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Original Article

Efficacy of levetiracetam combined with oxcarbazepine in the treatment of adults with temporal lobe epilepsy and its impact on memory and cognitive function

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Abstract: Objective: To explore the effect of levetiracetam combined with oxcarbazepine on the memory and cognitive function of adult patients with temporal lobe epilepsy. Methods: This retrospective analysis included 91 adult patients with temporal lobe epilepsy treated at Xianyang Hospital from June 2020 to December 2022. Based on their medication regimen, patients were categorized into an observation group (n=51) receiving levetiracetam plus oxcarbazepine and a control group (n=40) receiving only levetiracetam. Both groups underwent 3 months of continuous treatment. Therapeutic efficacy, pre- and post-treatment memory function (assessed using the Clinical Memory Scale, CMS), cognitive function (evaluated with the Wechsler Adult Intelligence Scale-Revised in China, WAISRC), anxiety and depression levels (measured by the Hamilton Anxiety Scale, HAMA, and Hamilton Depression Scale, HAMD), as well as adverse reactions, were compared between the two groups. Independent factors influencing treatment efficacy were also analyzed. Results: CMS and WAISRC scores significantly increased in both groups after treatment (both P=0.001), with the observation group showing more significant improvements than the control group (P=0.001). The improvements in HAMA and HAMD scores in the observation group were significantly better than the control group (all P<0.001). Adverse reaction occurrence showed no significant difference between the two groups (P>0.05). Prognostic analysis identified seizure frequency and treatment regimen as independent factors influencing efficacy. Conclusion: Levetiracetam combined with oxcarbazepine effectively improves cognitive dysfunction in adults with temporal lobe epilepsy, with superior efficacy to levetiracetam alone, and good safety.

Keywords: Oxcarbazepine, levetiracetam, adult temporal lobe epilepsy, memory, cognitive function

Introduction

Epilepsy is a prevalent neurologic syndrome characterized by transient, sudden seizures, with temporal lobe epilepsy being a common subtype [1]. The primary etiology of temporal lobe epilepsy is a highly abnormal synchronous discharge of neurons in the brain's temporal region. Manifesting as recurrent and unprovoked focal seizures, the persistent and frequent epileptic discharges can result in substantial damage to intelligence and cognitive function, significantly impacting the patient's quality of life [2, 3]. Furthermore, given the unpredictable nature of this condition, a majority of patients experience varying degrees of anxiety and depressive emotions, imposing a considerable psychological burden [4]. Effectively managing temporal lobe epilepsy is, therefore, a critical challenge that necessitates attention.

Currently, medication stands as the primary treatment for temporal lobe epilepsy; however, many patients encounter challenges in achieving complete seizure control with a single antiepileptic drug, necessitating the adoption of combination therapy [5]. Levetiracetam is commonly employed for treating temporal lobe epilepsy; nevertheless, approximately one-third of patients do not achieve satisfactory seizure control with monotherapy, highlighting the need for adjuvant therapy with other medications [6]. Oxcarbazepine, recognized as a novel antiepileptic drug, demonstrates effective suppression of excitatory postsynaptic potentials in glu-

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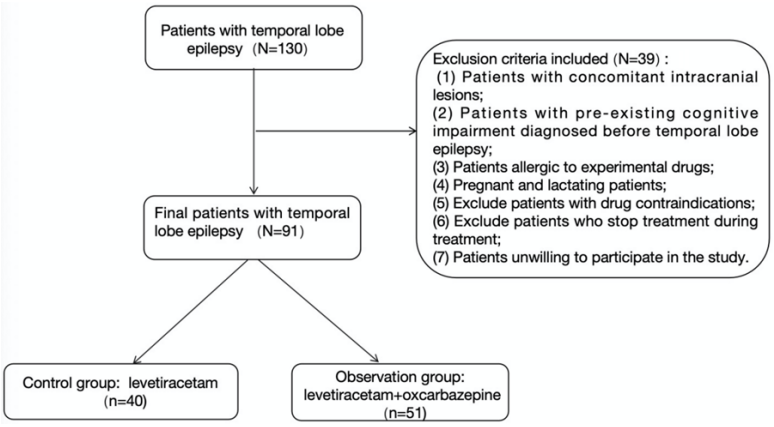

Figure 1. Research flow chart.

tamatergic synapses in clinical settings without negatively affecting brain-derived neurotrophic factor levels in the hippocampus. This preservation of neurological function contributes to significant enhancement in cognitive function [7, 8]. While levetiracetam and oxcarbazepine are extensively employed in clinical practice, there is limited literature on the efficacy of these two drugs for improving cognitive function in adults with temporal lobe epilepsy. Furthermore, most studies addressing cognitive function impairment in temporal lobe epilepsy patients have relied on single scales or electrophysiological research, which may pose limitations in the evaluation process [9].

The purpose of this study is to observe the efficacy of oxcarbazepine combined with levetiracetam in the treatment of adult patients with temporal lobe epilepsy and its impact on patients' memory and cognitive functions, in order to optimize treatment strategies for this patient population.

Materials and methods

Clinical data

The clinical data of 91 adult patients with temporal lobe epilepsy who were treated at Xianyang Hospital from June 2020 to December 2022 were retrospectively analyzed. Based on their medication regimens, they were divided into an observation group (n=51) receiving levetiracetam with adjunctive oxcarbazepine and a control group (n=40), treated with levetiracetam alone.

Inclusion criteria: (1) Adults diagnosed with temporal lobe epilepsy; (2) Patients aged 18 and above; (3) Patients with complete clinical data; (4) Patients who received medical treatment and had post-treatment outcome assessments; (5) Patients not previously treated for epilepsy. Exclusion criteria: (1) Patients with concomitant intracranial lesions; (2) Patients with pre-existing cognitive impairment diagnosed before temporal lobe epilepsy; (3) Patients allergic to experimental drugs; (4) Pregnant and lactating patients; (5) Patients with drug contraindications; (6) Patients who discontinued treatment; (7) Patients unwilling to participate in the study. This study was approved by the ethics committee of Xianyang Hospital and conforms to the Helsinki Declaration. The research flow chart is shown in **Figure 1**.

Treatment methods

The control group received oral levetiracetam (National Drug Approval Number: H20163115, Specification: 0.25 g), administered twice daily. The initial dose was 500 mg per dose, with increments of 500 mg per day based on the patient's condition after a 2-week treatment period. The treatment was maintained at the minimum effective dose, not exceeding 1500 mg per dose. In addition to the control group, the observation group received additional oral oxcarbazepine (Swiss Novartis Pharmaceuticals, Approval Number: 150 mg, Registration Number: H20080092) with an initial dose of 8-10 mg/(kg-d), twice a day. Subsequently, the dose was increased by 5-10 mg/(kg/d) per week based on the patient's condition, up to a maximum of 45 mg/(kg/d). The treatment duration for both groups was 3 months.

Primary observation indicators

(1) Therapeutic efficacy evaluation: The therapeutic outcomes were categorized as markedly effective, effective, or ineffective based on changes in seizure frequency from baseline. The number of epileptic seizures after taking the drug is reduced by more than 75% compared to before taking the drug. Effective: the seizure frequency decreased by 50%-75% compared to before treatment; Ineffective: the sei-

zure frequency decreased by approximately 50% after medication [10]. (2) Assessment of intelligence level: Before and 3 months after treatment, the Wechsler Adult Intelligence Scale-Revised Chinese version (WAIS-RC) [11] was used to assess patients' intelligence level. The WAIS-RC scale includes three dimensions: Verbal IQ (VIQ), Performance IQ (PIQ), and Full-Scale IQ (FIQ), with scores ranging from 0 to 95 for VIQ and PIQ and 0 to 190 for FIQ, where higher scores indicate higher intelligence levels.

Secondary observation indicators

(1) Memory assessment: The CMS scale [12] was employed for memory evaluation before and after medication for both groups. The CMS scale includes five subtests: directed memory, associative learning, free recall of images, meaningless graphic recognition, and recall of personal characteristics. The results were converted into a Memory Quotient (MQ) based on age-specific normative samples. (2) Anxiety and depression evaluation: Before and 3 months after treatment, patients were assessed using the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) [13], with higher scores indicating more severe anxiety or depression. (3) Adverse reactions rates: The incidence of adverse reactions during the treatment period, including nausea, vomiting, drowsiness, and rash were compared between the two groups. All adverse reactions were alleviated after symptomatic treatment. (4) Analysis of independent risk factors affecting patient efficacy.

Statistical methods

Data were organized using Excel and analyzed with SPSS 20.0 and GraphPad Prism 8 software for statistical processing, analysis, and visualization. Continuous data were presented as mean ± SD, and inter-group comparisons were conducted using independent sample t-tests, while intra-group comparisons were conducted using paired t-tests. Categorical data were expressed as percentages (%) and analyzed using the chi-square test. Logistic regression analysis was used to explore the independent risk factors affecting treatment efficacy. A $P<0.05$ was considered statistically significant.

Results

General data comparison

There were no significant differences between the two groups in terms of gender, age, or BMI ($P>0.05$), indicating the two groups were comparable (**Table 1**).

Comparison of treatment efficacy between the two groups

The overall treatment effectiveness in the observation group was 88.24%, significantly higher than 57.50% in the control group ($P=0.001$), as shown in **Table 2**.

Comparison of WAIS-RC scores before and after treatment between the two groups

Before treatment, there was no significant difference in WAIS-RC scores between the two groups ($P>0.05$). After treatment, improvements in VIQ, PIQ, and FIQ scores were noted in both groups. However, the post-treatment scores of VIQ, PIQ, and FIQ in the observation group were significantly higher than those of the control group (all $P<0.001$), as shown in **Figure 2**.

Comparison of memory function before and after treatment between the two groups

There were no significant differences in CMS scores (free recall, associative learning, directed recall) between the two groups before treatment (all $P>0.05$). However, after 3 months of treatment, the CMS scores in both groups (free recall, associative learning, directed recall) showed significant improvement. Notably, the observation group had significantly higher scores in free recall, associative learning, and directed recall compared to the control group (all $P<0.001$), as shown in **Figure 3**.

Comparison of negative emotions of patients before and after treatment between the two groups

There was no significant difference in HAMA or HAMD scores between the two groups of patients before treatment ($P>0.05$). After treatment, the HAMA and HAMD scores of the observation group were statistically lower than those of the control group (all $P<0.001$), as shown in **Figure 4**.

Table 1. Comparison of data between the two groups

Variable	Observation Group n=51	Control Group n=40	t/X^2	P
Gender			0.127	0.722
Male	30 (58.82)	25 (62.50)		
Female	21 (41.18)	15 (37.50)		
Age (years)			0.109	0.742
≥40	25 (49.02)	21 (52.50)		
<40	26 (50.98)	19 (47.50)		
BMI (kg/m^2)			0.061	0.804
≥23	23 (45.10)	17 (42.50)		
<23	28 (54.90)	23 (57.50)		
Smoking history			0.003	0.957
Yes	13 (25.49)	10 (25.00)		
No	38 (74.51)	30 (75.00)		
Drinking history			0.002	0.964
Yes	21 (41.18)	16 (40.00)		
No	30 (58.82)	24 (60.00)		
Duration of disease (years)	6.11±0.43	6.13±0.45	0.003	0.955
Number of attacks per month			0.066	0.798
≥4	10 (19.61)	7 (17.50)		
<4	41 (80.39)	33 (82.50)		
Presence of comorbidities			0.170	0.680
Yes	20 (39.22)	14 (35.00)		
No	31 (60.78)	26 (65.00)		

Table 2. Comparison of treatment efficacy between the two groups [n (%)]

Efficacy	Observation Group n=51	Control Group n=40	X^2	P
Markedly effective	30 (58.82)	15 (37.50)	4.087	0.041
Effective	15 (29.41)	8 (20.00)		
Ineffective	6 (11.76)	17 (42.50)		
Overall response rate	45 (88.24)	23 (57.50)	11.21	0.001

Comparison of the incidence of adverse reactions between the two groups

The incidence of adverse reactions was 15.69% in the observation group and 12.50% in the control group. There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05), as shown in **Table 3**.

Analysis of factors influencing patient treatment efficacy

Patients were divided into an effective group (68 cases) and an ineffective group (23 cases) based on their treatment outcome. Univariate analysis revealed that age, seizure frequency, and treatment plan were factors influencing the prognosis (**Table 4**). Subsequently, through assignment (**Table 5**), logistic regression analysis was conducted and revealed that seizure frequency and treatment plan were independent risk factors affecting the treatment efficacy (**Table 6**, all P<0.05).

Discussion

Temporal lobe epilepsy is a prevalent condition that often progresses to refractory focal epilepsy [14]. It arises from abnormal neuronal discharge affecting structures such as the corpus callosum, hippocampus, cingulate gyrus, fusiform gyrus, amygdala, and the peripheral system. Consequently, patients frequently experience cognitive impairment, including diminished attention, grammatical errors, memory

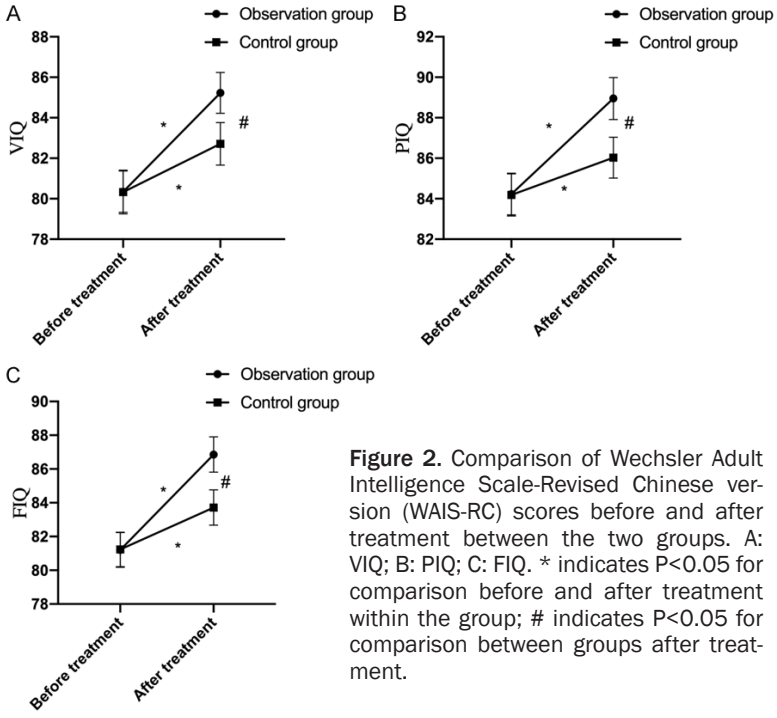

Figure 2. Comparison of Wechsler Adult Intelligence Scale-Revised Chinese version (WAIS-RC) scores before and after treatment between the two groups. A: VIQ; B: PIQ; C: FIQ. * indicates P<0.05 for comparison before and after treatment within the group; # indicates P<0.05 for comparison between groups after treatment.

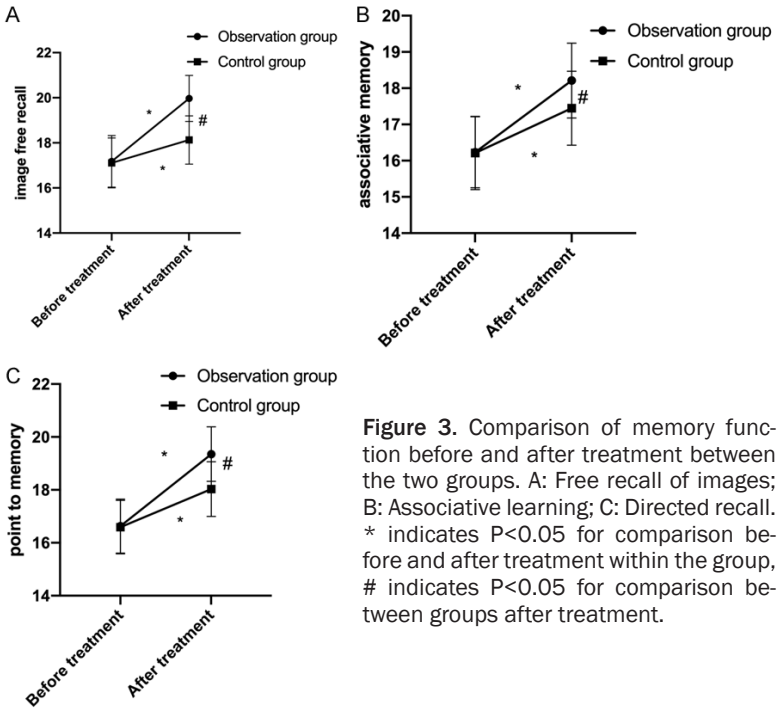

Figure 3. Comparison of memory function before and after treatment between the two groups. A: Free recall of images; B: Associative learning; C: Directed recall. * indicates P<0.05 for comparison before and after treatment within the group, # indicates P<0.05 for comparison between groups after treatment.

decline, emotional abnormalities, and slowed cognition [15]. Currently, drug therapy is the primary strategy for managing adult temporal lobe epilepsy, yet the efficacy of various drug regimens demands further exploration.

Levetiracetam is currently used in clinical practice for the treatment of temporal lobe epilepsy, selectively inhibiting epileptiform discharges and exerting an antiepileptic effect. However, its efficacy as monotherapy often falls short of achieving desired outcomes [16]. Oxcarbazepine, upon entering the human body, selectively blocks voltage-sensitive sodium channels, stabilizing hyperexcitable neurons and suppressing abnormal repetitive discharges in temporal neurons. Known for its good tolerability and minimal drug interactions, oxcarbazepine is an advantageous option for combination therapy [17]. Therefore, combining levetiracetam and oxcarbazepine in the treatment of patients with temporal lobe epilepsy may address the limitations of conventional treatment methods, enhancing therapeutic efficacy. Our observational results also demonstrate that this combination significantly improves treatment efficacy, reducing seizure frequency in patients with temporal lobe epilepsy.

We conducted a comprehensive analysis of the impact of levetiracetam combined with oxcarbazepine on the cognitive and memory functions of patients with temporal lobe epilepsy. Cognitive and memory impairments in these patients are influenced by multiple factors, with the frequency and type of seizures significantly compromising cognitive and memory function [18]. The WAIS-RC scale, widely used in clinical practice, detects cognitive impairments related to frequent seizures in epilepsy patients [19]. Our study revealed that the

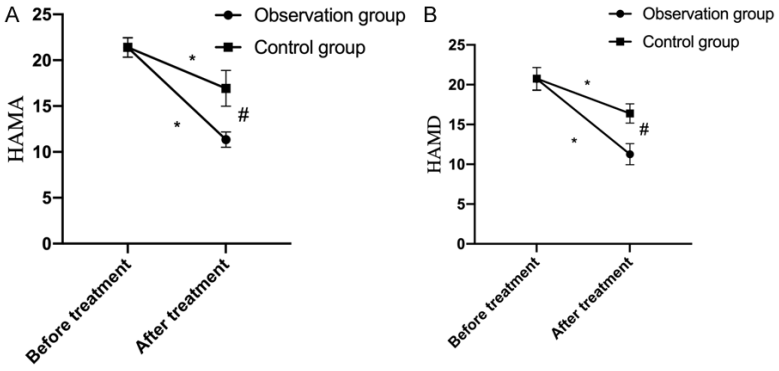

Figure 4. Comparison of negative emotions before and after treatment between the two groups. A: HAMA score; B: HAMD scores. * indicates P<0.05 for comparison before and after treatment within the group; # indicates P<0.05 for comparison between groups after treatment.

Full-Scale IQ (FIQ) in the observation group surpassed that in the control group after treatment. This suggests that levetiracetam combined with oxcarbazepine contributes to enhanced language skills, executive functions, and attention in patients with temporal lobe epilepsy.

The Clinical Memory Scale (CMS) is recognized for its efficacy in identifying memory impairments in patients with temporal lobe epilepsy [20]. Our investigation demonstrated that the observation group achieved higher scores in directional memory and free recall of images compared to the control group, highlighting a substantial enhancement in cognitive function, particularly in explicit memory, among patients treated with the combination of levetiracetam and oxcarbazepine. These outcomes align with the conclusions of the BRITTA study [21]. The multifaceted reasons contributing to this improvement encompass the impact of levetiracetam, which lowers intracellular calcium ion concentrations, thereby facilitating the restoration of normal activation patterns in the inner structures of the temporal lobe, resulting in cognitive enhancement. Furthermore, levetiracetam regulates neurotransmitter release by binding to central nervous synaptic vesicle proteins, moderating excessive activity in hippocampal cells, and augmenting memory [22]. On the other hand, oxcarbazepine impedes calcium ion efflux and enhances potassium ion influx, restraining the excitatory impulse transmission of synaptic abnormalities. This effect influences neurogenesis and the formation of new synapses, amplifying neurons' ability to acquire and process information. Consequently, it fortifies patients' capacities in learning, language, memory, attention, and other domains, thereby improving cognitive function and intellectual acuity [23].

Temporal lobe epilepsy, initially asymptomatic, typically presents through a sudden onset. Adult patients frequently experience varying degrees of anxiety and depression due to concerns about social discrimination, resulting in severe damage to the patients' mental well-being. This study observed that, after treatment, the HAMA and HAMD scores in the observation group were lower than those in the control group, suggesting that the adjunctive use of oxcarbazepine can effectively alleviate adverse emotions and reduce anxiety and depressive states in patients. The rationale behind this may lie in the fact that oxcarbazepine, as a second-generation antiepileptic drug, possesses favorable pharmacokinetics. It can block voltage-dependent calcium or sodium ion channels, inhibit hyperexcitability of neuronal membranes, reduce synaptic activity, stabilize emotions, and alleviate anxiety and depression [24, 25].

Furthermore, this study found that the incidence of adverse reactions such as somnolence, rash, nausea, and vomiting between the two groups showed no statistically significant differences. This suggests that the adjunctive use of oxcarbazepine does not exacerbate adverse drug reactions, indicating a relatively high level of drug safety. Subsequently, in order to analyze the independent impact of potential intervention factors on treatment efficacy, we conducted multifactorial regression analysis, revealing that seizure frequency and treatment method are independent risk factors leading to poor treatment outcomes in patients.

In conclusion, the concurrent administration of levetiracetam and oxcarbazepine exhibits notable efficacy in adults with temporal lobe epilepsy. It not only enhances cognitive function and memory capacity but also mitigates anxiety and depression, maintaining a favorable safety profile. This therapeutic approach merits con-

Table 3. Comparison of adverse reactions between the two groups [n (%)]

Adverse reaction	Observation Group n=51	Control Group n=40	X^2	P
Nausea	2 (3.92)	1 (2.50)	0.142	0.706
Vomiting	2 (3.92)	1 (2.50)	0.142	0.706
Lethargy	3 (5.88)	2 (5.50)	0.034	0.855
Rash	1 (1.96)	1 (2.50)	0.030	0.862
Overall incidence of adverse reactions	8 (15.69)	5 (12.50)	0.186	0.666

Table 4. Univariate analysis

Factor	Effective group (n=68)	Ineffective group (n=23)	X^2	P
Gender			0.294	0.588
Male (n=55)	40 (58.82)	15 (65.22)		
Female (n=36)	28 (41.18)	8 (34.78)		
Age			18.95	<0.001
≥40 (n=46)	17 (29.31)	19 (82.61)		
<40 (n=45)	41 (70.69)	4 (17.39)		
Body mass index			0.003	0.957
≥23 kg/m^2 (n=40)	30 (44.12)	10 (43.48)		
<23 kg/m^2 (n=51)	38 (55.88)	13 (56.52)		
Smoking history			0.204	0.652
Yes (n=23)	18 (26.47)	5 (21.74)		
No (n=68)	50 (73.53)	18 (78.26)		
Attack frequency			29.01	<0.001
≥4 (n=17)	4 (5.88)	13 (56.52)		
<4 (n=74)	64 (94.12)	10 (43.48)		
Treatment programs			11.21	<0.001
Levetiracetam single therapy (n=40)	23 (33.82)	17 (73.91)		
Levetiracetam combined with oxcarbazepine treatment (n=51)	45 (66.18)	6 (26.09)		

Table 5. Assignment table

Variable	Assignment
Age	≥40=1, <40=0
Attack frequency	≥4 times =1, <4 times =0
Treatment programs	Levetiracetam =1, Levetiracetam combined with oxcarbazepine =0

Table 6. Multivariate analysis

Variable	B	S.E.	Wals	P	Exp (B)	95% CI	
						Lower limit	Upper limit
Age	1.611	0.562	4.183	0.087	3.263	1.103	13.923
Attack frequency	1.588	0.664	5.591	0.021	4.986	1.313	17.963
Treatment programs	3.229	0.817	15.585	0.001	26.728	5.019	147.115

sideration for clinical use. However, this study has certain limitations, such as a relatively small sample size. Although the results remain internally consistent, further validation is necessary. Additionally, apart from medication, there are other relevant physical therapies for the treatment of temporal lobe epilepsy. The impact of physical therapy intervention on the effectiveness of combination drug therapy for remains uncertain and also deserves further investigation.

Disclosure of conflict of interest

None.

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