Long-term Effectiveness of Antiepileptic Drug Monotherapy in Partial Epileptic Patients: A 7-year Study in an Epilepsy Center in China

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Abstract

Background: It is important to choose an appropriate antiepileptic drug (AED) to manage partial epilepsy. Traditional AEDs, such as carbamazepine (CBZ) and valproate (VPA), have been proven to have good therapeutic effects. However, in recent years, a variety of new AEDs have increasingly been used as first-line treatments for partial epilepsy. As the studies regarding the effectiveness of new drugs and comparisons between new AEDs and traditional AEDs are few, it is determined that these are areas in need of further research. Accordingly, this study investigated the long-term effectiveness of six AEDs used as monotherapy in patients with partial epilepsy.

Methods: This is a retrospective, long-term observational study. Patients with partial epilepsy who received monotherapy with one of six AEDs, namely, CBZ, VPA, topiramate (TPM), oxcarbazepine (OXC), lamotrigine (LTG), or levetiracetam (LEV), were identified and followed up from May 2007 to October 2014, and time to first seizure after treatment, 12-month remission rate, retention rate, reasons for treatment discontinuation, and adverse effects were evaluated.

Results: A total of 789 patients were enrolled. The median time of follow-up was 56.95 months. CBZ exhibited the best time to first seizure, with a median time to first seizure of 36.06 months (95% confidential interval: 30.64–44.07). CBZ exhibited the highest 12-month remission rate (85.55%), which was significantly higher than those of TPM (69.38%, $P = 0.006$), LTG (70.79%, $P = 0.001$), LEV (72.54%, $P = 0.005$), and VPA (73.33%, $P = 0.002$). CBZ, OXC, and LEV had the best retention rate, followed by LTG, TPM, and VPA. Overall, adverse effects occurred in 45.87% of patients, and the most common adverse effects were memory problems (8.09%), rashes (7.76%), abnormal hepatic function (6.24%), and drowsiness (6.24%).

Conclusion: This study demonstrated that CBZ, OXC, and LEV are relatively effective in managing focal epilepsy as measured by time to first seizure, 12-month remission rate, and retention rate.

Key words: 12-month Remission Rate; Antiepileptic Drug; Partial Epilepsy; Retention Rate

INTRODUCTION

Epilepsy is a common chronic neurological disorder that affects approximately nine million people in China with an annual number of 0.4–0.6 million newly diagnosed epileptic patients.[1] Standard antiepileptic drugs (AEDs), such as carbamazepine (CBZ) and valproate (VPA), have served as a therapeutic paradigm since the 1960s.[2] However, several new AEDs were licensed in recent decades, such as topiramate (TPM), oxcarbazepine (OXC), lamotrigine (LTG), and levetiracetam (LEV). These AEDs are increasingly used as first-line treatments for partial epilepsy.[3] However, current evidence for the effectiveness of new medications is still insufficient, and the few comparison studies between standard and new medications are restricted in the number of AEDs investigated. Moreover, only two or three AEDs were typically compared in these studies. Therefore, we investigated the effectiveness of six standard and new AEDs currently used as monotherapies in partial epileptic patients to elucidate whether these medicines are good choices for

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the treatment of partial epilepsy and whether these medicines are comparatively better.

METHODS

Patients and procedures

This is a retrospective, long-term observational study. We identified patients with partial epilepsy (simple partial epilepsy and secondary epilepsy) who were prescribed CBZ, VPA, TPM, OXC, LTG, or LEV as a monotherapy using an electronic record database in the Epilepsy Center of Chinese PLA General Hospital during the period from May 2007 to October 2014. All patients were followed up for at least 1 year. The Ethics Committee and Institutional Review Board of Chinese PLA General Hospital approved the protocol, and all patients were informed about the study objectives, procedures, and benefits.

To be eligible, patients had to meet the following criteria: (1) Be at least 13 years of age; (2) have a definite diagnosis of partial epilepsy;[4] (3) be taking AEDs as a monotherapy; and (4) exhibit no contraindications to AED treatment. The following patients were included in our study: Patients with newly diagnosed and untreated partial seizures; patients who had failed treatment with a previous monotherapy; and patients in epilepsy remission who had relapsed after treatment withdrawal. Patients using multiple AEDs and patients who declined to participate, failed to follow-up, or did not take the medications as advised were excluded. The demographic and clinical characteristics of the cases were shown in Table 1.

Follow-up data were collected from the epilepsy center's well-established database into which the data were recorded following the epilepsy experts' clinical visits. Clinical epilepsy experts based their diagnoses of epilepsy on a combination of information that included detailed case histories, physical and neurological examinations, and related tests. Clinicians classified seizure type using International League Against Epilepsy classifications,[4] at least when differentiating between partial and generalized onset seizures. Routine blood tests, liver and kidney function test, and so on, were performed before treatment and after treatment initiation. Detailed data for each patient were collected and recorded on case record forms. Baseline seizure frequency was defined as monthly seizure frequency (i.e., the number of seizures per month) during the 3-month baseline period before the initiation of AEDs. Experts chose the best AED according to seizure type, and the patient initially received the minimum dose of the AED. The dose was gradually increased over approximately 2–8 weeks until the target dose was reached. Dose adjustments, made at the discretion of the physician, depended on the balance between drug efficacy in reducing seizure frequency and the tolerability of side effects. When the clinical response was not satisfactory or when any adverse effects occurred, plasma concentrations were measured to determine whether they were within the accepted therapeutic range. Patients were followed up for at least 1 year, and follow-up data were obtained directly from general visits or indirectly via telephone interviews. The dose, effects of the AEDs, details of seizure occurrences, period/length of drug continuation, the date and reason for discontinuation, and the occurrence of any adverse events were recorded during follow-up interviews.

Patient registration information contained baseline demographic data such as gender, age of first seizure onset,

Table 1: Basic characteristics of patients with partial epilepsy taking the six AEDs							
Items	Total	CBZ	VPA	TPM	OXC	LTG	LEV
Number of patients	789	193	233	52	93	115	103
Gender, n (%)							
Male	430 (54)	110 (57)	145 (62)	30 (58)	46 (49)	41 (37)*	56 (55)
Female	359 (46)	83 (43)	88 (38)	22 (42)	47 (51)	73 (63)	46 (45)
Age of drug initiation, n (%)							
13–17 years	270 (34)	78 (40)	100 (43)	9 (17)	29 (31)	19 (17)	35 (34)
≥18 years	519 (65)	115 (60)	133 (57)	43 (83)	64 (69)	96 (83)	68 (67)
≥45 years	113 (14)	19 (10)	31 (13)	8 (16)	10 (11)	25 (21)	20 (20)
≥60 years	23 (3)	3 (2)	8 (3)	1 (2)	1 (1)	4 (3)	6 (6)
Age of onset, years, mean (SD)	19.65 (13.91)	16.95 (12.22)	18.94 (14.95)	22.02 (14.25)	19.50 (11.05)	22.82 (14.51)	22.16 (15.18)
Seizures of 6 months before randomization, n (%)							
0–12	557 (71)	131 (68)	165 (71)	36 (69)	61 (66)	84 (73)	80 (78)
≥13	232 (29)	62 (32)	68 (29)	16 (31)	32 (34)	31 (27)	23 (22)
AED administration							
Mean dose, mg/d, mean (SD)		306 (172)	773 (311)	128 (56)	730 (347)	114 (54)	985 (344)
Initial dose, mg/d		100	250	25	150	12.5	500
Increment of dose, mg/w		100	250	25	150	12.5	250
Target dose, mg/d		200–1200	1000–2000	100–200	600–1800	100–200	500–2000
Follow-up time, months, mean (SD)	56.95 (29.51)	55.22 (28.68)	59.75 (29.10)	66.46 (25.18)	56.88 (29.14)	57.48 (30.70)	48.86 (31.23)

*P<0.05, LTG versus LEV, TPM, CBZ, VPA. SD: Standard deviation; AED: Antiepileptic drug; LTG: Lamotrigine; LEV: Levetiracetam; TPM: Topiramate; CBZ: Carbamazepine; VPA: Valproate; OXC: Oxcarbazepine.

age of drug initiation, course of epilepsy, seizure type, time from drug initiation to drug discontinuation, follow-up period, time to first seizure, frequency of seizures before and after treatment, percentage of seizure reduction, remission rate, retention rate, reason for discontinuation, adverse effects, underlying etiology (birth history, brain injury, cerebral infection, stroke, etc.), febrile history, familial history, and examination results, such as blood routine examination, liver function and kidney function, brain imaging, and electroencephalogram.

Evaluations and assessments

Effectiveness was evaluated for both efficacy and tolerability and was measured using the following methods.

Efficacy was determined according to the following four calculations: (1) The percent of seizure reduction rate: Seizure frequency reduction after treatment divided by the seizure frequency before treatment; (2) time to first seizure: Time from initiation to first seizure; (3) responder rate: ≥50% seizure reduction; and (4) 12-month remission rate (seizure-free rate): No seizures for a minimum of 12 months.

Tolerability was assessed according to the following factors: (1) Time to withdrawal/long-term retention rate: Time from drug initiation to treatment failure (terminating drug administration, prescribing additional AEDs, changing to another AED); (2) reasons for treatment discontinuation; (3) risk factors associated with AED discontinuation; and (4) adverse effects that resulted in treatment discontinuation.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 software (IBM, Armonk, New York, USA). Cox regression analysis assessed the time to first seizure and the time to withdrawal, adjusting for the effect of baseline factors, and the Kaplan-Meier survival analysis was used to estimate the cumulative probability of retention and seizure remission rate. Differences in the Kaplan-Meier curves between the six groups were estimated using 95% confidence interval (*CI*), a one-way analysis of variance (ANOVA) was used to analyze differences in seizure frequency reduction, and Pearson's Chi-square test was used to analyze the efficacy of the data. A Cox proportional hazard model was established to analyze the risk factors of AED discontinuation. A $P < 0.05$ was considered statistically significant.

RESULTS

Basic demographic information

We recruited patients from May 22, 2007 to October 21, 2014 in our epilepsy center. A study flow diagram was presented in Figure 1. A total of 789 cases were enrolled in the study, and case numbers in each group were as follows: CBZ 193; VPA 233; TPM 52; OXC 93; LTG 115; and LEV 103. The male to female ratio was 1.19:1 (430/359 cases), the mean age of first seizure onset was 19.65 years (ranging from 3 days to 81 years), and the median time of follow-up was 56.95 months.
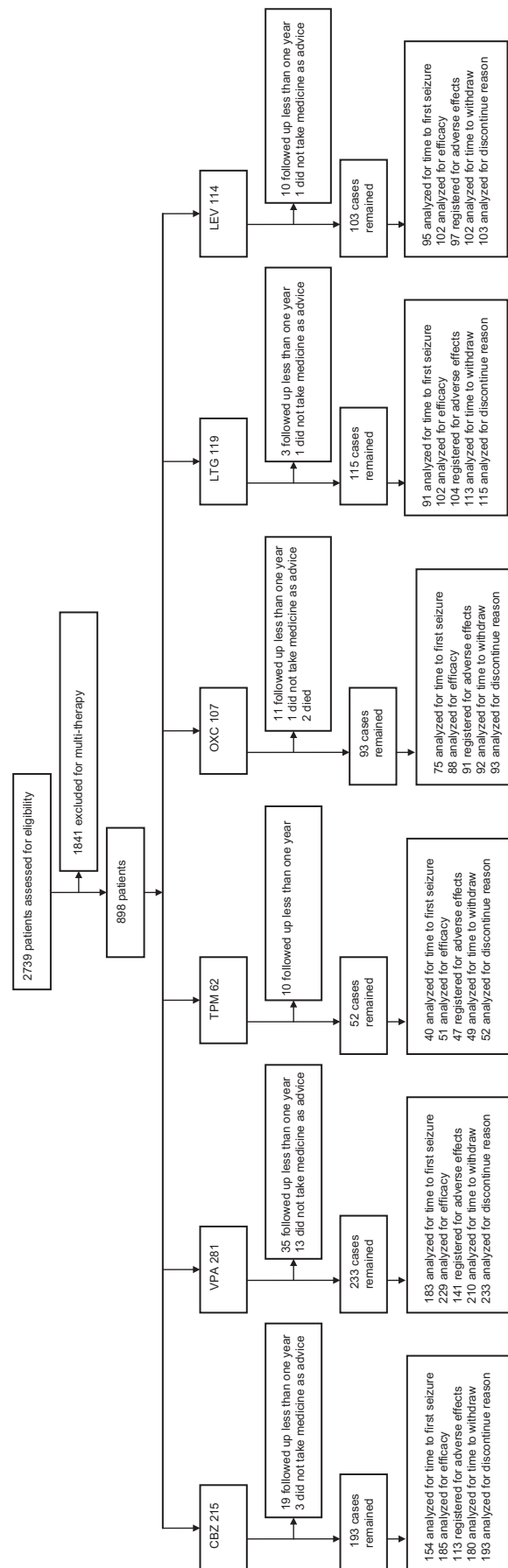

Figure 1: Study flow diagram. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam.
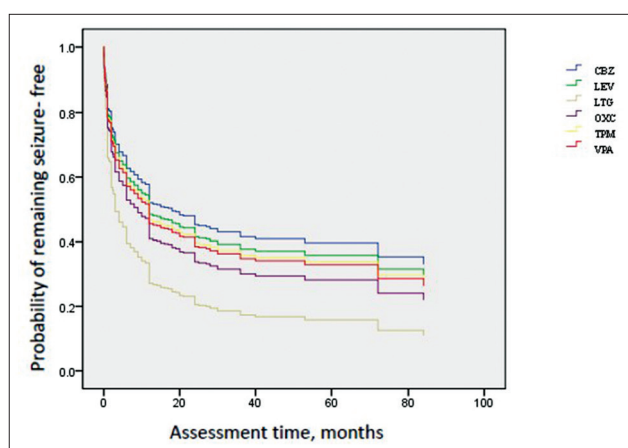
Evaluation of efficacy

Time to first seizure

The evaluation data of time to first seizure after treatment, as presented in Figure 2 and Table 2, suggested that time to first seizure differed significantly among the six groups ($P = 0.001$). The CBZ, LEV, TPM, VPA, and OXC groups included a high percentage of people without seizures over time, and there were no significant differences between any two drugs. However, LTG seemed least effective in the prevention of first seizures after treatment. Pairwise comparisons for the entire period indicated that CBZ (relative risk (RR) = 0.498, 95% CI: 0.356–0.696), LEV (RR = 0.556, 95% CI: 0.381–0.810), and VPA (RR = 0.623, 95% CI: 0.451–0.860) were significantly better than LTG in time to first seizure. However, there were no significant differences between LTG and any other drugs in time to first seizure (all $P > 0.05$).

Percentage of seizure reduction

There were significant differences among the six groups in the percent of seizure reduction ($F = 5.589$, $P = 0.025$), which was significantly higher in the OXC group than in the LTG group ($P = 0.030$) and significantly higher in the CBZ group than in the LTG group ($P = 0.018$). However, no significant differences were observed between any other two groups ($P > 0.05$).

Twelve-month remission rate and responder rate

Twelve-month remission rate and responder rates for all AEDs were provided in Table 3. All of the drugs had good 12-month remission rates of approximately 50% with the exception of LTG (32.35%), which was significantly inferior to any other drug (all $P < 0.05$). No other significant differences between any AEDs were observed in this analysis (all $P > 0.05$). OXC (86.36%), which seemed the preferred option for responder rate, was significantly better than that of LTG (68.63%) ($P = 0.004$). However, there were no significant differences between any other two drugs (all $P > 0.05$). Furthermore, there was no significant difference between any two drugs for seizure frequency reductions ≥25% and ≥75% (all $P > 0.05$).

Comparative rates of 12-month consecutive remission rate from randomization

Overall, the average 12-month consecutive remission rate from randomization for any AED was 76.14%. The results of the 12-month remission rate for all AEDs were presented in Figure 3. CBZ had the highest 12-month remission rate (85.55%), which was significantly higher than the rates for LTG (70.79%), VPA (73.33%), LEV (72.54%), and TPM (69.38%) (all $P < 0.05$). However, there were no significant differences between any other two drugs (all $P > 0.05$).

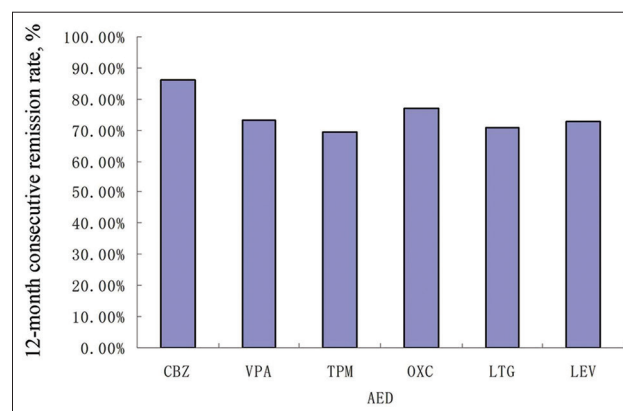

Figure 2: Time to first seizure. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam.

Figure 3: Twelve-month remission rates of six antiepileptic drugs (AEDs). CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam.

Table 2: Time to first seizure and percentage of people without seizure

AEDs	Median time to first seizure (months, 95% *CI*)	Percentage of people without seizure (%)				
		3 months	6 months	12 months	2 years	3 years
CBZ	36.07 (30.649–44.071)	76.20	66.80	54.10	44.30	39.20
VPA	32.69 (26.135–39.249)	61.30	55.80	43.60	41.80	36.90
TPM	32.34 (26.072–38.599)	59.80	51.90	51.90	39.20	39.20
OXC	23.81 (16.267–31.347)	70.70	61.30	42.60	25.20	17.20
LTG	17.49 (11.255–23.727)*	42.30	32.50	28.70	25.40	25.40
LEV	36.06 (28.395–45.731)	67.30	58.70	43.90	40.70	40.10

*$P<0.05$, means LTG versus CBZ, VPA and LEV. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam; AED: Antiepileptic drug; *CI*: Confidence interval.

Possibility of antiepileptic drug continuation
Time to withdrawal (long-term retention rate)
Cox model analyses adjusted for designed factors revealed a Kaplan-Meier curve of time to withdrawal [Figure 4]. There were significant overall differences among the six drugs ($P = 0.038$) with CBZ exhibiting the best retention rate, followed by OXC, LEV, and LTG, and the likelihood of TPM and VPA continuation was the lowest. Pairwise comparisons indicated that the retention rates of CBZ and OXC appeared broadly similar, and were significantly better than the retention rates of LTG, VPA, and TPM (all $P < 0.05$) [Table 4]. And LEV was significantly better than VPA ($P = 0.021$).

Reasons for drug discontinuation
The most common time to discontinuation
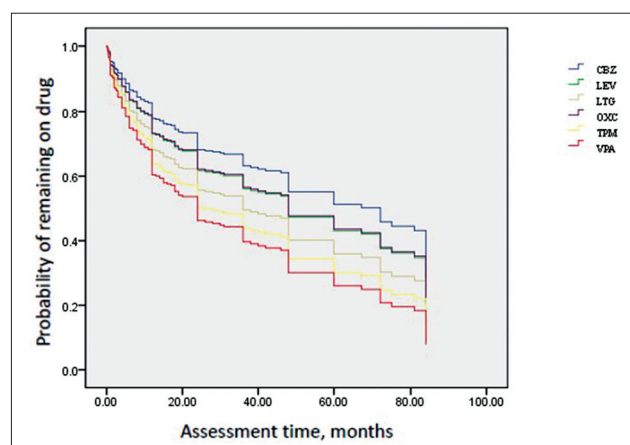
Figure 4: Long-term retention rates of six antiepileptic drugs. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam.

was ≤1-month (22.05%). The primary reason for discontinuation during this early period was the adverse effects associated with the drug. This was followed by inadequate seizure control during the next few months. The median time for unacceptable adverse events was 1.89 months (ranging from 3 days to 12 months). The mean time for inadequate seizure control was 15.4 months (ranging from 20 days to 84 months).

The primary reason for the discontinuation of all AEDs was a lack of efficacy, and the second reason was the intolerable adverse effects. CBZ and LTG were most frequently associated with treatment failure for unacceptable adverse effects (23.73% and 23.29%, respectively), while LEV (9.09%) was the least likely to result in treatment failure, none of the differences among the AEDs with respect to treatment failure were statistically significant (all $P > 0.05$).

Discontinuation due to intolerability of adverse effects
Overall, 7.10% of the patients experienced intolerable adverse effects from an AED [Table 5]. The most common adverse effect related to treatment withdrawal was rash (51.79%). Abnormal hepatic function (16.07%), dizziness (7.14%), low leukocyte counts (7.14%), and nausea (5.36%) were other common adverse effects. Twenty-nine cases terminated treatment because of rash, a symptom that most commonly occurred with the administration of LTG ($n = 10$), CBZ ($n = 8$), and OXC ($n = 7$). Of all terminated cases, LTG demonstrated the highest rate (8.69%) of discontinuation due to rash, followed by OXC (7.53%) and CBZ (4.14%). The incidences of rash from these drugs were significantly higher than the incidences from VPA (0.43%) ($P < 0.05$). LTG also had a significantly higher rate of intolerable rash discontinuation than did LEV ($P = 0.009$). The abnormal

Table 3: Change in seizure frequency from baseline and 12-month seizure-free rate

Seizure frequency	Antiepileptic drugs, n (%)						P
	CBZ	VPA	TPM	OXC	LTG	LEV	
Reduced by							
≥25%	156 (84.32)	189 (82.53)	43 (84.31)	77 (87.50)	78 (76.47)	79 (77.45)	0.298
≥50%	151 (81.62)	178 (77.73)	42 (82.35)	76 (86.36)	70 (68.63)*	78 (76.47)	0.051
≥75%	30 (16.22)	46 (20.09)	8 (15.69)	21 (23.86)	22 (21.57)	19 (18.63)	0.670
12-month seizure free rate	101 (54.59)	109 (47.60)	30 (58.82)	45 (51.14)	33 (32.35)†	53 (51.96)	0.006

*The responder rate of LTG was lower than OXC significantly, $P = 0.001$; †The remission rate of LTG was lower than any other drug significantly, $P<0.05$. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam.

Table 4: Pairwise comparisons of retention rates

Antiepileptic drugs	P, RR (95% CI)				
	CBZ	VPA	TPM	OXC	LTG
VPA	0.008, 1.923 (1.183–3.126)*				
TPM	0.049, 1.837 (1.004–3.362)*	0.477, 1.218 (0.707–2.098)			
OXC	0.846, 1.046 (0.567–1.997)	0.021, 1.962 (1.108–3.474)*	0.032, 2.021 (1.061–3.847)*		
LTG	0.041, 1.888 (1.027–3.472)*	0.986, 1.005 (0.569–1.775)	0.862, 1.060 (0.548–2.051)	0.049, 0.576 (0.332–0.997)*	
LEV	0.922, 1.028 (0.588–1.797)	0.021, 1.755 (1.087–2.833)*	0.104, 1.646 (0.902–3.001)	0.550, 0.839 (0.471–1.493)	0.160, 1.450 (0.863–2.438)

*$P<0.05$. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam; RR: Relative risk; CI: Confidence interval.

Table 5: Intolerable adverse effects of AEDs, _n_							
Adverse effects	CBZ	VPA	TPM	OXC	LTG	LEV	Total
Rash	8	1	2	7	10	1	29
Skin redness, itching					1		1
Skin black spots					1		1
Dizziness	1	1			1	1	4
Drowsiness	2						2
Abnormal hepatic function	3	6					9
Low leucocyte	1	3					4
Nausea	2	1					3
Renal calculus			1				1
Weight loss			1				1
Numbness			1				1
Anxiety/irritability/ nervousness					1	1	2
Total	17	10	5	7	14	3	56

Tata was described as number of cases. CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam; AED: Antiepileptic drug.

hepatic function was the most intolerable adverse effect from VPA, which was 60% of all intolerable adverse effects in discontinued cases.

Adverse effects of antiepileptic drugs

Of all patients in the study, 45.87% patients reported AEs [Table 6]. LTG (35.58%) and LEV (36.08%) had the lowest percentages of adverse effects, while TPM (55.32%), VPA (53.90%), and CBZ (50.44%) had the highest percentages, and the percentages of the latter three drugs were significantly higher than the percentages of LTG and LEV (all $P < 0.05$). However, there were no significant differences between any other AEDs (all $P > 0.05$).

Risk factors for antiepileptic drug discontinuation

The results of the Cox proportional hazard model revealed that drug continuation was more frequent in patients with a familial history of epilepsy (RR = 0.595, 95% CI: 0.368–0.963, P = 0.035). Other factors, such as choice of drugs, gender, age of onset, age of drug initiation, adverse effects, and febrile history, were not risk factors for treatment discontinuation in our study ($P > 0.05$).

DISCUSSION

In this study, we investigated the differences in the effectiveness of six standard and new AEDs as monotherapies for partial epileptic patients. Additionally, we evaluated the most complete index as it estimated both efficacy (time to first seizure, seizure frequency reduction, 12-month remission rate, and responder rate) and tolerability (12-month retention rate, time to withdrawal, reasons for treatment discontinuation, and adverse effects). We found that while the efficacy of standard drugs, CBZ, and VPA, was similar, the retention rate of CBZ was significantly better than that of VPA, which indicated that CBZ is a superior treatment for partial epileptic patients. Moreover, our results were similar to previous studies.[5,6]

CBZ was the most effective drug of the six AEDs because CBZ exhibited the best efficacy and retention rate. CBZ was significantly better than LTG for time to first seizure, 12-month remission rate, and seizure frequency reduction. CBZ also exhibited the best retention rate, which was extremely better than the retention rates for LTG, TPM, and VPA. Therefore, it is concluded that CBZ is the best choice for partial epilepsy and is, therefore, worthy of recommendation.

OXC was broadly similar to CBZ in efficacy and tolerability. While CBZ performed better than OXC for time to first seizure, seizure frequency reduction, remission rate, and retention rate, there were no significant differences between these two drugs, a finding that was consistent with previous reports.[7] Though the incidences of adverse effects related to CBZ were higher than the incidences related to OXC, this difference was not statistically significant. To summarize, CBZ and OXC exhibited similar efficacy and tolerability, and there were no overall differences with respect to time to treatment withdrawal in partial epileptic patients.

The effectiveness of LEV was similar to those of CBZ and OXC, and no significant differences among these three drugs were observed for time to first seizure, seizure frequency reduction, remission rate, and time to discontinuation. Additionally, the incidence of adverse effects of LEV was the lowest among the six drugs, and it was significantly lower than TPM, VPA, and CBZ. These results suggested that LEV demonstrated good efficacy and is the safest and most tolerable drug among these six AEDs. Accordingly, LEV is recommended for the treatment of partial epilepsy, even in patients with systemic disorders.

Our research assumed that high retention rates did not necessarily mean better efficacy, and vice versa, an assumption also common in extant studies cited herein.[8] Many patients continued treatment despite the lack of AED efficacy. For example, LTG exhibited good retention despite its suboptimal efficacy. Furthermore, the efficacy of TPM was not sufficiently poor enough to result in a poor retention rate.

TPM had good efficacy, although it was not significantly different than any other drug except LTG. However, the tolerability of TPM was poor, and the incidence rate of adverse effects for TPM was the highest of all ADEs, which led to poor retention rate for TPM compared with the other drugs. The retention rate for TPM was extremely lower than the rates for CBZ and OXC. Marson _et al_.[9] compared the effectiveness of CBZ, LTG, OXC, and TPM and found that TPM performed poorly in time to withdrawal. Chung _et al_.[8] compared the retention rates of LEV, LTG, OXC, TPM, and ZNS and found that the retention rate of TPM was the lowest among these five drugs. These results were similar to our study.

LTG exhibited the worst performance of the six AEDs with respect to time to first seizure, which was most likely

Table 6: Adverse effects of six AEDs

Adverse effects	AEDs, n (%)						Total
	CBZ	VPA	TPM	OXC	LTG	LEV	
Abnormal hepatic function	12 (10.62)	19 (13.48)	1 (2.12)	4 (4.39)		1 (1.03)	37 (6.24)
Rash	14 (12.39)	1 (0.71)	4 (8.51)	8 (8.79)	18 (17.31)	1 (1.03)	46 (7.76)
Skin redness, itching					2 (1.92)		2 (0.34)
Skin black spots					1 (0.96)		1 (0.17)
Drowsiness	9 (7.96)	6 (4.25)	3 (6.38)	9 (9.89)	1 (0.96)	9 (9.28)	37 (6.24)
Dizziness	4 (3.54)	1 (0.71)	1 (2.12)	8 (8.79)	4 (3.85)		18 (3.04)
Headache	1 (0.88)		1 (2.12)	1 (1.10)		2 (2.06)	5 (0.84)
Menstrual disorder	2 (1.77)	5 (3.55)			1 (0.96)		8 (1.35)
Memory problems	9 (7.96)	9 (6.38)	5 (10.64)	12 (13.19)	5 (4.81)	8 (8.25)	48 (8.09)
Weight gain	2 (1.77)	22 (15.60)		1 (1.10)	1 (0.96)		26 (4.38)
Weight loss		1 (0.71)	3 (6.38)	1 (1.10)			5 (0.84)
Nausea	5 (4.42)	7 (4.96)		4 (4.39)		1 (1.03)	17 (2.87)
Stomachache						1 (1.03)	1 (0.17)
Anorexia	1 (0.88)		1 (2.12)				2 (0.34)
Diarrhoea				1 (1.10)		1 (1.03)	2 (0.34)
Constipation						1 (1.03)	1 (0.17)
Abnormal renal function	2 (1.77)						2 (0.34)
Renal calculus			1 (2.12)				1 (0.17)
Language problems/difficulty in finding words	1 (0.88)		3 (6.38)				4 (0.67)
Numbness			4 (8.51)				4 (0.67)
Cough						1 (1.03)	1 (0.17)
Alopecia		3 (2.13)		1 (1.10)			4 (0.67)
Low leucocyte	5 (4.42)	12 (8.51)	1 (2.12)		1 (0.96)		19 (3.20)
Low blood platelet		6 (4.25)	2 (4.26)	1 (1.10)			9 (1.52)
Low erythrocyte		3 (2.13)					3 (0.51)
Hyponatremia				1 (1.10)			1 (0.17)
High blood uric acid		4 (2/84)		1 (1.10)			5 (0.84)
Tremor		6 (4.25)			1 (0.96)	1 (1.03)	8 (1.35)
Dreaminess						1 (1.03)	1 (0.17)
Face acne						1 (1.03)	1 (0.17)
Ataxia	1 (0.88)						1 (0.17)
Nianniansuodry/dry eyes				1 (1.10)			1 (0.17)
Cognitive effects (confusion/poor/ concentration/difficulty thinking)	2 (1.77)	3 (2.13)	2 (4.26)				7 (1.18)
					2 (1.92)	4 (4.12)	6 (1.01)
Anxiety/irritability/nervousness	1 (0.88)	1 (0.71)	1 (2.12)	2 (2.20)	1 (0.96)	9 (9.28)	15 (2.53)
Psychiatric (depression/want to suicide)						1 (1.03)	1 (0.17)
Decreased libido						1 (1.03)	1 (0.17)
Identical persons	14 (12.39)	33 (23.40)	7 (14.89)	15 (16.48)	1 (0.96)	9 (9.28)	9 (1.52)
Total	57 (50.44)	76 (53.90)	26 (55.32)	41 (45.05)	37 (35.58)	35 (36.08)	272 (45.87)

CBZ: Carbamazepine; VPA: Valproate; TPM: Topiramate; OXC: Oxcarbazepine; LTG: Lamotrigine; LEV: Levetiracetam; AED: Antiepileptic drug.

due to the initiation dose and the titration of LTG, both were very low in our study. As time from initiation to target dose was almost 8 weeks, it was difficult to control seizures during the early stages. The slow titration also led to poor medication compliance, and some patients did not increase their drug dose according to their doctors' recommendations. Although the efficacy of LTG was poor, the retention rate was not the worst because LTG was the best tolerated AED, and the incidence of adverse effects was the lowest compared with other drugs. Moreover, the incidence rate of adverse effects for LTG was significantly lower than the rates for TPM, VPA, and CBZ. As rash was the most intolerable adverse effect, it is the primary factor affecting the tolerability of LTG.

Comparisons of CBZ and LTG yield paradoxical results.[10] On the one hand, Marson et al.[9] and Gamble et al.[11] found that LTG was significantly superior to CBZ regarding time to treatment failure. On the other hand, Steinhoff et al.[12] found that the retention rates of LTG were higher than those of CBZ (91% and 81%, respectively), albeit this difference was not significant. Gamble et al.[11] found that the time to first seizure and seizure freedom at 6 months favored CBZ, although the results were not significant when compared to LTG. Steinhoff et al.,[12] however, suggested that LTG was not inferior to CBZ in the proportion of patients who achieved 12-month remission. With respect to this dichotomy in the findings, our research found that CBZ was significantly superior to LTG in efficacy and tolerability and concluded

that CBZ was a better choice than LTG for the treatment of partial epileptic patients.

Comparisons of the effectiveness of the four new drugs revealed that LEV and OXC were the better choices because LTG and TPM exhibited the lowest remission rate and retention rate, respectively. Studies regarding the effectiveness of new AEDs as monotherapies in partial epileptic patients are few. Marson *et al*.[9] compared the effectiveness of CBZ, LTG, OXC, and TPM and concluded that LTG was the best of the five and that it was significantly better than TPM for time to treatment failure. LTG also exhibited a nonsignificant advantage over OXC. Chung *et al*.[8] found that LTG had the highest retention rate and that this rate was significantly different than the rates for LEV, OXC, and TPM. While these cited studies suggested that LTG has the best retention rate, the retention rate of LTG in our study was not the best, and in fact, it was significantly lower than that of OXC. Our analysis presumed that the slow titration was one reason for poor medication compliance. Additionally, rash was the major factor that affected the tolerability of LTG as the incidence rate of rash for LTG was 17.31% in our center, a rate that was higher than the rates published in previous reports, which were 5–15%.[8-10] Therefore, we hypothesized that Chinese people exposed to LTG are more prone to rashes and will more readily discontinue treatment due to intolerable rashes. However, this hypothesis requires further confirmation.

The comparison of new drugs and standard drugs demonstrated that CBZ was a better choice than LTG and TPM but was similar to OXC and LEV. VPA appeared no better than the new AEDs in efficacy or tolerability, and the retention rate of VPA was even lower than the rates of OXC and LEV.

In conclusion, CBZ, OXC, and LEV are relatively effective in managing focal epilepsy as measured by time to first seizure, 12-month remission rate, and retention rate.

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Conflicts of interest

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