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ORIGINAL RESEARCH

Efficacy and Safety of Clobazam Adjunctive Therapy in Pediatric Patients with Drug-Resistant Epilepsy

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Objective: To determine the efficacy and safety of clobazam, a benzodiazepine derivative endorsed for adjunctive therapy in drug-resistant epilepsy due to its broad-spectrum efficacy and tolerability profile, as an adjunctive treatment for pediatric patients with drug-resistant epilepsy.

Methods: This was a multicenter, real-world, self-controlled study. Pediatric drug-resistant epilepsy patients receiving clobazam adjunctive treatment at three centers were retrospectively included. The primary outcomes were response rates and seizure-free rates at 6 and 12 months of treatment. The secondary outcomes included retention rates at months 6 and 12 of treatment and adverse events that occurred during the addition of clobazam therapy.

Results: A total of 146 patients were included. The retention rates were 87.67% (128/146) and 81.51% (119/146) at 6 and 12 months, respectively. The response rates were 58.99% (82/139) and 62.41% (83/133), and the seizure-free rates were 36.69% (51/139) and 35.34% (47/133) at 6 and 12 month, respectively. Clobazam has shown good efficacy in patients with epilepsy due to genetic variants (60.42%, 29/48) and its significantly better efficacy for the SCN1A genotype than for other genotypes (P=0.048). The independent factor associated with clinical response was a lower baseline seizure frequency (seizure frequency <1 seizure/day). Adverse reactions occurred in 24 (24/146, 16.64%) patients, with excessive salivation/hypersalivation (4/146, 2.74%) and loss of appetite (4/146, 2.74%) being the most common.

Conclusion: Clobazam adjunctive therapy is effective, safe and well tolerated in pediatric patients with drug-resistant epilepsy.

Keywords: clobazam, drug-resistant epilepsy, adjunctive therapy, pediatric patient

Introduction

Pediatric drug-resistant epilepsy poses significant therapeutic challenges, with approximately 30%-40% of children failing to achieve sustained seizure free status despite the combined use of antiseizure medications (ASMs).[1–3] This condition not only impacts neurodevelopment or quality of life but also places a substantial burden on families and healthcare systems. The causes of pediatric epilepsy vary, with genetic or presumed genetic factors accounting for one-third of childhood-onset epilepsy cases[4,5] and 80% of infantile-onset epilepsy cases.[6] Combination therapy with multiple ASMs remains a cornerstone of treatment, yet the quest for effective and well-tolerated adjunctive agents persists owing to the heterogeneity of etiologies and high rates of pharmacoresistance in this population.[7]

Clobazam (CLB) is a novel 1,5-benzodiazepine drug. Compared with typical 1,4- benzodiazepines, CLB is highly selective for the α-2 subunit of the γ-aminobutyric acid A receptor, resulting in strong anxiolytic and anticonvulsant properties, as well as fewer side effects of sedation, and is well tolerated.[8,9] While CLB has been endorsed for Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in children≥2 years of age,[10,11] robust real-world evidence on its

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efficacy and safety in broader pediatric drug-resistant epilepsy populations remains limited. Existing studies predominantly focus on adult cohorts or specific syndromes,[12,13] leaving critical gaps in understanding its applicability across diverse pediatric etiologies and genetic subtypes.

This study is a multicenter, real-world, retrospective, self-controlled study aimed at evaluating the efficacy and safety of CLB as an adjunctive therapy for pediatric drug-resistant epilepsy, elucidating the factors affecting its efficacy and and also investigating the effect of gene-specific etiology on the response to treatment to provide a reference basis for the rational use of the drug in clinical practice.

Methods

Study Design and Patient Inclusion

We conducted a multicenter, real-world, retrospective, self-controlled research study to investigate the clinical outcome of CLB adjunctive therapy for drug-resistant epilepsy in three tertiary-level hospitals in China. This study was approved by the ethical committees of the Second Affiliated Hospital of Zhejiang University School of Medicine (20241487). Informed consent was waived as part of the approval due to the retrospective nature of the study. This study complied with the Declaration of Helsinki. Patients' personal information was accessible only to authorized investigators and was not documented or disseminated.

Pediatric patients (<18 years of age) with drug-resistant epilepsy who received CLB adjunctive therapy for at least one month at three hospitals between December 20, 2019, and December 4, 2023, were included. Drug-resistant epilepsy is defined as the failure to achieve sustained seizure-free status despite the application of two correctly selected and tolerated ASMs (alone or in combination).[3] The patients with insufficient clinical information to assess the primary outcomes were excluded.

Data Collection

Patients' demographic characteristics, epilepsy history, neurological examination results, and medical consultations were collected and recorded in detail from the medical system in accordance with the clinical information registry form. The following baseline information was collected: (1) demographic information: sex and age; (2) patient epilepsy history: history of febrile convulsions, history of brain injury, family history of epilepsy, EEG, imaging findings (CT or MRI), whole-exome sequencing (WES) results and the presence of developmental delays. The seizure history included the time of first seizure, cause of epilepsy, frequency of seizures before starting CLB treatment and seizure classification; (3) current and previous ASM; (4) comorbidities; and (5) other treatment options, such as vagus nerve stimulation (VNS), epilepsy surgery, and a ketogenic diet. The following information was collected during follow-up: (1) seizure frequency and severity and (2) adverse events during follow-up.

Treatment Outcome

The primary outcomes were response rates and seizure-free rates at 6 and 12 months of treatment. The secondary outcomes included (1) the degree of reduction in seizure frequency at months 6 and 12 of treatment; (2) retention at months 6 and 12 of treatment; and (3) adverse events that occurred during the addition of CLB. Baseline seizure frequency was defined as the average number of seizures per month during the three months prior to CLB adjunctive treatment. The baseline seizure frequency was also stratified as follows: (1) higher frequency: seizure frequency ≥1 seizure/day; and (2) lower frequency: seizure frequency <1 seizure/day. The degree of reduction in seizure frequency was compared with the baseline seizure frequency and can be categorized into four grades: 100% reduction in seizure frequency (seizure-free), 75–99% reduction in seizure frequency (marked effect), 50–74% reduction in seizure frequency (effective), and reduction in seizure frequency by <50% (ineffective).[14] Treatment response was defined as a ≥50% seizure frequency reduction compared with baseline.[15]

Statistical Analysis

Statistical analyses were performed via SPSS version 23, with descriptive statistics for baseline characteristics, continuous data expressed as medians, and categorical data expressed as percentages. Univariate logistic regression analysis was performed with seizure decline frequency ≥50% as the dependent variable and baseline clinical characteristics as the independent variables. To avoid the effect of multicollinearity, variables with $p<0.1$ in the univariate analysis were included in the multivariate logistic regression to analyze factors affecting the efficacy of CLB ($p<0.05$). For the gene-specific response to CLB, we combined information from Jie Wang et al[16] and the human gene mutation database (HGMD® home page (cf.ac.uk)) to categorize WES-positive genes according to the function of the encoded protein. We subsequently used Fisher's exact test to compare the therapeutic efficacy of CLB adjunctive treatment in pediatric patients with epilepsy in different gene categories.

Results

Baseline Clinical Characteristics

Between December 20, 2019, and December 4, 2023, 146 patients received at least one month of CLB adjunctive treatment and were included in the analysis. The baseline demographics are summarized in Table 1. The median age at CLB onset was 5.08 years (range 0.33–17.25), and 51.37% were female. The most common seizure types were focal epilepsy (40.10%, 60/146), generalized epilepsy (20.55%, 30/146) and combined generalized and focal epilepsy (8.22%, 12/146). The most common epileptic syndrome was infantile spasms (10.96%, 16/146), followed by DS (4.11%, 6/146). The causes of epilepsy were diverse and were hereditary (42.47%, 62/146), followed by structural (21.23%, 31/146), infectious (1.37%, 2/146), metabolic (0.68%, 1/146) and unknown (34.25%, 50/146). WES was performed in 68 out of 146 patients, 55 (37.67%) of whom were positive for WES, SCN1A (6.16%, 9/146) and SCN2A (4.79%, 7/146). More than half of the children had physical developmental delay (65.07%, 95/146). Among patients with a history of non-pharmaceutical interventions, 18 (12.33%) had previously received ketogenic dietary therapy, 14 (9.59%) had undergone vagus nerve stimulation (VNS), and 13 (8.90%) had undergone epilepsy surgery prior to study participation. The median number of types of ASMs taken regularly before the addition of CLB was 3 (range 2--12). The median number of ASM classes combined with CLB was 2 (range 1--5), with sodium valproate (n=89) being the most frequently combined class, followed by topiramate (n=46) and levetiracetam (n=34). The combination of ASMs is detailed in Table S1. There were 79 (54.11%) patients with a lower baseline seizure frequency and 67 (45.89%) with a higher baseline seizure frequency.

Patient Retention

At the 6-month follow-up, 4 patients discontinued CLB due to adverse events, 3 patients discontinued CLB for personal reasons, and 11 patients discontinued CLB due to unsatisfactory efficacy. At 12 months, 4 patients were lost to follow-up, 2 patients discontinued CLB for personal reasons, and 3 patients discontinued CLB within 6–12 months of administration due to unsatisfactory efficacy. Overall, a total of 4 patients (4/146, 2.74%) discontinued CLB due to adverse effects, which were concentrated in the first 6 months, and 14 patients (14/146, 9.59%) discontinued CLB due to a lack of efficacy. The 6-month retention rate was 87.67% (128/146), and the 12-month retention rate was 81.51% (119/146). A flow chart of patient retention is shown in Figure 1. The median dose of CLB at the last follow-up was 9.7 mg/day (range 2.5–40 mg/day).

Efficacy Analysis

The efficacy of adjuvant CLB treatment was calculated for different time periods (Figure 2). The response rates at 6 and 12 months were 58.99% (82/139) and 62.41% (83/133), and the seizure-free rates were 36.69% (51/139) and 35.34% (47/133), respectively.

The response and seizure-free rates of CLB adjuvant therapy across clinical characteristics are shown in Figure 3. The response rates for CLB adjuvant therapy for focal seizures and focal epilepsy with secondary generalization were 66.67% (36/54) and 54.55% (6/11), respectively, which were higher than those for generalized seizures (46.15%, 12/26). The response rates for CLB adjuvant treatment in West syndrome patients and DS patients were 61.65% (8/13) and 60% (3/5),

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Table 1 Demographics and Baseline Characteristics

Characteristics	Total N=146 (%)	Responder n=83 (%)	Nonresponder n=50 (%)	[a]OR, 95% CI	[a]p- value	[b]OR, 95% CI	[b]p- value
Sex, female	75 (51.37)	46 (55.42)	24 (48.00)	1.347, 0.666–2.722	0.407		
CLB initiation age, median (range)	5.08 (0.33–17.25)	5 (0.67–14.83)	5.42 (0.33–17.25)	0.990, 0.911–1.076	0.812		
Epileptic seizure type							
Focal seizures	60 (40.10)	36 (43.37)	18 (36.00)	0.897, 0.378–2.129	0.805	1.003, 0.438–2.827	0.822
Generalized seizures	30 (20.55)	12 (14.46)	14 (28.00)	0.384, 0.140–1.056	0.064*	0.416, 0.140–1.232	0.113
Combined generalized and focal epilepsy	12 (8.22)	6 (7.23)	5 (10.00)	0.538, 0.139–2.086	0.370	0.712, 0.165–3.070	0.649
Unclassified epilepsy	44 (30.14)	29 (34.94)	13 (26.00)				
Epileptic syndromes	23 (15.75)	12 (14.46)	7 (14.00)				
West-Syndrome	16 (10.96)	8 (9.64)	5 (10.00)	0.969, 0.298–3.153	0.958		
Dravet-Syndrome	6 (4.11)	3 (3.61)	2 (4.00)	0.908, 0.146–5.657	0.918		
Tuberous sclerosis	1 (0.68)	1 (1.20)	0		1.000		
Etiology							
Genetic	62 (42.47)	36 (43.37)	19 (38.00)	1.011, 0.444–2.301	0.980		
Structural	31 (21.23)	16 (19.28)	13 (26.00)	0.656, 0.254–1.698	0.385		
Infectious	2 (1.37)	0	2 (4.00)		0.999		
Metabolic	1 (0.68)	1 (1.20)	0		1.000		
Unknown	50 (34.25)	30 (36.14)	16 (32.00)				
N of ASM prior to CLB, median (range)	3 (2–12)	3 (2–9)	3 (2–12)	0.926, 0.775–1.107	0.400		
< 5 ASM, n (%)	111 (76.03)	65 (78.31)	37 (74.00)	0.788, 0.347–1.789	0.569		
≥ 5 ASM, n (%)	35 (23.97)	18 (21.69)	13 (26.00)				
First-line ASM prior to CLB							
Valproate sodium	55(37.67)	30(36.14)	19(38.00)				
Levetiracetam	23(15.75)	14(16.87)	8(16.00)				
Topiramate	14(9.59)	6(7.23)	5(10.00)				
Lamotrigine	10(6.85)	5(6.02)	5(10.00)				
Oxcarbazepine	10(6.85)	6(7.23)	3(6.00)				
Others	34(23.29)	22(26.51)	10(20.00)				
N of Concomitant ASMs, median (range)	2 (1–5)	2 (1–4)	2 (1–3)	1.216, 0.702–2.108	0.485		
1 ASM, n (%)	25 (17.12)	13 (15.66)	8 (16.00)	0.739, 0.233–2.345	0.607		
2 ASM, n (%)	82 (56.16)	48 (57.83)	32 (64.0)	0.682, 0.285–1.629	0.389		
≥ 3 ASM, n (%)	39 (26.71)	22 (26.51)	10 (20.0)				
WES, n (%)	68 (46.57)	37 (44.58)	22 (44.0)				
Gene mutation	55 (37.67)	29 (34.94)	19 (38.0)	1.083, 0.524–2.237	0.830		
Delayed development, n (%)	95 (65.07)	51 (61.45)	32 (64.0)	1.115, 0.539–2.308	0.768		
Previous ketogenic diet, n (%)	18 (12.33)	9 (10.84)	9 (18.0)	1.805, 0.664–4.904	0.247		
Previous epilepsy surgery	13 (8.90)	9 (10.84)	3 (6.0)	0.525, 0.135–2.038	0.352		
Previous VNS	14 (9.59)	8 (9.64)	5 (10.00)	1.042, 0.321–3.379	0.946		
Baseline seizure frequency							
Lower frequency	79 (54.11)	59 (71.08)	17 (34.00)	4.772, 2.247–10.136	<0.001*	4.875, 2.244–10.590	<0.001**
Higher frequency	67 (45.89)	24 (28.92)	33 (66.00)				

Notes: [a]Represents univariate logistic analysis, and [b]Represents multifactorial logistic analysis. *P<0.1, **P<0.05.
Abbreviations: ASMs, antiseizure medications; VNS, vagus nerve stimulation; WES, whole-exome sequencing.

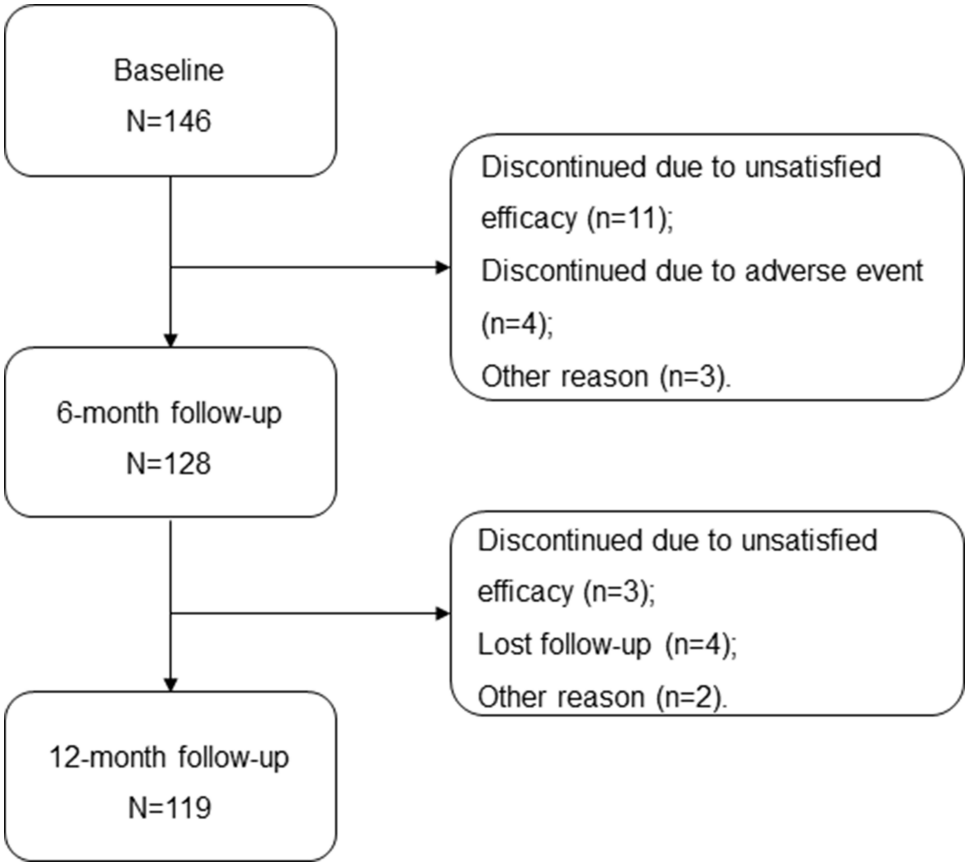
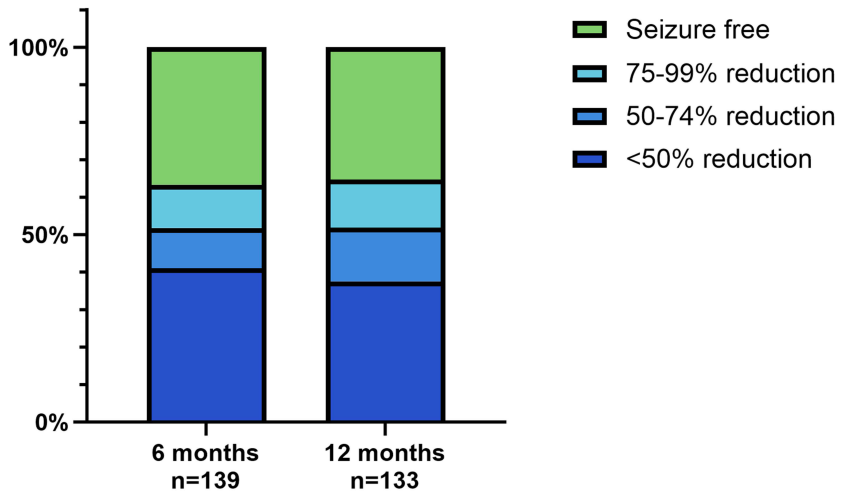


Figure 1 Flowchart of patient data collection and the primary reasons for discontinuation during the follow-up period.



	6 months N=139	12 months N=133
Seizure free	51 (36.69)	47 (35.34)
75-99% reduction	16 (11.15)	17 (12.78)
50-74% reduction	15 (10.79)	19 (14.29)
<50% reduction	57 (40.01)	50 (37.59)

Figure 2 Follow-up at different time intervals with CLB adjuvant therapy.

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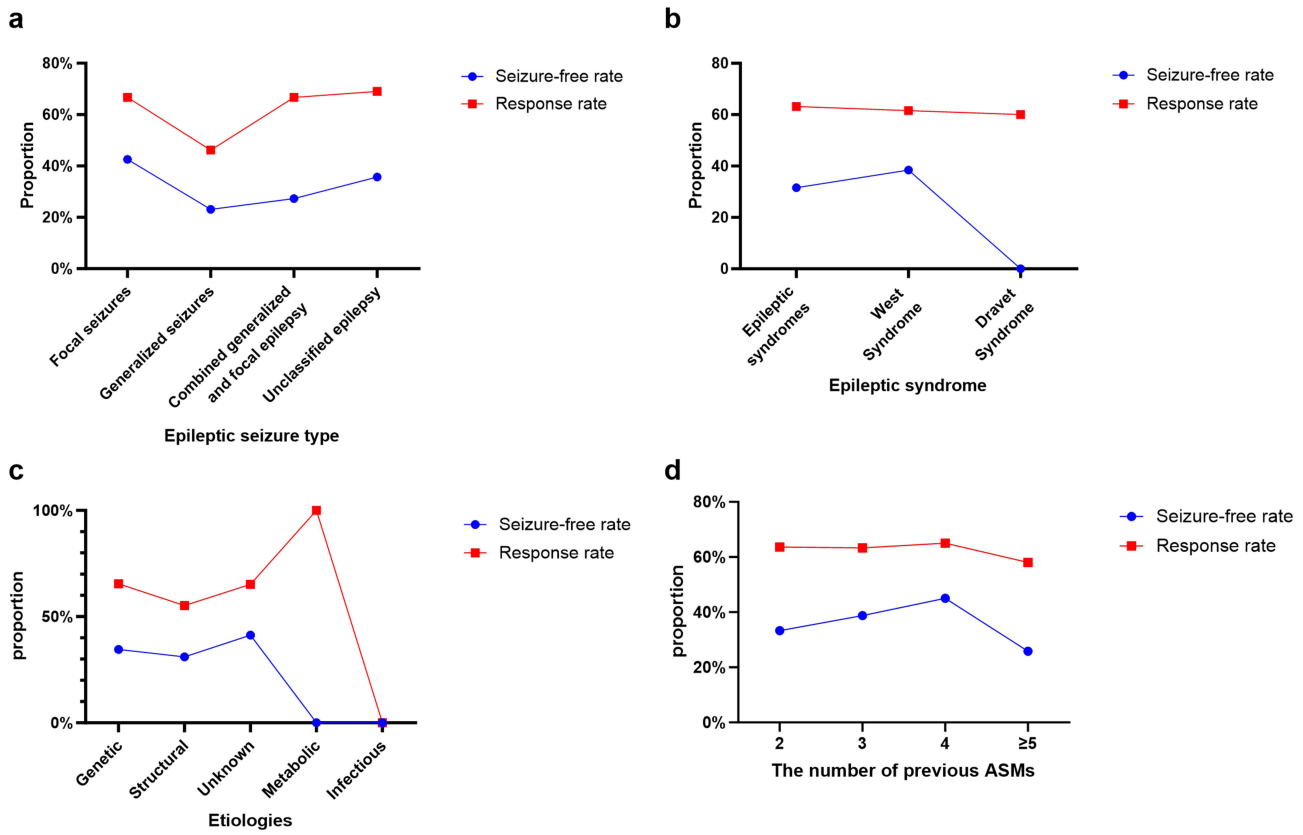


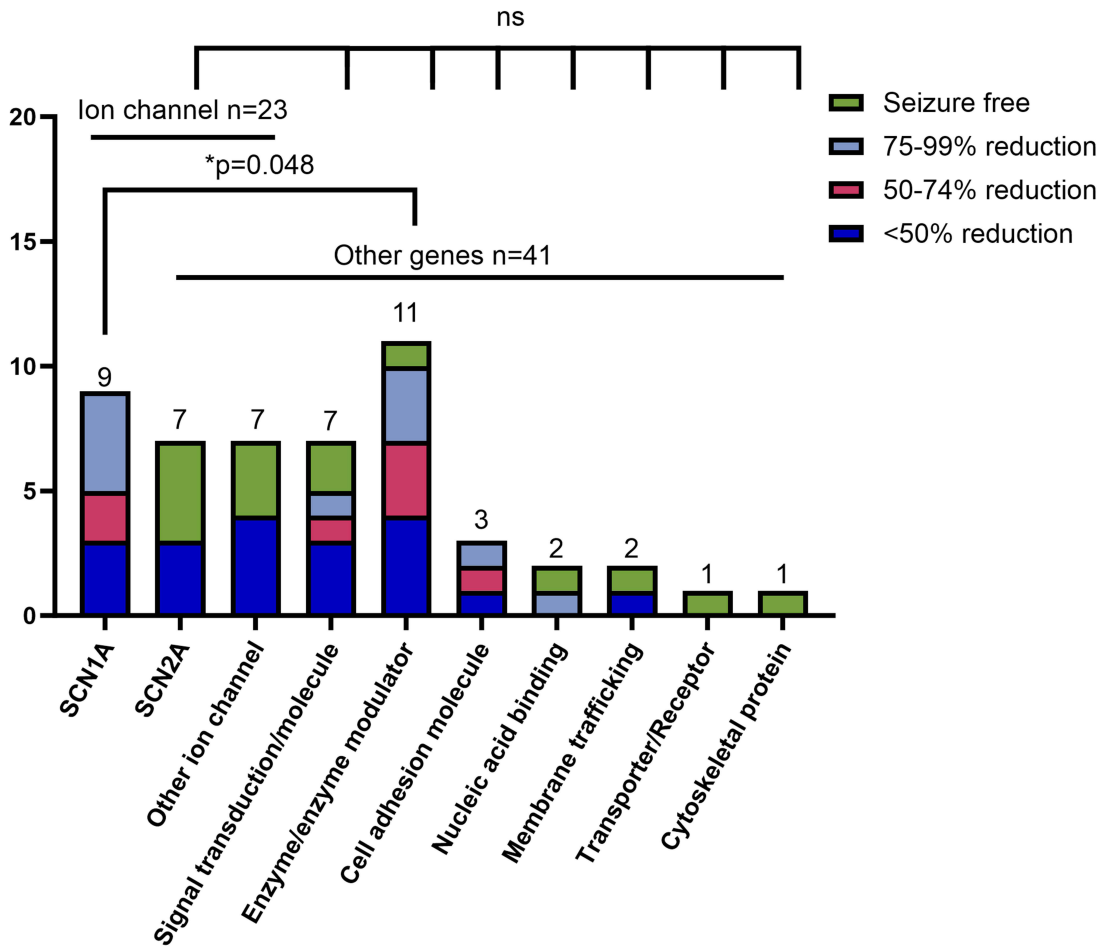
Figure 3 Efficacy analysis of adjunctive CLB treatment in pediatric patients with drug-resistant epilepsy. (**a**) Analysis of response rates and seizure-free rates of different seizure types in pediatric patients with drug-resistant epilepsy treated with CLB. (**b**) Analysis of response and seizure-free rates in pediatric patients with drug-resistant epilepsy diagnosed with epilepsy syndromes treated with CLB. (**c**) Analysis of response and seizure-free rates in pediatric patients with drug-resistant epilepsy of different etiologies treated with CLB. (**d**) Analysis of response and seizure-free rates in pediatric patients with drug-resistant epilepsy who had used different numbers of ASMs prior to CLB treatment.

respectively. We also analyzed the response rates for the different causes of epilepsy, which were 65.45% (36/55) for genetic causes and 55.17% (16/29) for structural causes. In addition, the response rate was 63.73% (65/102) in patients with <5 ASMs used prior to CLB and 58.06% (18/31) in those with ≥5 ASMs used.

Gene-Specific Response to CLB

Genetic etiology was identified in 62 (42.47%) of the 146 patients with epilepsy. Sixty-eight patients underwent WES, which revealed pathogenic or potentially pathogenic variants in the genes of 55 (37.67%) patients, three of whom had two variants. First, 48 of 55 patients were eligible for 12-month follow-up, and the response rate of WES-positive patients was not significantly different from that of the other patients (60.42% vs 63.53%, P=0.722).

These genes were categorized into different gene groups based on the function of the encoded proteins and counted in numbers, with the most common number being ion channels (23/48), followed by signal transduction/molecules (11/48), enzyme/enzyme modulators (7/48), cell adhesion molecules (3/48), nucleic acid binding (2/48), membrane trafficking (2/48), transporters/receptors (1/48) and cytoskeletal proteins (1/48). The gene groupings are shown in Table S2. We evaluated the response of different genomes (Figure 4); however, there were no significant differences among these groups. We further divided the ion channel group into three subgroups: SCN1A (n=9) and SCN2A (n=7). Interestingly, there was a significant difference in the efficacy of CLB between children with the SCN1A gene versus those with the SCN2A gene (P=0.009) and other ion channel-related genes (P=0.001). We then compared the efficacy of 9 patients with the SCN1A gene with 41 patients with other genes, and the results also revealed a significant difference (P=0.048). CLB was significantly more effective in treating the SCN1A genotype than other genotypes were, supporting its potential value as a personalized therapeutic target.



Seizure free	0	4	3	2	1	0	1	1	1	1
75-99% reduction	4	0	0	1	3	1	1	0	0	0
50-74% reduction	2	0	0	1	3	1	0	0	0	0
<50% reduction	3	3	4	3	4	1	0	1	0	0

Figure 4 Gene-specific responses to CLB. The efficacy of these detected genes from our patients was evaluated by sorting them into different gene sets according to protein function. *P<0.05.

Correlation of Clinical Characteristics with Treatment Efficacy

Univariate logistic regression with the frequency of seizure decline ≥50% as the dependent variable and baseline clinical characteristics as the independent variables revealed that generalized epilepsy and baseline seizure frequency strongly correlated with treatment outcome. Variables with $p<0.1$ in the univariate analysis were included in the multivariate logistic regression analysis, which revealed that only baseline seizure frequency was an independent risk factor for treatment efficacy ($p<0.001$) (Table 1).

Adverse Drug Reactions

During the follow-up, 24 (24/146, 16.44%) patients reported one or two adverse reactions of varying severity (Table 2). The most common adverse reactions were excessive salivation/hypersalivation (4/146, 2.74%), loss of appetite (4/146, 2.74%), increased sputum production (3/146, 2.05%), and fatigue/tiredness/weakness (3/146, 2.05%). Four people discontinued medication due to adverse reactions, which were concentrated in the first 6 months. The reasons for discontinuation were (1) sleep disorders, (2) irritability/agitation, (3) increased sputum production and loss of appetite and (4) increased sputum production and somnolence.

Table 2 Adverse Effects of CLB

Adverse Events	N (%)
Excessive salivation/Hypersalivation	4 (2.74)
Loss of appetite	4 (2.74)
Increased sputum production	3 (2.05)
Fatigue/Tiredness/Weariness	3 (2.05)
Weight gain	2 (1.37)
Irritability/Agitation	2 (1.37)
Drowsiness/Somnolence	2 (1.37)
Mood swings/Emotional fluctuations	1 (0.68)
Ataxia	1 (0.68)
Memory impairment/Forgetfulness	1 (0.68)
Sleep disorders	1 (0.68)
Insomnia	1 (0.68)
Sluggish response/Dulled reaction	1 (0.68)
Impaired intelligence	1 (0.68)
Behavioral disorder	1 (0.68)

Discussion

The results of this study show that CLB is effective as an adjunctive therapy in children with drug-resistant epilepsy and is well tolerated and safe. The response rate and seizure freedom rate reached 62.41% and 35.34% at 12 months, respectively. The good efficacy of CLB in patients with epilepsy due to genetic variants and its significantly better efficacy for the SCN1A. The factors associated with clinical response was a lower baseline seizure frequency.

The effectiveness of CLB in childhood epilepsy has been evaluated in several retrospective studies. A recent study revealed that 37.5% of pediatric patients with drug-resistant epilepsy achieved complete seizure freedom with CLB, whereas 40% of patients experienced a reduction in seizure frequency of more than 50%.[17] A large retrospective cohort study showed that 28% of pediatric patients with drug-resistant epilepsy achieved complete seizure freedom with CLB, and 67.7% had a more than 50% reduction in seizure frequency.[18] In conclusion, for pediatric patients with drug-resistant epilepsy, previous studies have reported CLB adjunctive therapy response rates of 58.6–77.5% and seizure-free rates of 16–37.5%,[17–23] and the results of the present study are similar to those of previous studies.

Multifactorial analysis revealed a significant correlation between baseline seizure frequency and response rate, with a higher response rate in patients with a lower baseline seizure frequency (77.63%, 59/76) and a lower response rate in patients with a higher baseline seizure frequency (42.11%, 24/57). Future studies could perform more fine-grained analyses. Furthermore, in our study, the response rate for generalized epilepsy was lower than that for focal seizures, combined generalized and focal epilepsy, and unclassifiable epilepsy, and univariate analysis suggested a possible correlation between generalized epilepsy and the response rate ($P<0.1$). However, no studies that have specifically evaluated how the efficacy of CLB differs for different types of epilepsy.

In general, although drug-resistant epilepsy is not the same as not responding to any ASMs, the probability of achieving seizure-free status with a newly tried medication decreases as the number of previously failed treatments increases.[24] However, this study revealed that the number of ASMs previously treated with CLB had no effect on efficacy, which suggests, in part, that CLB is not inferior in patients with drug-resistant epilepsy who have failed multiple drug treatments.

The WES positivity rate in patients reached approximately 40%, and we obtained a relatively large sample of patients for further gene-specific analysis. Although there was no significant difference in efficacy between the eight genomes, the SCN1A gene, an the ion channel-related gene, had significantly better efficacy than the other genotypes. This is the first time that the gene specificity of CLB has been analyzed, and larger sample sizes will be needed in the future to determine the specific treatment response of CLB to the SCN1A genotype.

The most frequently encountered side effects in studies concerning CLB are altered mood, irritability/hyperactivity, somnolence, behavioral disorders, and fatigue, and the incidence of adverse reactions observed in this study was lower

than that reported in previous studies (15–45%).[25] This may be due to the low doses used in most of the patients or to the retrospective nature of the study, where patients did not accurately determine whether certain conditions were adverse reactions produced by the drug.

There were several limitations in our study. First, this was a retrospective study that lacked some details in the medical records, such as the specific date on which patients discontinued CLB, which prevented us from predicting long-term retention rates. Second, the seizure count data used to determine seizure frequency are based on patient self-reports and medical paperwork, which can lead to inaccurate judgments. Third, all of the patients included in the study were on multiple ASMs, and other ASMs were adjusted while the patients were taking CLB, implying that the changes in CLB dosage did not occur in isolation. The potential drug interactions between CLB and other ASMs were not evaluated. Finally, this was an own-control study with no directly comparable control group, and the efficacy of CLB in specific subgroups, such as those receiving VNS and ketogenic diet, should be re-evaluated in future studies.

Conclusion

Adjunctive therapy with CLB is effective, safe and well tolerated in pediatric patients with drug-resistant epilepsy. These benefits are observed across heterogeneous etiologies and genetic subtypes. Sustained retention and meaningful seizure reduction, especially in patients with low baseline seizure loads, enhance its clinical utility. Future prospective trials are warranted to validate long-term benefits, optimize dosing strategies, and elucidate genetic predictors of response, further refining its role in personalized epilepsy management.

Abbreviations

CLB, clobazam; ASMs, antiseizure medications; LGS, Lennox-Gastaut syndrome; DS, Dravet syndrome; WES, whole-exome sequencing; VNS, vagus nerve stimulation.

Data Sharing Statement

All data are within the manuscript and supplementary material.

Ethics Approval Statement

This study was approved by the ethical committees of the Second Affiliated Hospital of Zhejiang University School of Medicine (20241487).

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Disclosure

The authors report no conflicts of interest in this work.

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