors whose coefficients were reduced to zero in the model sequentially included status epilepticus, concomitant VNS, perinatal high-risk factors, epileptic seizure types, concomitant ketogenic diet, EEG background slow activity, etiology, cranial MRI, epilepsy syndromes 2 (childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, GTCA, variants of SeLECTS, LGS, West syndrome, Dravet

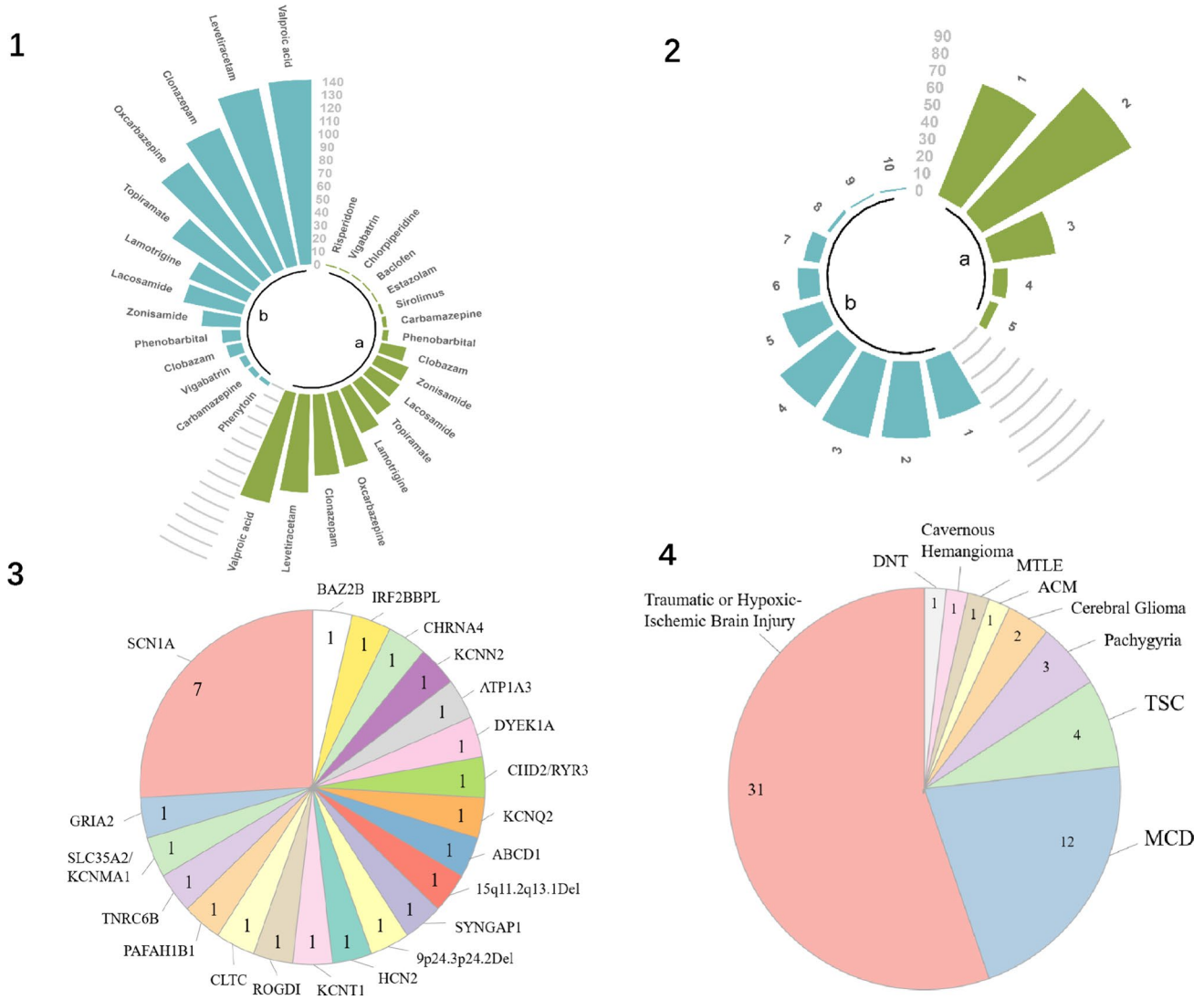

Fig. 2 Clinical Characteristics of 216 Patients at Baseline. 2-1 Types of concomitant antiseizure medications (ASMs) at baseline (**a**) and types of ASMs previously received (**b**), with bar charts showing the types of ASMs on the *x*-axis and the number of cases on the *y*-axis. 2-2 Number of concomitant ASMs at baseline (**a**) and the number of ASMs previously received (**b**), with bar charts showing the number of ASMs on the *x*-axis and the number of cases on the *y*-axis. 2-3 Classification and number of cases with genetic etiology among the 216 patients. 2-4 Classification and number of cases with structural etiology among the 216 patients. Abbreviations: *DNT* dysembryoplastic neuroepithelial tumor, *MCD* malformation of cortical development, *TSC* tuberous sclerosis, *ACM* Arnold-Chiari malformation, *MTLE* mesial temporal lobe epilepsy

syndrome, Rasmussen syndrome, SHE, GLUT1DS, HHE, MTLE-HS, FIRES), family history, and the number of concomitant ASMs (Fig. 3-7). Variables with coefficients reduced to zero at the optimal penalty strength (lambda) included the number of previous ASMs, absence seizures, comorbidities, and epilepsy syndromes 1 (DEE, IGEs).

The multivariable model indicated that focal non-motor onset seizures with or without impaired awareness, FBTCS, LGS, variants of SeLECTS, the number of concomitant ASMs, family history of epilepsy, and focal lesions on cranial MRI were independent risk factors affecting efficacy (Table 1).

Retention rate and safety

The median exposure time for the 216 pediatric patients with epilepsy receiving adjunctive PER therapy was 12 months (range 0.23–12 months). The median discontinuation time due to efficacy or intolerance was 3 months (IQR = 0.93–5.94). The retention rates after 3, 6, 9, and 12 months of adjunctive PER therapy were 90.7%, 84.7%, 74.7%, 64.9% (Fig. 4-1). The Kaplan–Meier curve estimates the cumulative probability of continuing treatment at 12 months was 81.9% (95% CI = 76.9–87.2) (Fig. 4-2).

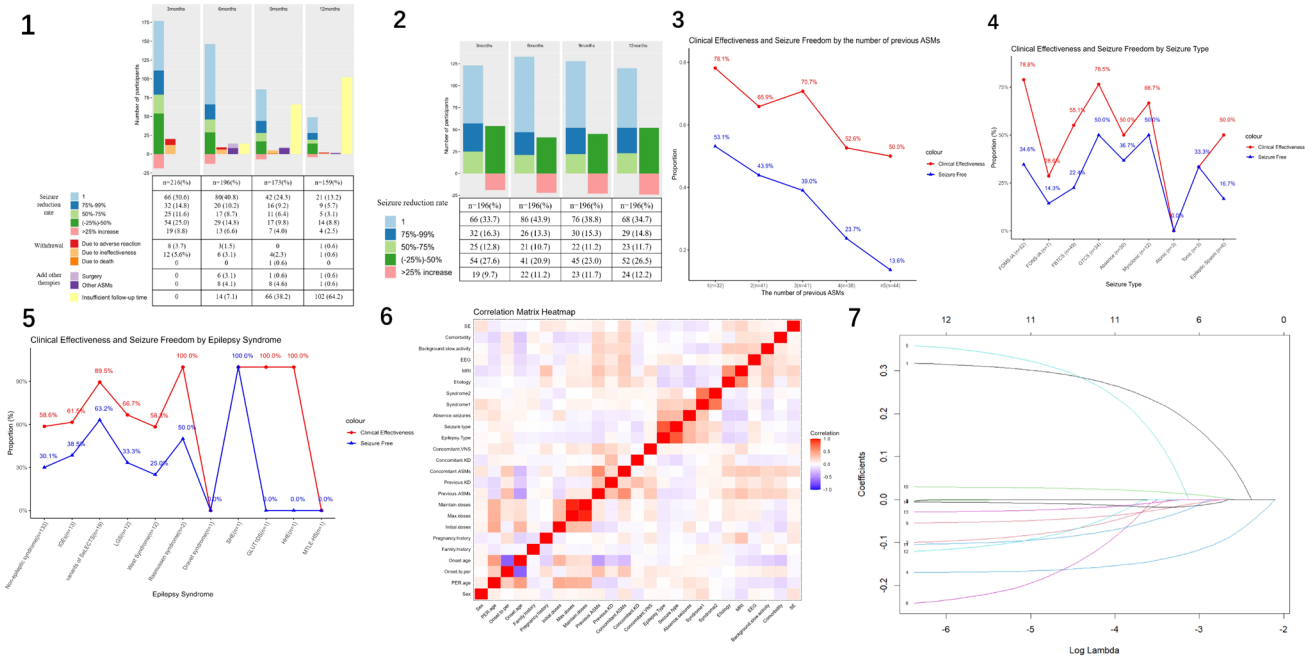

Fig. 3 Efficacy analysis of perampanel (PER) adjuvant therapy in treating epileptic seizures in children aged 4–12 years. 3-1 Follow-up at different time intervals with PER adjuvant therapy; 3-2 Efficacy analysis at different time points for epilepsy in children aged 4–12 with PER adjuvant therapy (after data imputation, n = 196). 3-3 Analysis of clinical efficacy and complete seizure control rate in young children with epilepsy under different PER administration sequences. 3-4 Analysis of clinical efficacy and complete seizure control rates for different types of seizures in young children with epilepsy treated with PER. 3-5 Analysis of clinical efficacy and complete seizure control rates for different epilepsy syndromes in young children treated with PER. 3-6 Heatmap of the correlation matrix for all independent variables, with syndrome 1 being developmental and epileptic encephalopathy (DEE) and idiopathic generalized epilepsy syndromes (IGEs), and syndrome 2 being childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), generalized tonic–clonic seizures alone (GTCA), variants of self-limited epilepsy with centrotemporal spikes (SeLECTS), Lennox-Gastaut syndrome (LGS), West syndrome (WS), Dravet syndrome (DS), Rasmussen syndrome (RS), sleep-related hypermotor/hyperkinetic epilepsy (SHE), glucose transporter 1 deficiency syndrome (GLUT1DS), hemiconvulsion–hemiplegia–epilepsy (HHE), mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), and febrile infection-related epilepsy syndrome (FIRES). Epilepsy type includes focal seizures, generalized seizures, and epileptic spasms, while seizure type includes focal motor onset seizures with or without impaired awareness, focal non-motor onset seizures with or without impaired awareness, focal to bilateral tonic–clonic seizures, generalized tonic–clonic seizures, absence seizures, myoclonic seizures, atonic seizures, tonic seizures. 3-7 Reduction path of standardized coefficients with increasing penalty factor in Lasso-Cox regression. Factors 1–15 respectively represent: family history, perinatal high-risk factors, the number of previous ASMs, the number of concomitant ASMs, concomitant ketogenic diet, concomitant vagus nerve stimulation, absence seizures, epilepsy syndrome 1 (DEE/IGEs), etiology, epilepsy syndrome 2 (CAE, JAE, JME, GTCA, variants of SeLECTS, LGS, WS, DS, RS, SHE, GLUT1DS, HHE, MTLE-HS, and FIRES), EEG background activity slowing, status epilepticus, seizure type, cranial magnetic resonance imaging, and comorbidities

During the follow-up, 45 cases (45/216, 20.8%) reported adverse reactions of varying degrees, with 15.3% (33/216) classified as mild-to-moderate in severity (Table 2). Twelve patients (12/216, 5.6%) discontinued medication because of intolerance. In 12 cases, adverse reactions were gradually alleviated after dose reduction, and adverse reactions resolved spontaneously in 21 cases. The most common adverse reactions were irritability/aggressive behavior (18/216, 8.3%), somnolence (14/216, 6.5%), ataxia, fatigue/mental state deterioration, dizziness/vertigo, and headache. One case of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes resulted in death due to the progression of the primary disease.

Discussion

Clinical research in the pediatric population is limited because of the small population size and potential for unforeseen adverse effects. Compared with traditional clinical trials, real-world studies can offer a research environment and interventions that are closer to real clinical practice, providing broader applicability in pediatric medicine. This study demonstrated that, in real-world research, PER showed efficacy consistent with clinical trials, demonstrating good safety and tolerability as an adjunctive therapy in young Chinese patients with epilepsy.

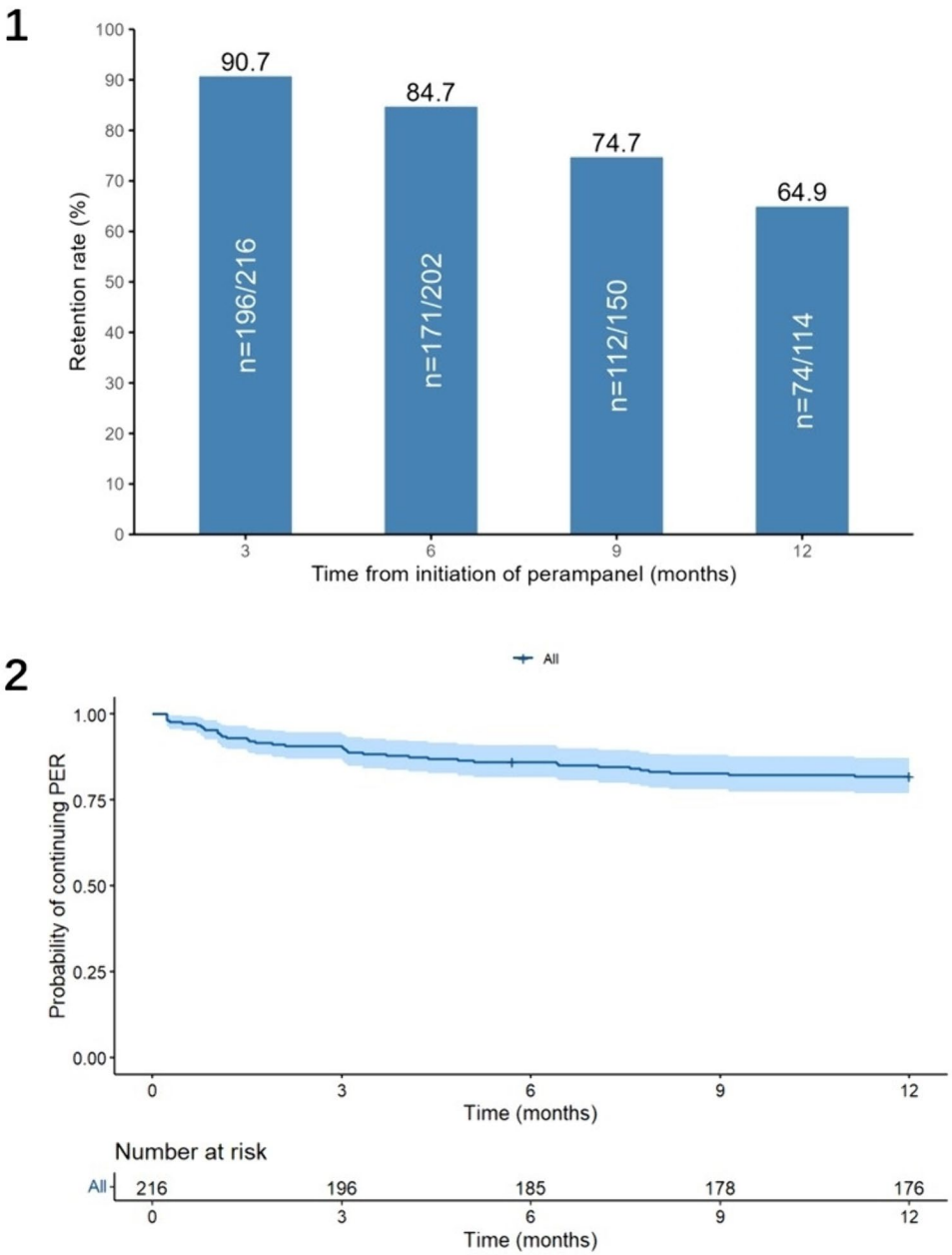

Fig. 4 Retention rates of perampanel (PER) adjuvant therapy. 4-1 Retention rates at 3, 6, 9, and 12 months. 4-2 Kaplan–Meier curve depicting overall retention time

Table 2 Adverse drug reaction events at different time points after perampanel adjuvant therapy

Adverse events	Months 0–3 n = 216 (%)	Months 3–6 n = 196 (%)	Months 6–9 n = 185 (%)	Months 9–12 n = 177 (%)
Irritable/Aggressive	11 (5.1%)	5 (2.6%)	2 (1.1%)	
Somnolence	10 (4.6%)	3 (1.5%)	1 (0.5%)	
Ataxia (walking unsteadily, ataxic gait)	9 (4.2%)	1 (0.5%)		
Fatigue/Lethargy	4 (1.9%)	2 (1.0%)	2 (1.1%)	
Dizziness/Vertigo	3 (1.4%)		1 (0.5%)	1 (0.56%)
Headache	2 (0.9%)			
Gastrointestinal response (nausea, decreased appetite)		2 (1.0%)		
Allergic reaction	1 (0.5%)			

Note: Some patients experienced more than one type of adverse reaction

Efficacy analysis.

In children aged ≥ 4 years with epilepsy, the effectiveness of PER ranged from 47.3% to 67.6%, with seizure-free rates between 12.2% and 33.8% [7, 8]. In this study, 69.9% of patients reported seizure reduction after 12 months of PER treatment, with average seizure reduction, clinical effectiveness, and seizure-free rates at 12 months of 50.1%, 61.2%, and 34.7%, respectively. Multivariate Cox regression analysis confirmed that focal non-motor onset seizures with or without impaired awareness, FBTCS, LGS, variants of SeLECTS, the number of concomitant ASMs, a family history of epilepsy, and focal lesions on cranial MRI are independent factors affecting efficacy. Recovering missing data and using the full dataset for Cox regression analysis were useful to accurately assess the impact of different clinical characteristics on the effectiveness of PER treatment and trends of treatment effects over time. Sensitivity analysis through the MMRM model further validated the reliability of the treatment approach.

In this study, focal non-motor onset seizures with or without impaired awareness and FBTCS were identified as risk factors for a < 50% seizure reduction rate, with effectiveness rates of 28.6% and 55.1%, respectively, which are lower than those for absence seizures (50.0%) and GTCS (76.5%). PER has shown efficacy for various seizure types in pediatric patients with epilepsy, including focal seizures (FS), idiopathic generalized tonic–clonic seizures, FBTCS, myoclonic seizures, and absence seizures [9–12]. Open-label core study 311 (NCT02849626) involving patients aged 4–12 years with FS, FBTCS, and GTCS receiving PER treatment showed ≥ 50% seizure reduction rates of 47%, 65%, and 64%, respectively [13]. A randomized, double-blind, phase III clinical study in China demonstrated that the effectiveness of PER adjuvant therapy in patients with FS (with or without FBTCS) or GTCS was 37.4% and 61.1%, respectively [9]. In a cohort of 858 participants aged ≥ 12 years with FBTCS or GTCS receiving PER treatment, the percentage reductions in seizure frequency per 28 days were 66.7% and 80.6% [10]. A double-blind study in Germany reported seizure-free rates of 16.7% and 22.2% for myoclonic seizures and absence seizures respectively, during the double-blind PER treatment period, with similar efficacy observed in the open-label extension phase [11]. PER monotherapy showed a higher seizure-free rate for FBTCS than for focal impaired awareness seizures (64.6% *vs*. 58.5%) [14], and PER add-on therapy was more effective in patients with focal seizures with FBTCS than in those without FBTCS [15]. After 12 months of PER treatment, the seizure-free rates for all seizure types were about 59%, with GTCS at about 63%, myoclonic seizures at about 65%, and absence seizures at about 51% [16]. These studies provide evidence supporting the use of PER as a broad-spectrum ASM, indicating that PER does not exacerbate any type of epilepsy seizures or epilepsy syndrome.

Our study confirms that adjunctive therapy with PER shows considerable efficacy in patients with LGS and variants of SeLECTS. The efficacy and seizure-free rates for adjunctive treatment of LGS were 66.7% and 33.3%, respectively; for variants of SeLECTS, they were 89.5% and 63.2%, respectively. A multicenter retrospective study on adjunctive PER treatment for LGS showed a 12-month medication retention rate of 45.8%, with efficacy rates of 66.1% at 12 months and 62.2% at 36 months [17]. In 71 patients with LGS who were treated with PER, the treatment was effective in about two-thirds of the study cohort, with 35.2% achieving a ≥ 75% seizure reduction [18]. A study of 54 children with electrical status epilepticus in sleep (ESES) treated with adjunctive PER reported a total ESES resolution rate of 53.7% at 24 weeks [19]. In a cohort of eight children with SeLECTS treated with PER for 6 months, the efficacy rate was 100%, with a seizure-free rate of 75% [8].

In this study, the number of concomitant ASMs was an independent risk factor affecting efficacy. However, the order of PER administration did not affect the treatment response, which was different from the results of studies on other ASMs [4, 21–24]. After introducing PER as the first adjunctive ASM in treating children with epilepsy, the efficacy and seizure-free rates were 78.1% and 53.1%, respectively; for patients unresponsive to five or more ASMs, these rates remained at 50.0% and 13.6%. This could be due to the unique mechanism of action and target sites of PER, which is the only known drug that can effectively inhibit all AMPA receptor subtypes without affecting the NMDA or kainate receptor subunits [25]. Despite the decreasing likelihood of new ASMs alleviating seizures as the number of previously failed medications increases, refractory epilepsy does not necessarily indicate a lack of response to any treatment [21]. Previous studies [26, 27] have indicated that a higher number of available ASMs does not significantly enhance the likelihood of achieving seizure freedom through medication. However, these studies did not evaluate newly developed ASMs such as PER, brivaracetam, everolimus, cannabidiol, cenobamate, fenfluramine, and ganaxolone.

Our research also confirms that focal lesions on cranial MRI are an independent risk factor affecting therapeutic efficacy, which is consistent with previous reports [20, 21]. A family history of epilepsy is an independent predictive factor for PER efficacy, with previous studies suggesting that a family history of epilepsy is an independent risk factor for refractory epilepsy associated with polygenic disease risk [4, 34]. This could be because of the inclusion of young children in our study, whose family history of epilepsy often included benign epilepsy.

Retention rate is another important indicator of long-term therapeutic efficacy. In this study, the actual patient retention

rates at 3, 6, 9, and 12 months were 90.7%, 84.7%, 74.7%, and 64.9%, respectively. Twenty-eight patients (13.0%) discontinued treatment because of low efficacy. These retention rates are similar to those observed in other real-world observational studies (60.2%–70.0%) [7, 14] and studies of focal seizures in individuals aged ≥ 12 (62.6%) [28].

Safety analysis

In previous studies, PER adjunctive therapy was well-tolerated in children aged 4–12 years, with adverse event rates of 57–81% [29–31]. Somnolence was the most common adverse event [29–31], and dropout rates due to intolerance ranged from 4% to 11% [13]. The main reasons for cessation of PER treatment were adverse events, followed by insufficient efficacy [7, 13]. In real-world studies of PER treatment in patients with pediatric and adolescent epilepsy, adverse event rates ranged from 37.1% to 43% [7, 14]. The most common adverse events in patients with pediatric epilepsy included somnolence, dizziness, aggressive behavior, and gait disturbances, which often occurred during the titration phase with the incidence decreasing over time; most adverse events resolved after dose reduction or slow titration [7, 8, 14, 28, 32, 33] In the present study, 45 patients (20.8%) experienced adverse events, primarily manifesting as irritability/aggressive behavior (8.3%), somnolence (6.5%), ataxia, fatigue/lethargy, dizziness/vertigo, headache, gastrointestinal symptoms, and allergic reactions. The dropout rate owing to intolerance was 5.6%.

Conclusions

Future prospective studies with longer follow-up periods may reduce potential biases and further elucidate the long-term efficacy and safety of PER adjunctive therapy in young Chinese children with epilepsy, providing clinical evidence for its use as a broad-spectrum ASM in young children.

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Data availability The data that support the findings are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest None of the authors has any conflict of interest to disclose.

Ethical approval Ethics approval was granted by the Ethics Committee of the Children's Hospital affiliated with Chongqing Medical University [Ethical Approval Number: (2023) LunShen (Yan) No. 473]. All steps performed in our study (data collection and interviews) were in accordance with the ethical standards of the national research committee, with the 1964 Helsinki declaration and its later amendments and with the national data protection office requirements.

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