■ Original article

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Epileptic Disorders

Use of perampanel in children with refractory epilepsy of genetic aetiology

Rui Qu[1,2], Yuanyuan Dai[1], Xiangju Qu[3], Yan Li[2], Xuejun Shao[2], Rui Zhou[2], Yali Zhu[1], Xuqin Chen[2]

[1] Department of Paediatric Neurology, The Affiliated Hospital of Xuzhou Medical University,
[2] Department of Neurology, Children's Hospital of Soochow University,
[3] Department of Mechanical and Electronic Engineering, Xuzhou University of Technology, Jiangsu Province, China

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ABSTRACT

Objective. Pathogenic mutations in refractory childhood epilepsy are being increasingly discovered. In this study, we analysed the efficacy and tolerability of perampanel as treatment for genetically-related refractory childhood epilepsy.

Methods. This prospective study, conducted in China, included 50 patients with refractory epilepsy of genetic aetiology, who were treated with adjunctive perampanel therapy. Perampanel treatment was considered effective when the seizure frequency was reduced by >50%. Perampanel treatment was evaluated over at least nine months, from January 2020.

Results. A total of 184 paediatric patients with refractory epilepsy received add-on perampanel therapy, and of these, 128 received treatment for ≥nine months and underwent genetic analysis. Fifty children were identified with pathogenic or likely pathogenic variants. A total of 24 different causative monogenic mutations were found, and the most common causative monogenic variants were observed in the *SCN1A* gene (*n* = 15). The mean maximal dose of perampanel was 3.4±1.2 mg/day in responders. The response rates to perampanel in children with genetically-related refractory epilepsy (*n*=50) were 68.0%, 58.0%, and 46.0% at three, six and nine months post-initiation, respectively. Adverse events were reported in 23 patients (46.0%) with genetic aetiology. Somnolence, ataxia, and irritability were the most common adverse events. The response rates to perampanel in children with pathogenic or likely pathogenic variants associated with Dravet syndrome, tuberous sclerosis, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, Rett syndrome, and dentatorubral-pallidoluysian atrophy were high.

Significance. A low maintenance dose of perampanel may be effective and well-tolerated as adjunctive treatment in children with refractory epilepsy of genetic aetiology.

Key words: refractory epilepsy, genetic aetiology, perampanel, Dravet syndrome, tuberous sclerosis, mitochondrial encephalopathy

• **Correspondence:**
Xuqin Chen
Department of Neurology, Children's Hospital of Soochow University, Suzhou Industrial Park, Jiangsu Province 215003, China
<xuqinlili@163.com>

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Epilepsy is a common neurological disease in children. Around 30% of individuals with epilepsy remain unresponsive to current medical treatments [1]. The common aetiologies of drug-resistant epilepsy include genetic, structural, and unknown origins [2]. Nearly 40% of epilepsy is genetic [3]. Thus, it is important to identify safe and effective anti-seizure medications (ASMs), particularly in the setting of adjunctive treatment [4].

Perampanel is a structurally novel, selective, non-competitive AMPA-type

glutamate receptor antagonist. It is a third-generation ASM used for focal-onset seizures (FOS), with or without focal to bilateral tonic-clonic seizures (FBTCS), in patients ≥four years of age (monotherapy and adjunctive therapy), and for generalized tonic-clonic seizures (GTCS) in patients with epilepsy aged 12 years and above in multiple countries around the world [5]. In September 2019, perampanel was approved as an adjunctive therapy for the treatment of FOS, with or without FBTCS, in patients aged 12 years and older in China. Biró *et al*. conducted the first clinical trial for the use of perampanel in patients aged 2-17 years with refractory epilepsies, which revealed that perampanel is effective in paediatric patients with refractory epilepsy with acceptable tolerability [6]. A retrospective study demonstrated the efficacy and tolerability of perampanel in patients aged 0-6 years (mean age: 4 ± 1.6 years) with intractable epilepsy [7]. Other studies [8, 9] have provided clinical evidence indicating that perampanel may be a broad-spectrum ASM for various seizure types. Moreover, perampanel has not been found to aggravate any type of epilepsy, including myoclonic seizures or absences [8, 9]. However, the current literature focuses on one particular genetic aetiology [10-13].

In this study, we analysed and compared responses to perampanel between patients with various genetic aetiologies. This prospective study aimed to evaluate the efficacy and tolerability of perampanel in paediatric patients with intractable epilepsy, and compare the effects of perampanel according to the different types of genetic mutations.

Materials and methods

Patients

This prospective study was conducted between January 2020 and June 2021 at two centres: the Department of Paediatric Neurology, Children's Hospital of Soochow University and the Affiliated Hospital of Xuzhou Medical University. The Institutional Review Board approved the study, and all the parents of the patients provided written informed consent before participation. Since perampanel is only approved by the Chinese Food and Drug Administration for the treatment of seizures in patients aged 12 years and above, informed consent was obtained for the off-label use of perampanel for patients <12 years.

Patients were enrolled based on the following inclusion criteria:

- age 2-14 years and failure to achieve seizure freedom with ≥two ASMs before perampanel treatment;
- initation of perampanel therapy from January 2020 to June 2021, with a minimum observation period of nine months;
- and specific genetic aetiology determined through karyotyping, mtDNA sequencing, epilepsy gene panels, fragment analysis, chromosomal microarray, whole-exome sequencing, or trio- whole-exome sequencing.

The exclusion criteria were as follows:

- a proven aetiology other than genetic aetiology, such as infectious, structural, or immune encephalopathies;
- or incomplete data or unsuccessful patient contact.

Collected data

The following data were collected at baseline: age at epilepsy onset, age at perampanel initiation, seizure and epilepsy type, the number of concomitant ASMs, epilepsy syndrome, the specific genetic aetiology, and personal and family medical histories. In case of any queries, adverse events (AEs), or other clinical problems, the parents contacted us. We evaluated seizure frequency and AEs. Seizure frequency was calculated every three months after perampanel initiation. Efficacy was evaluated after three, six and nine months of perampanel treatment and at the last follow-up visit. Reduction in seizure frequency was calculated relative to seizure frequency three months prior to perampanel initiation. The efficacy endpoint was the proportion of responders (patients with ≥50% seizure reduction from baseline). Further, we compared the responses to perampanel between paediatric patients with different identified mutations.

Data analysis

Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were represented as frequency and percentage. The Chi-square test or Fischer's exact test was used for the analysis of the between-group differences in discrete variables. *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 25 software (IBM Corp., Armonk, NY, USA).

Results

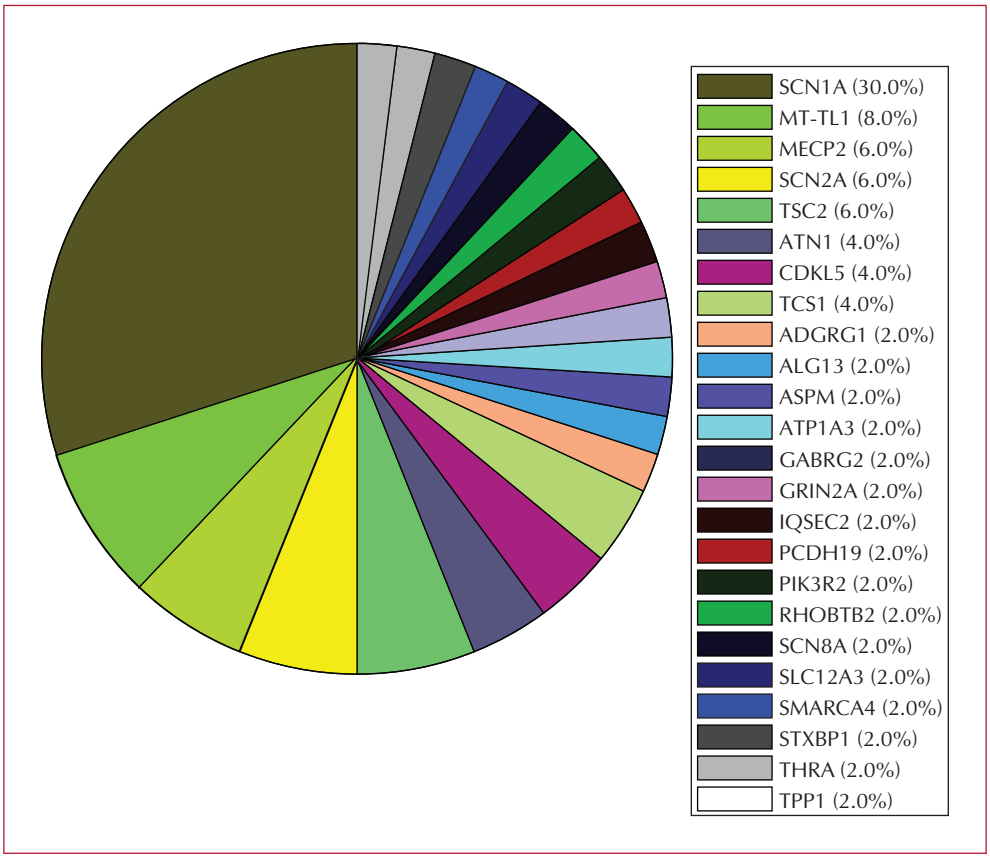
Demographic and baseline characteristics

A total of 184 paediatric patients aged 2-14 years, who experienced pharmacoresistant epilepsy, underwent

treatment with adjunctive perampanel from January 2020 to June 2021. Among these, 128 children, who underwent genetic testing, were included in the analysis. Fifty children were identified to have pathogenic or likely pathogenic mutations. Twenty-four different causative monogenic mutations were found in these 50 patients. The pathogenic or likely pathogenic mutations affected genes that included *SCN1A* (15), *MT-TL1* (4), *MECP2* (3), *SCN2A* (3), *TSC2* (3), *CDKL5* (2), *TSC1* (2), *ADGRG1* (1), *ALG13* (1), *ASPM* (1), *ATP1A3* (1), *GABRG2* (1), *GRIN2A*(1), *IQSEC2* (1), *PCDH19* (1), *PIK3R2* (1), *RHOBTB2* (1), *SCN8A* (1), *SLC12A3* (1), *SMARCA4* (1), *STXBP1* (1), *THRA* (1), *TPP1* (1) and *CAG* tri-nucleotide repeat in the *ATN1* gene (2) (*figure 1*).

Of the 50 pathogenic or likely pathogenic variants, 31 (62.0%) were *de novo*, and the remaining 19 (38.0%) were hereditary mutations. There were 15 patients with Dravet syndrome, five with tuberous sclerosis complex (TSC), and four with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Four patients with refractory epilepsy associated with MELAS syndrome had inherited it from their mothers. However, the mothers of these patients with MELAS were asymptomatic even with mutant mtDNA (three mutations corresponded to m.3243A>G, and one to m.3252A>G). Additionally, two patients were diagnosed with Rett syndrome and both carried *MECP2* variants. Two patients were brothers and suffered from DRPLA, confirmed by the presence of a CAG tri-nucleotide repeat in the *ATN1* gene. Two patients had Lennox-Gastaut syndrome. The remaining 19 children were diagnosed with unclassified refractory epilepsy with pathogenic or likely pathogenic variants.

In total, 50 paediatric patients with refractory epilepsy of genetic aetiology were included in the analysis (26 girls; aged 2-14 years, mean: 6.7 ± 2.7 years) (*table 1*). All patients had complete data from ≥nine months of follow-up. The average number of concomitant ASMs was 2.2 ± 0.9. The most common concomitant ASMs taken by patients were levetiracetam (*n* = 32 [64.0%]), topiramate (*n* = 22 [44.0%]) and valproic acid (*n* = 21 [42.0%]). The average loading dose of perampanel was 3.4 ± 1.2 mg/day in all patients with genetic aetiology, depending on the clinical response (*table 1*).



■ **Figure 1.** The pathogenic or likely pathogenic mutations in children with refractory epilepsy who received perampanel treatment.

▼ **Table 1.** Demographics of children with refractory epilepsy of genetic aetiology, and comparison between responders and non-responders to perampanel at the last follow-up visit.

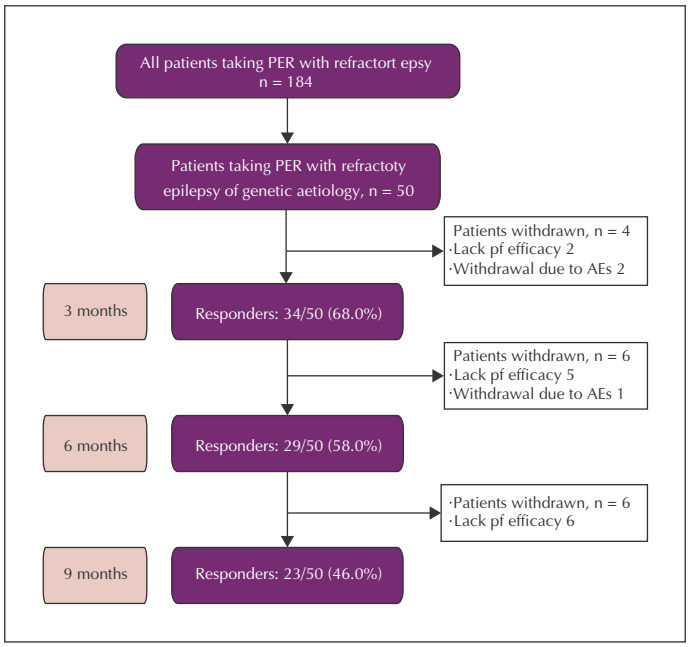
	Total (*n* = 50)	Responders (*n* = 23)	Non-responders (*n* = 27)	*p* value
Mean age[a], years (SD)	6.7 (2.7)	6.8 (2.7)	6.6 (2.7)	0.789
Female, *n* (%)	26 (52%)	12 (52.2%)	14 (51.9%)	0.982
Mean perampanel[b] dosage, mg (SD)	3.4 (1.2)	3.3 (1.1)	3.4 (1.2)	0.675
Seizure types, *n* (%)				
Focal aware without motor signs	9 (18.0%)	4 (17.4%)	5 (18.5%)	0.918
Focal aware with motor signs	15 (30.0%)	7 (30.4%)	8 (29.6%)	0.951
Focal impaired awareness	19 (38.0%)	9 (39.1%)	11 (40.7%)	0.908
Focal with FBTCs	18 (36.0%)	10 (43.5%)	8 (29.6%)	0.309
GTCS	16 (32.0%)	8 (34.8%)	8 (29.6%)	0.697
Atypical absence	11 (22.0%)	5 (21.7%)	6 (22.2%)	0.967
Myoclonic	16 (32.0%)	7(30.4%)	9 33.3%)	0.827
Clonic	9 (18.0%)	3 (13.0%)	6(22.2%)	0.400
Tonic	10 (20.0%)	4 (17.4%)	6 (22.2%)	0.670
Epileptic spasms	6 (12.0%)	2 (8.7%)	4 (14.8%)	0.906
Mean number of concomitant ASMs, *n* (SD)	2.2 (0.9)	2.1 (0.8)	2.3 (0.9)	0.429
Most common concomitant ASMs (at least 10% patients), *n* (%)				
Levetiracetam	32 (64.0%)	15 (65.2%)	17 (63.0%)	0.869
Topiramate	22 (44.0%)	9 (39.1%)	13 (48.1%)	0.522
Valproic acid	21 (42.0%)	9 (39.1%)	12 (44.4%)	0.704
Oxcarbazepine	12 (24.0%)	6 (26.1%)	6 (22.2%)	0.750
Lamotrigine	12 (24.0%)	4 (17.4%)	7 (25.9%)	0.468

[a]Age calculated at the date of perampanel initiation.
[b]Maximum perampanel dose.
ASM: anti-seizure medication; FBTCS: focal to bilateral tonic-clonic seizure; GTCS: generalized tonic-clonic seizure; SD: standard deviation.

Efficacy of perampanel

The mean duration of follow-up was 13.6 months (range: 9-24). Of the 50 paediatric patients with refractory epilepsy of genetic aetiology, 34 (68.0%) patients responded to perampanel at three months, 29 (58.0%) responded at six months and 23 (46.0%) responded at nine months (*figure 2*). Four patients discontinued perampanel within the first three months, six between 3-6 months, and six between 6-9 months (*figure 2*). A lack of efficacy in 81.2% (*n* = 13) patients and intolerability of AEs in 18.8% (*n* = 3) patients were the main reasons for drug discontinuation. At the last follow-up visit, 23 patients (46.0%) were considered responders and 27 patients (54.0%), who showed <50% seizure reduction, were considered non-responders. No statistically significant differences in clinical variables, such as age at perampanel initiation, sex, average loading dose of perampanel, seizure type, and number of concomitant ASMs, were identified between responders and non-responders (*table 1*).

In the subset of patients with Dravet syndrome with *SCN1A* mutations, we observed 73.3%, 66.7% and 60.0% efficacy at three, six and nine months of perampanel treatment, respectively. The response rates were 60.0% (3/5), 60.0% (3/5) and 60.0% (3/5) in patients with TSC, respectively. In the four patients

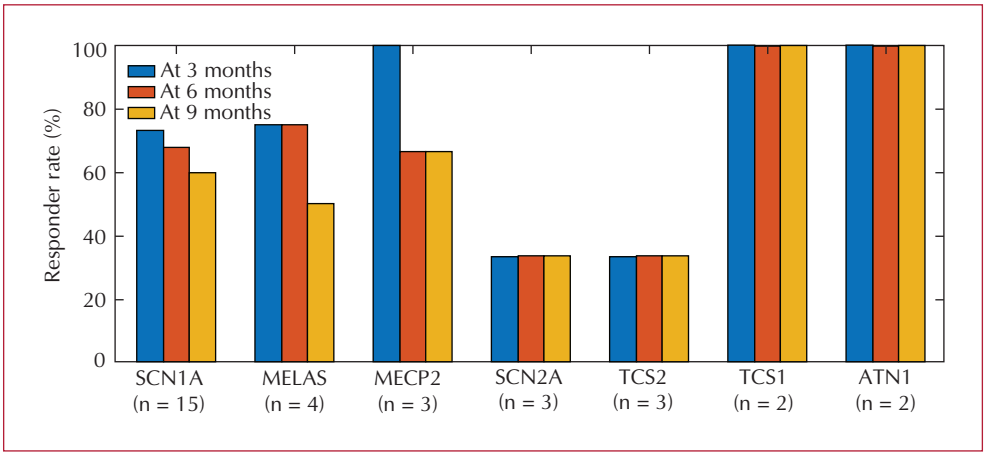


■ **Figure 2.** Response to perampanel after three, six and nine months in patients with childhood refractory epilepsy of genetic aetiology.

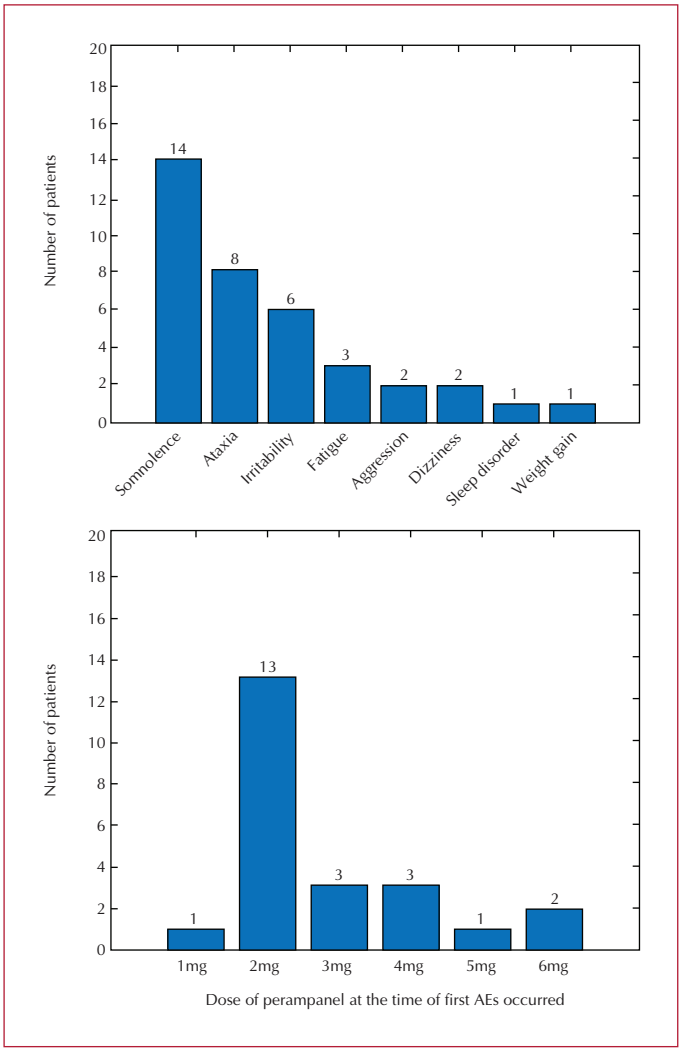
with refractory epilepsy associated with MELAS syndrome in our study, we observed response rates of 75.0% (3/4), 75.0% (3/4) and 50.0% (2/4) after three, six, and nine months of perampanel treatment, respectively. In addition, two patients with Rett syndrome and two with DRPLA had good responses to adjunctive perampanel treatment at the nine-month follow-up visit. In particular, two patients with DRPLA suffered daily myoclonic seizures, weekly GTCS, and ataxia, followed by neurological and intellectual deterioration. Remarkably, their myoclonic seizures had almost stopped, and the frequency of GTCS reduced following low-dose perampanel treatment. The efficacy of the treatment was maintained for >nine months (*figure 3*).

Safety and tolerability of perampanel

Overall, 23 patients (46.0%) reported eight types of AEs (*figure 4A*). Most AEs occurred within eight weeks



■ **Figure 3.** Response to perampanel in patients with childhood refractory epilepsy with pathogenic or likely pathogenic genetic mutations (≥two patients/mutation) at three, six and nine months of follow-up.



■ **Figure 4.** Adverse events (AE) during perampanel treatment showing the types of AEs and number of affected patients (A), and perampanel dose when the AEs initially occurred (B).

after the initiation of perampanel. All AEs improved when the perampanel dosage was tapered or discontinued. The most frequent AEs were somnolence (14 patients, 28.0%), ataxia (eight patients, 16.0%) and irritability (six patients, 12.0%). Overall, 6.0% patients discontinued perampanel due to AEs. Fatigue was seen in three patients (6.0%), aggression and dizziness were both reported in two patients (4.0%), and sleep disorders (*i.e.*, insomnia) and weight gain were noted in one patient (2.0%). Over 60% patients (14/23, 60.9%) reported their treatment-related AEs at a perampanel dose of 2 mg/day or less (*figure 4B*). Twenty patients, who experienced some AEs at least once, maintained perampanel until their last visit. Among the patients, symptoms improved in three when the dose was reduced, while the rest maintained the same dose. Aggression, ataxia, and somnolence were the main reasons for perampanel dose reduction and discontinuation.

Discussion

Refractory epilepsy in children is a broad phenotypic spectrum with genetic heterogeneity [14]. To date, more than 500 genes have been implicated in epilepsy [15, 16]. In our study, perampanel was found to be effective for childhood refractory epilepsy of genetic aetiology with response rates at three, six and nine months of 68.0%, 58.0%, and 46.0%, respectively. Therefore, the efficacy of perampanel treatment in genetically-related refractory childhood epilepsy was

good. Patients presented with almost any seizure type, including FOS, atypical absence, clonic, tonic, myoclonic, or GTCS. We suggest that perampanel may effectively treat all types of seizures in childhood refractory epilepsy with genetic aetiology. A previous study showed that perampanel treatment improves many different types of seizures in paediatric patients with Dravet syndrome, including FOS with impaired awareness, GTCS, and myoclonic seizures [10]. We speculate that the efficacy of perampanel in childhood refractory epilepsy with genetic aetiology may not be associated with a specific seizure type, but with the underlying disease itself. Perampanel targets glutamate activity at AMPA receptors located in the postsynaptic membranes, thereby reducing neuronal hyperexcitation associated with seizures [17]. Moreover, it shortens the after-discharge duration and prolongs the latency of generalized seizure onset [18]. Our study indicates that perampanel might have broad-spectrum anti-seizure effects.

Patients with various pathogenic mutations who had Dravet syndrome, TSC, MELAS, Rett syndrome, or DRPLA showed better responses to perampanel. In patients with Dravet syndrome, the response rates were 73.3%, 66.7% and 60.0 % after three, six and nine months of perampanel treatment, respectively. Previous studies have shown high response rates to perampanel in children with Dravet syndrome after short- and long-term follow-up, similar to the rates observed in our study. The response rates reached 50% and 80% during a minimum observation period of three months [6, 19]. Children with Dravet syndrome may achieve 50-66.7% seizure reduction using perampanel treatment after one or nearly one year [7, 10]. Here, all patients with Dravet syndrome had an *SCN1A* gene mutation. The *SCN1A* gene is mainly expressed in somatic cells, in neurons of the central nervous system. It encodes the alpha-subunit of neuronal voltage-gated sodium ion channels, type one (NaV 1.1) [12]. *SCN1A* mutations can affect Nav1.1 channel expression and impair neuronal activity, causing Dravet syndrome [20]. AMPAR antagonists may reduce seizure frequency by attenuating impaired GABAergic transmission in Dravet syndrome [7]. This suggests that perampanel treatment is effective for *SCN1A*-related epilepsy, however, further studies are warranted.

TSC is an autosomal dominant disorder, of which epilepsy is one of the most common clinical manifestations, affecting 80-90% of patients, and is refractory in up to 75% of cases [10]. According to previous studies [7, 21], perampanel reduced seizure frequency by more than 50% in five of seven patients (71.4%) with TSC. Moreover, efficacy in four patients (57.1%) was sustained after one year. All patients had a pathogenic or likely pathogenic variant, including one mutation in *TSC1* and six in *TSC2*. Previous studies have provided evidence for glutamatergic dysregulation in TS; neuron-specific knockout of *TSC1* may lead to activation of AMPA receptors [22]. Perampanel might attenuate neuronal excitability by inhibiting AMPA current to control seizures in TSC. MELAS is an inherited, mitochondrial disease, usually caused by m.3243A>G mutation and is characterized by seizures, lactic acidosis, vomiting, headache and recurrent stroke-like episodes [23, 24]. Seizures occur in 71-96% of patients with MELAS [25]. MELAS includes FOS, FBTCS, epilepsia partialis continua, and generalized seizures [13, 26]. The findings of our study indicate that perampanel may be an effective option for treating refractory epilepsy associated with MELAS syndrome. This is consistent with a previous study which reported a favourable experience with perampanel as treatment for three cases of status epilepticus in patients with mitochondrial disorders [13]. Shiraishi *et al*. [11] reported a paediatric patient with DRPLA who had a remarkable clinical outcome with a low dose of perampanel. The seizures and myoclonus were eliminated in this patient, along with improvement in activities of daily living. Oi *et al*. [27] reported 16 Japanese patients with progressive myoclonic epilepsies, including two DRPLA patients, who received treatment of low-dose perampanel after several months of follow-up. They described clinical improvement in myoclonus and scores for activities of daily living in two DRPLA patients. It is speculated that the AMPA system is responsible for the pathogenesis of DRPLA, and that perampanel plays a role in the excitatory neurotransmission process in patients with DRPLA [12]. Low-dose perampanel improves refractory cortical myoclonus, which may be because it disperses and inhibits paroxysmal depolarization transfer in the sensorimotor cortex and reduces the synchronous firing degree of postsynaptic neurons in motor efferent pathways [27]. Therefore, perampanel could be an effective treatment for patients with DRPLA.

In the present study, AEs and related ASM discontinuation or dose reduction accounted for 46.0% and 12.0% of the cohort, respectively. We also recognize that many AEs were reported during low-dose perampanel use. The average dose of perampanel associated with the occurrence of AEs was 2.8 mg/day. Fourteen patients (14/23, 60.9%) reported AEs at 2 mg/day or less. We infer that a high burden of concomitant ASMs influenced these events. Furthermore, in clinical practice, careful observation is required for the initiation of perampanel in patients with multiple ASMs.

Leading AEs were somnolence (28.0%), ataxia (16.0%) and irritability (12.0%), which is consistent with previous findings [28, 29]. Ataxia is considered to be

caused by cerebellar/brainstem dysfunction, resulting from perampanel, which may inhibit excitatory neurotransmission [30]. Somnolence was another characteristic sedative AE associated with perampanel treatment. Irritability and aggression were two psychiatric AEs significantly associated with perampanel, and the inhibitory effect of perampanel on glutamatergic transmission through the AMPA receptor may lead to these side effects [7, 31].

Conclusion

Low-dose perampanel may be an effective treatment for genetically-related refractory childhood epilepsy that is well-tolerated among this patient population in daily clinical practice. Furthermore, perampanel treatment may be promising for children with refractory epilepsy with Dravet syndrome, TSC, MELAS, Rett syndrome, and DRPLA caused by pathogenic or likely pathogenic mutations. Future research is warranted to fully elucidate the efficacy of perampanel in this patient population. ■

Key points

- We analysed the efficacy and tolerability of perampanel as treatment for genetically-related refractory childhood epilepsy.
- Response rates to perampanel in children with genetic refractory epilepsy were 68.0%, 58.0% and 46.0% at three, six and nine months.
- A low maintenance dose of perampanel may be effective and well-tolerated as an adjunctive treatment in children with refractory epilepsy.

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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The authors have no conflict of interest to declare.

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TEST YOURSELF

(1) Which of the following anti-epileptic drugs does NOT induce perampanel metabolism?

A. Carbamazepine
B. Oxcarbazepine
C. Levetiracetam

(2) What were the most frequent adverse events found among patients treated with perampanel in the current study?

A. Somnolence
B. Irritability
C. Vomiting

(3) What factors were found to be irrelevant between responders and non-responders?

A. Sex
B. Number of concomitant ASMs
C. Pathogenic or likely pathogenic mutant gene types

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.