

# Effect of Lamotrigine on Refractory Epilepsy: Clinical Outcomes and EEG Changes

Zheng Li<sup>1,\*</sup>, Peng Wu<sup>1,\*</sup>, Qiushuo Chen<sup>2</sup>, Xinqiang Tong<sup>1</sup>, Qichao Yang<sup>1</sup>

<sup>1</sup>Shijiazhuang Rongkang Hospital of Traditional Chinese Medicine Co., Ltd., Internal Medicine, Shijiazhuang, 050000, People's Republic of China;

<sup>2</sup>Department of Neurology, Baoding First Central Hospital, Baoding, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Zheng Li, Email lizheng741789@163.com

**Background:** Refractory epilepsy poses significant challenges in clinical management due to its resistance to standard antiepileptic therapies, necessitating the exploration of more effective treatment regimens. Lamotrigine, with its proven efficacy and tolerability, offers potential benefits when combined with traditional medications like valproate, though its comprehensive impact on clinical outcomes and neurological markers requires further study.

**Objective:** To analyze the improvement effect of combined application of lamotrigine on refractory epilepsy patients and its impact on patients' EEG and neurological function.

**Methods:** This retrospective cohort study analyzed the clinical data of 93 patients with refractory epilepsy who were admitted to our hospital between January 2023 and June 2024. Based on the treatment interventions received, patients were divided into a control group (n=46, treated with valproate) and an observation group (n=47, treated with lamotrigine in addition to valproate). The clinical treatment effects, EEG ( $\delta$ ,  $\theta$ ,  $\alpha$ ,  $\beta$ ) power levels, neurological function indicators [brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), pro-apoptotic protein Bcl-2, Bax], inflammatory response indicators [interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), prostaglandin E2 (PGE2)], and the incidence of adverse reactions were compared between the two groups.

**Results:** The clinical treatment effect in the observation group was significantly better than that in the control group, with a higher total effective rate (93.62% vs 76.09%,  $P < 0.05$ ). The monthly seizure frequency was significantly reduced in both groups after treatment ( $P < 0.05$ ). The observation group demonstrated a significantly greater reduction in seizure frequency compared to the control group ( $P = 0.014$ ). Regarding EEG power levels, both groups showed decreases in  $\delta$  and  $\theta$  power levels and increases in  $\alpha$  and  $\beta$  power levels after treatment, with the observation group exhibiting more pronounced changes ( $P < 0.05$ ). Neurological function indicators revealed that Bcl-2 levels decreased, while BDNF, NGF, and Bax levels increased in both groups after treatment, with the observation group showing more significant improvements ( $P < 0.05$ ). Similarly, inflammatory response indicators, including IL-1 $\beta$ , IL-6, and PGE2, decreased in both groups, with the observation group demonstrating greater reductions ( $P < 0.05$ ). The incidence of adverse reactions was comparable between the two groups, with no significant difference observed (23.40% vs 17.39%,  $P > 0.05$ ).

**Conclusion:** Compared to valproate treatment alone, the combined application of lamotrigine can further enhance the efficacy in refractory epilepsy patients, Lower the seizure frequency, improve EEG power levels and neurological function, reduce inflammatory responses, and does not increase the risk of related adverse reactions.

**Keywords:** valproate, lamotrigine, refractory epilepsy, efficacy, EEG, neurological function, inflammatory response, impact

## Introduction

Epilepsy is a common neurological disorder affecting approximately 70 million people worldwide, with nearly 10 million patients in China, second only to cerebrovascular diseases.<sup>1</sup> Despite advancements in antiepileptic therapies, around 70% of patients achieve sufficient seizure control through anti-seizure medications (ASMs). However, 20–30% of patients are classified as drug-resistant, a figure that may be underestimated due to diagnostic variability.<sup>2</sup> Refractory epilepsy, also known as drug-resistant epilepsy (DRE), is defined by the International League Against Epilepsy (ILAE) as the failure of adequate trials of at least two appropriately chosen and tolerated ASMs (in monotherapy or combination) to achieve

sustained seizure freedom. This persistent seizure activity often results in cognitive impairments, emotional disturbances, social isolation, and economic burdens, significantly reducing quality of life for patients and their families.<sup>3</sup>

Valproate is one of the earliest and most widely used ASMs, primarily exerting its effects by enhancing the inhibitory function of gamma-aminobutyric acid (GABA) and reducing the release of excitatory neurotransmitters. While valproate has shown significant efficacy in managing various forms of epilepsy, its use alone may not suffice for patients with refractory epilepsy.<sup>4</sup> Lamotrigine, on the other hand, has emerged as a promising adjunctive therapy. This drug acts by inhibiting abnormal neuronal discharge, stabilizing membrane potentials, and reducing postsynaptic excitatory activity. The combination of these two drugs is hypothesized to have synergistic effects, potentially improving seizure control in refractory epilepsy patients.<sup>5</sup>

Several studies have investigated the efficacy of lamotrigine and valproate, either as monotherapies or in combination. For instance, research by<sup>6</sup> demonstrated the benefits of combining lamotrigine with other ASMs in reducing seizure frequency, though their focus was limited to specific subtypes of epilepsy. Similarly,<sup>7</sup> explored the impact of valproate on refractory epilepsy but did not examine its synergistic effects with lamotrigine. The current study differs from previous research by examining not only clinical efficacy but also the effects on neurological function, EEG power levels, and inflammatory markers, providing a more comprehensive evaluation.<sup>8,9</sup>

This study aims to analyze the combined application of valproate and lamotrigine in patients with refractory epilepsy, exploring their synergistic mechanisms and providing theoretical and practical insights for the treatment of this challenging condition.

## Materials and Methods

### Basic Information

This retrospective cohort study analyzed the clinical data of 93 patients with refractory epilepsy who were admitted to our hospital between January 2023 and June 2024. Inclusion criteria: ① Meet the diagnostic criteria for refractory epilepsy established by the ILAE,<sup>10</sup> confirmed by EEG examination; ② Patients aged  $\geq 18$  years, regardless of gender; ③ Imaging scans did not reveal intracranial structural lesions such as tumors, hematomas, or other lesions affecting the nervous system; ④ Had received treatment with two or more first-line antiepileptic drugs with unsatisfactory results; ⑤ Patients with stable vital signs, normal cognitive, intellectual, and language functions, a strong desire for treatment, and able to adhere to medication regimens as prescribed; ⑥ Complete and authentic clinical data available for analysis. Exclusion criteria: ① Epilepsy caused by intracranial tumors or other lesions compressing the nervous system; ② Severe dysfunction of important organs; ③ Comorbid metabolic or autoimmune diseases; ④ Severe infections; ⑤ Allergic reactions or contraindications to the medications and methods used in this study; ⑥ Comorbid cognitive impairment, consciousness disorders, and/or mental illnesses; ⑦ Withdrawal or abandonment of treatment during the study. Patients were divided into a control group (n=46, treated with valproate) and an observation group (n=47, treated with lamotrigine in addition to valproate). This study was approved by the Medical Ethics Committee of our hospital, ensuring strict adherence to ethical standards during the research process to protect patient privacy and rights.

### Methods

The control group received treatment with valproate, taking valproate sustained-release tablets (Sanofi Pharmaceuticals, National Drug Approval No. H20010595), with an initial dosage of 20 mg/(kg·d), gradually increasing the dosage based on the alleviation of symptoms [maximum dosage not exceeding 50 mg/(kg·d)] until seizure control was achieved. The observation group was treated with lamotrigine in addition to valproate, taking lamotrigine tablets (GlaxoSmithKline, National Drug Approval No. J20130026), with an initial dosage of 25.0 mg/d, gradually increasing the dosage to 50 mg/d after 3 weeks, and then adjusting the maintenance dosage to less than 100 mg/d based on the alleviation of symptoms. Both groups continued treatment for 6 months.

## Observation Indicators

### Primary Outcomes

- (1) Clinical Treatment Effect: Effective: EEG results show no abnormalities, and the frequency of seizures decreased by more than 75% compared to before treatment; Effective: EEG results show partial improvement in abnormal neuronal discharges, and the frequency of seizures decreased by 50%-75%; Ineffective: EEG results still show significant abnormalities, no improvement in condition, and the frequency of seizures decreased by less than 50%. Total effective rate = 100% - (number of ineffective cases / total cases × 100%).
- (2) EEG Power Levels: Before and after treatment, EEG power levels were collected from patients. During the collection process, patients were required to remain awake, quiet, with their eyes closed, and relaxed. They were instructed to alternate between opening and closing their eyes and taking deep breaths. The recording time was 10 minutes, and 30 seconds of stable baseline state was selected as the evaluation range, assessing the power of EEG signals in the  $\delta$  (1–3.5 Hz),  $\theta$  (4–7.5 Hz),  $\alpha$  (8–14 Hz), and  $\beta$  (14–30 Hz) frequency bands.<sup>11</sup>
- (3) Record seizure frequency before and after the therapy.

### Secondary Outcomes

- (1) Neurological Function Indicators: Before and after treatment, 5 mL of fasting morning blood samples were collected from the antecubital vein of patients, and the supernatant was sent for routine centrifugation to determine levels of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), pro-apoptotic protein Bcl-2, and Bax.
- (2) Inflammatory Response Indicators: Before and after treatment, serum samples were collected from patients (method as above) to determine levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and prostaglandin E2 (PGE2).
- (3) Adverse Reactions: During treatment, adverse reactions in patients were recorded, including nausea, vomiting, dizziness, headache, drowsiness, skin reactions, gastrointestinal reactions, etc.

## Statistical Analysis

GraphPad Prism 8 was used for charting; Statistical analyses were performed using SPSS 22.0 software. Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed data were expressed as ( $\bar{x} \pm s$ ) and analyzed using independent sample t-tests for between-group comparisons and paired t-tests for within-group comparisons. Non-normally distributed data were expressed as medians (interquartile range) and analyzed using Mann–Whitney *U*-tests. Categorical variables were expressed as percentages and analyzed using chi-square tests (The chi-square test was applied only to the total effective rates or total incidence rates in the tables, ensuring compliance with the assumption of expected frequencies  $\geq 5$ . Subcategories were not independently analyzed using chi-square testing). For multiple comparisons, the Bonferroni correction was applied to adjust the significance threshold. A *P*-value  $< 0.05$  was considered statistically significant unless otherwise noted.

## Results

### Basic Information

The basic information of the two groups was comparable ( $P > 0.05$ ), as detailed in [Table 1](#).

### Comparison of Clinical Treatment Effects

The overall effective rate of treatment in the observation group (93.62%) was significantly higher than that in the control group (76.09%) ( $P < 0.018$ ), as shown in [Table 2](#).

### Comparison of Seizure Frequency Before and After the Therapy

The monthly seizure frequency was significantly reduced in both groups after treatment ( $P < 0.05$ ). The observation group demonstrated a significantly greater reduction in seizure frequency compared to the control group ( $P = 0.014$ ), as shown in [Table 3](#).

**Table 1** Basic Information ( $\bar{x} \pm s$ , n[%])

	Control (n=46)	Observation (n=47)	t/x <sup>2</sup>	P
Gender	–	–	0.559	0.454
Male	28 (60.87)	25 (53.19)	–	–
Female	18 (39.13)	22 (46.81)	–	–
Age (years)	30.67±6.43	30.32±6.75	0.255	0.798
Duration (months)	5.72±1.38	5.94±1.43	0.754	0.452
Monthly Seizures	4.35±0.98	4.27±0.94	0.401	0.688
Disease Type	–	–	0.224	0.635
Simple Partial Seizures	13 (28.26)	12 (25.53)	–	–
Complex Partial Seizures	10 (21.74)	11 (23.40)	–	–
Partial Seizures Secondarily Generalized	8 (17.39)	10 (21.28)	–	–
Generalized Seizures	15 (32.61)	14 (29.79)	–	–
Medication History			0.527	0.466
Carbamazepine	41	43		
Topiramate	12	11		
Valpromide	3	4		
Phenytoin Sodium	2	2		
Gabapentin	2	2		
Combination Therapy			0.431	0.366
Patients using 2 medications	27	28		
Patients using 3 medications	12	12		
Patients using 4 medications	5	5		
Patients using 5 medications	2	2		

**Table 2** Comparison of Clinical Treatment Effects [n(%)]

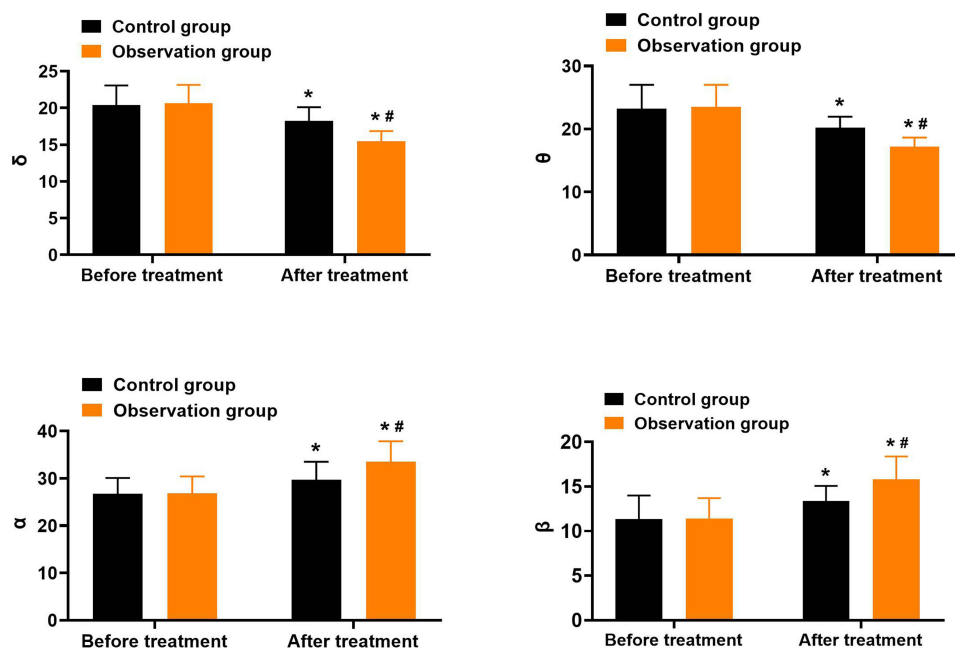
Group (n)	Effective	Valid	Invalid	Total Effective Rate
Control (n=46)	12 (26.09)	23 (50.00)	11 (23.91)	35 (76.09)
Observation (n=47)	19 (40.43)	25 (53.19)	3 (6.38)	44 (93.62)
x <sup>2</sup>	–	–	–	5.586
P	–	–	–	0.018

**Table 3** Comparison of Seizure Frequency Before and After the Therapy

	Before the Therapy	After the Therapy
Control (n=46)	4.35±0.98	2.67±0.45
Observation (n=47)	4.27±0.94	1.15±0.42
t	0.401	0.227
P	0.688	0.014

## Comparison of EEG Power Levels

Before treatment, there were no statistically significant differences in the  $\delta$ ,  $\theta$ ,  $\alpha$ , and  $\beta$  band powers between the two groups ( $P > 0.05$ ). After treatment, the  $\delta$  and  $\theta$  band powers in both groups decreased, with the observation group showing significantly lower  $\delta$  and  $\theta$  band powers compared to the control group ( $P < 0.05$ ). Similarly, the  $\alpha$  and  $\beta$  band powers in both groups increased after treatment, with the observation group exhibiting significantly higher  $\alpha$  and  $\beta$  band powers than the control group ( $P < 0.05$ ), as shown in [Figure 1](#).

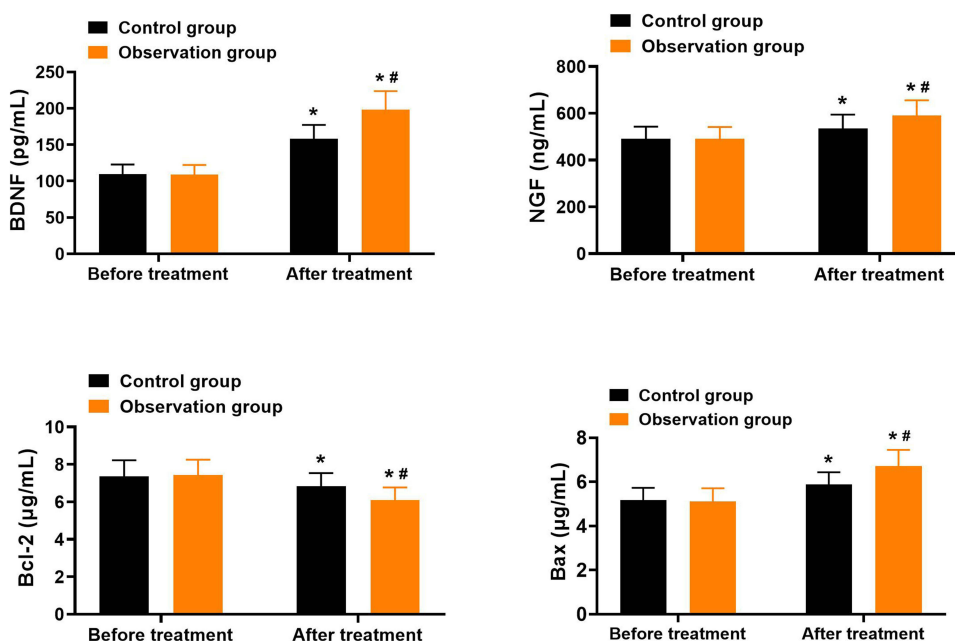


**Figure 1** Comparison of EEG Power Levels ( $\bar{x} \pm s$ , Hz).

**Note:** Compared with before treatment within the same group, \* $P < 0.05$ ; compared with the control group after treatment, # $P < 0.05$ .

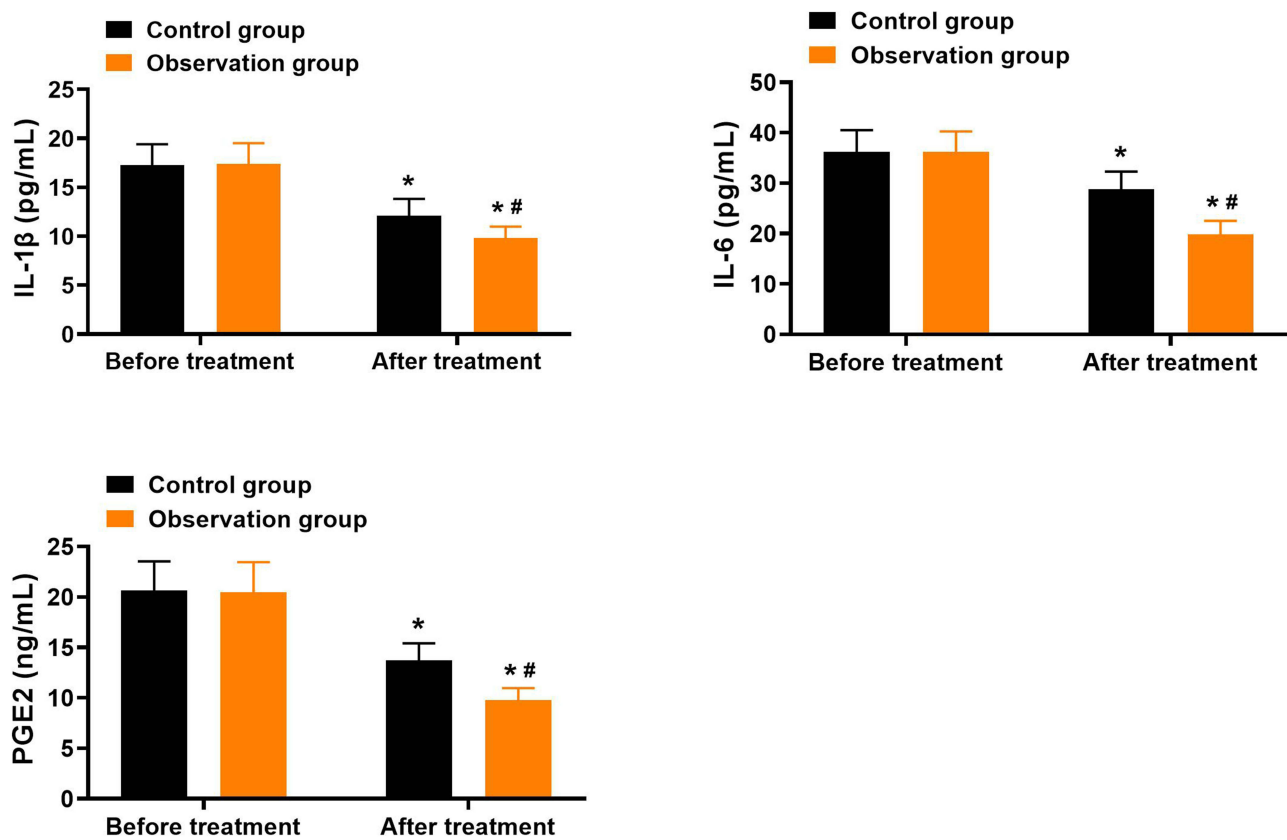
## Comparison of Neurological Function Indicators

Before treatment, there were no statistically significant differences in Bcl-2, BDNF, NGF, and Bax levels between the two groups ( $P > 0.05$ ). After treatment, Bcl-2 levels decreased in both groups, with the observation group showing significantly lower Bcl-2 levels compared to the control group ( $P < 0.05$ ). Meanwhile, BDNF, NGF, and Bax levels increased in both groups after treatment, with the observation group exhibiting significantly higher BDNF, NGF, and Bax levels than the control group ( $P < 0.05$ ), as shown in Figure 2.



**Figure 2** Comparison of Neurological Function Indicators ( $\bar{x} \pm s$ ).

**Note:** Compared with before treatment within the same group, \* $P < 0.05$ ; compared with the control group after treatment, # $P < 0.05$ .



**Figure 3** Comparison of Inflammatory Response Indicators ( $\bar{x} \pm s$ ).  
**Note:** Compared with before treatment within the same group, \* $P < 0.05$ ; compared with the control group after treatment, # $P < 0.05$ .

### Comparison of Inflammatory Response Indicators

Before treatment, there were no statistically significant differences in IL-1 $\beta$ , IL-6, and PGE2 levels between the two groups ( $P > 0.05$ ). After treatment, IL-1 $\beta$ , IL-6, and PGE2 levels decreased in both groups, with the observation group showing significantly lower levels compared to the control group ( $P < 0.05$ ), as shown in Figure 3.

### Comparison of Adverse Reaction Incidences

The incidence of adverse reactions in the observation group (23.40%) compared to the control group (17.39%) showed no significant difference ( $P > 0.05$ ), as presented in Table 4.

**Table 4** Comparison of Adverse Reaction Incidences [n(%)]

Adverse Reaction	Control (n=46)	Observation (n=47)	$\chi^2$	P
Nausea and Vomiting	2 (4.35)	3 (6.38)	–	–
Dizziness and Headache	1 (2.17)	1 (2.13)	–	–
Drowsiness	1 (2.17)	2 (4.26)	–	–
Skin Reactions	2 (4.35)	2 (4.26)	–	–
Gastrointestinal Reactions	2 (4.35)	3 (6.38)	–	–
Total Incidence	8 (17.39)	11 (23.40)	0.517	0.472

## Discussion

Epilepsy is a complex neurological disorder, with its pathogenesis involving multiple factors, particularly the abnormal discharge activity of neurons within the brain.<sup>12</sup> For patients with refractory epilepsy, the treatment process is often accompanied by a high recurrence rate and low drug sensitivity. Many patients experience poor outcomes with monotherapy, and even when two or more first-line antiepileptic drugs are used, the effects remain limited.<sup>13,14</sup> Therefore, finding more effective treatment options is of utmost importance. A comparative study of various antiepileptic drugs revealed the following findings: Among 1,721 patients with partial seizures evaluated for efficacy, lamotrigine was significantly superior to carbamazepine, gabapentin, and topiramate, while the difference with oxcarbazepine was not statistically significant. Regarding seizure termination, there was no statistically significant difference between carbamazepine and lamotrigine, oxcarbazepine, or topiramate.<sup>15</sup> In an evaluation of 716 children with primary generalized seizures and unclassified epilepsy, valproate was superior to topiramate in terms of efficacy, while there was no statistically significant difference when compared with lamotrigine. However, for seizure termination, valproate was superior to lamotrigine.<sup>16</sup> Ramey et al reviewed the prognosis of 962 cases of primary generalized epilepsy and concluded that valproate was the most effective treatment. If valproate was ineffective, the first choice should be to add lamotrigine rather than switching to another monotherapy.<sup>17</sup> The combination of lamotrigine and valproate broadens the antiepileptic spectrum, addressing the challenges of selecting treatments for refractory epilepsy with multiple seizure types, such as absence seizures, myoclonic seizures, partial seizures, and certain specific seizures like asymmetric tonic or postural seizures. This combination improves the specificity and effectiveness of treatment. Additionally, valproate enhances the plasma concentration of lamotrigine, allowing for reduced dosage and improved therapeutic efficacy.<sup>18</sup> The results of this study indicate that the total effective rate of treatment in the observation group was higher than that in the control group ( $P < 0.05$ ). The observation group demonstrated a significantly greater reduction in seizure frequency compared to the control group ( $P = 0.014$ ), while there was no significant difference in the incidence of adverse reactions between the two groups ( $P > 0.05$ ). This finding aligns with previous studies.<sup>19,20</sup> It suggests that the combination of lamotrigine with sodium valproate can not only enhance the therapeutic effects in patients with refractory epilepsy but also does not increase the risk of adverse reactions. The reasons for this can be analyzed from two aspects. First, sodium valproate, as a non-alkaline drug that does not contain nitrogen, can prevent excessive neuronal excitation by inhibiting the release of glutamate, thus reducing the risk of seizures.<sup>21</sup> Moreover, the metabolism of sodium valproate is relatively stable, allowing it to bind to plasma proteins and increase the concentration of free drug in the blood, which is especially important for patients who do not respond well to other antiepileptic medications. However, sodium valproate may also produce some side effects on the liver, kidneys, and gastrointestinal tract,<sup>22</sup> leading to limited efficacy when used alone. Lamotrigine, as a newer weakly alkaline drug and a sodium channel antagonist, can regulate membrane potential by inhibiting the release of glutamate and aspartate, thereby reducing abnormal discharges of neurons and effectively decreasing the frequency of seizures.<sup>23</sup> Additionally, lamotrigine has a rapid absorption rate, high blood concentration, and minimal first-pass effect,<sup>24</sup> giving it advantages of quick onset, prolonged efficacy, and fewer adverse reactions. By combining sodium valproate and lamotrigine, patients can utilize the different mechanisms of action of both drugs to synergistically block the abnormal discharges of neurons in the brain, significantly reducing seizure frequency while ensuring treatment safety.

Electroencephalography (EEG) is an indispensable tool in the diagnosis of epilepsy, capable of real-time monitoring of abnormal electrical activities in the brain and reflecting the electrographic features during seizures.<sup>25</sup> The results of this study showed that the  $\delta$  and  $\theta$  band powers were lower in the observation group after treatment, while the  $\alpha$  and  $\beta$  band powers were higher compared to the control group ( $P < 0.05$ ). This finding indicates that the combined use of the two medications effectively reduces abnormal activities on the EEG of patients with epilepsy. The occurrence of epilepsy is often accompanied by changes in electrical currents in the brain, leading to a slowing of the EEG background rhythm.<sup>26</sup> Prior to or during a seizure, the EEG may show abnormal waveforms such as spikes or sharp waves, which typically indicate abnormal discharge behavior of neurons. After a seizure, the EEG may present slow waves, indicating suppressed neuronal activity. In some types of epilepsy, characteristic rhythmic discharges, such as generalized spike-and-wave or multiple spike-and-wave patterns, may also be observed, closely associated with synchronous abnormal

discharges of neurons. Lamotrigine primarily acts on voltage-dependent sodium ion channels, inhibiting the release of glutamate, thereby effectively controlling high-frequency discharges and neuronal depolarization induced by epilepsy.<sup>27</sup> This mechanism helps maintain the stability of neuronal membrane potential, reducing the frequency of abnormal discharges in the brain. When used in conjunction with sodium valproate, this treatment strategy can intervene in brain neurons through different mechanisms, further reducing the release of glutamate, thus suppressing seizures from multiple angles.

The fundamental cause of seizures lies in the frequent occurrence of abnormal discharges in the focal area of neurons, which not only impairs neuronal function but also diminishes their neurotrophic status. BDNF, as a key member of neurotrophic factors, can activate the activity of various downstream enzymes by binding to tyrosine receptor kinases, thereby reducing the release of excitatory amino acids and inhibiting excessive calcium influx into neurons, thus protecting neuronal function.<sup>28</sup> NGF is also a crucial neurotrophic factor, primarily synthesized by glial cells and brain neurons, promoting the formation of myelin and axons, and accelerating neuronal proliferation.<sup>29</sup> In terms of neuronal damage, frequent seizures in epilepsy, especially refractory epilepsy, often accelerate neuronal apoptosis, ultimately leading to irreversible neurological impairment. Bcl-2 and Bax are two proteins with opposing functions; Bcl-2 promotes apoptosis, while Bax acts in an anti-apoptotic manner.<sup>30</sup> Furthermore, some studies<sup>31</sup> have found that inflammatory factors play a promoting role in seizures, and the high expression of various inflammatory factors in the epileptogenic focus indicates that these mediators not only exacerbate the inflammatory response in local brain tissue but can also regulate neuronal excitability by binding to specific receptors on neurons. The results of this study showed that the levels of Bcl-2, IL-1 $\beta$ , IL-6, and PGE2 were lower in the observation group after treatment, while BDNF, NGF, and Bax levels were higher compared to the control group ( $P < 0.05$ ). This suggests that the treatment strategy effectively improves the neurotrophic status of patients with refractory epilepsy, inhibits neuronal apoptosis, and reduces the inflammatory response in neural tissue, thereby helping to stabilize the epilepsy condition.

## Conclusion and Limitations

This study explored the efficacy of lamotrigine combined with sodium valproate in the treatment of refractory epilepsy. The results indicate that this combined therapy can further enhance efficacy compared to sodium valproate alone, Lower the seizure frequency, improve EEG frequency and neurological function, reduce inflammatory responses, and maintain good safety. This finding provides new therapeutic insights for clinical practice and emphasizes the importance of combination therapy in patients with refractory epilepsy. The study has certain limitations. As a retrospective cohort analysis, multivariate adjustments to control for potential confounders could not be performed. Although the baseline characteristics of the two groups were comparable, the possibility of residual confounding cannot be entirely excluded. Additionally, the relatively small sample size may limit the generalizability of the findings. Future studies with larger cohorts and prospective designs are recommended to further explore these associations and validate the results.

## Data Sharing Statement

All data generated or analysed during this study are included in this published article.

## Ethics

This study was approved by the ethics committee of Shijiazhuang Rongkang Hospital of Traditional Chinese Medicine Co., LTD. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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