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Seizure Control, Tolerability, and Direct Drug Cost of Lamotrigine Versus Carbamazepine in Adults With Focal Epilepsy in a Randomized Open-Label Trial in Bangladesh

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Abstract

Background: Carbamazepine and lamotrigine are both widely used as initial monotherapy for focal epilepsy, but they differ in tolerability and price. In Bangladesh, where most patients pay for medicines themselves, that difference often determines which drug is actually taken. To our knowledge, no randomized comparison of the two drugs has been reported in this population. This trial aimed to compare seizure freedom at six months between lamotrigine and carbamazepine in adults with focal epilepsy and, as secondary objectives, time to first seizure recurrence, serious clinical events, adverse events, adherence, and direct drug cost.

Methods: We conducted a prospective, randomized, open-label, parallel-group trial at the Department of Neurology, Dhaka Medical College Hospital, between November 2022 and October 2023. A total of 100 adults with focal epilepsy were allocated in a 1:1 ratio by lottery in blocks of six, with 50 assigned to lamotrigine and 50 to carbamazepine, and followed for six months. The primary outcome was seizure freedom between the month 3 and month 6 visits. Secondary outcomes were seizure freedom at months 1 and 3, time to first seizure recurrence, status epilepticus, hospital admission, death, adverse events, adherence on the four-item Morisky scale, and direct drug cost. Seizure freedom was analyzed in the intention-to-treat population (n = 100), counting missing outcomes as failures, and in the per-protocol population (n = 95), using risk differences with 95% confidence intervals (CIs) and the prespecified noninferiority margin of 30% points.

Results: The groups were similar at baseline. Seizure freedom at month 6 was 33 of 50 (66.0%) with lamotrigine and 35 of 50 (70.0%) with carbamazepine in the intention-to-treat analysis (risk difference, -4.0% points; 95% CI, -21.6 to 14.0) and 33 of 48 (68.8%) versus 35 of 47 (74.5%) in the per-protocol analysis (risk difference, -5.7% points; 95% CI, -23.2 to 12.3). Continuous freedom from recurrence through six months was 50.0% versus 55.3% (log-rank $p = 0.597$). At least one adverse event was reported by 17 (35.4%) participants receiving lamotrigine and 33 (70.2%) receiving carbamazepine ($p < 0.001$), mainly sedation and fatigue. Two deaths occurred, both in the carbamazepine group. Adherence was similar. The median direct drug cost over six months was 6480 Taka with lamotrigine and 3510 Taka with carbamazepine ($p < 0.001$).

Conclusions: Over six months, seizure freedom did not differ significantly between lamotrigine and carbamazepine, but the CIs were wide, and equivalence or noninferiority against a conventional margin cannot be claimed. Fewer adverse events were reported with lamotrigine, whereas the direct drug cost of carbamazepine was about half that of lamotrigine. Drug choice should be individualized, and larger multicenter trials with longer follow-up are needed.

Categories: Therapeutics, Neurology, Pharmacology
Keywords: adverse effects, bangladesh, carbamazepine, drug cost, focal epilepsy, lamotrigine, randomized controlled trial

Introduction

Epilepsy is among the most common serious neurological disorders worldwide. The Global Burden of Disease Study 2021 estimated that more than 50 million people live with the condition and that most of the resulting disability is concentrated in low- and middle-income countries [1]. In the first nationwide household survey in Bangladesh, the prevalence of epilepsy was 8.4 per 1,000 population, 63.4% of people with epilepsy were not receiving treatment, and 72.5% of those who were treated had low adherence [2]. Reviews of epilepsy care in low- and middle-income countries identify affordability and the reliability of drug supply as important obstacles to closing this treatment gap [3-5].

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Focal epilepsy accounts for the majority of newly diagnosed epilepsy in adults, and long-term antiseizure medication remains the foundation of its management [6,7]. Carbamazepine has long served as the reference first-line drug for focal seizures and remains widely prescribed in many low- and middle-income settings, whereas some current guidelines, including the 2022 guideline of the National Institute for Health and Care Excellence, suggest lamotrigine or levetiracetam as first-line monotherapy for focal seizures and place carbamazepine among the second-line options [8,9]. Recommendations differ between guidelines, and the choice for an individual patient also depends on seizure type, comorbidity, sex and reproductive plans, interacting medicines, and expected tolerability [7].

Both drugs act principally by blocking voltage-gated sodium channels, yet they differ in attributes that matter in a resource-constrained health system [10,11]. Carbamazepine requires divided daily dosing, induces hepatic enzymes, interacts with many other medicines, and carries a recognized burden of sedation and cognitive slowing [10]. Its risk of Stevens-Johnson syndrome and toxic epidermal necrolysis is strongly associated with the HLA-B15:02 allele, and HLA-A31:01 is associated with a wider range of hypersensitivity reactions [12,13]. The carrier frequency of HLA-B*15:02 varies considerably between and within Asian populations, so this risk cannot be assumed to be uniform across South Asia [12,13]. Lamotrigine has a longer elimination half-life that permits simpler dosing, produces less sedation, and has shown a longer time to treatment failure than carbamazepine in a large pragmatic trial [9,14,15]. However, lamotrigine costs considerably more than carbamazepine in Bangladesh and is stocked less reliably [4,16]. Where medicines are paid for largely out of pocket, the first drug prescribed is often the only one a patient takes, and poor tolerability or unaffordable cost may lead to discontinuation rather than a switch [3,17,18]. Tolerability and cost therefore need to be weighed together with seizure control.

The comparative evidence for these two drugs comes largely from high-income health systems with free or subsidized medicines, different formulations, and different genetic backgrounds [11,19]. The individual participant data review and the network meta-analysis compared the drugs in terms of time to treatment withdrawal or failure and time to six- or twelve-month remission, and neither reported the visit-based seizure freedom, adverse event burden, or out-of-pocket drug cost that guide prescribing in Bangladesh [11,19]. To our knowledge, no randomized comparison of lamotrigine and carbamazepine has been published from Bangladesh, where published work has mainly described the prevalence and treatment gap of epilepsy [2]. The economic question addressed here is deliberately narrow. A comparison of direct drug expenditure describes what patients pay for the medicine, but it is not a cost-effectiveness analysis and cannot by itself establish which treatment offers better overall value.

We therefore conducted a randomized, open-label trial in adults with focal epilepsy at a tertiary referral hospital in Bangladesh. The primary objective was to compare seizure freedom at six months between lamotrigine and carbamazepine. The secondary objectives were to compare seizure freedom at one and three months, time to first seizure recurrence, status epilepticus, hospital admission, death, adverse events, treatment adherence, and direct drug cost over six months. The sample size was planned for a noninferiority comparison of lamotrigine with carbamazepine as the reference treatment, using a margin of 30% points for seizure freedom at six months. Because this margin is wide, the efficacy comparison is reported as an estimate with its confidence interval (CI) and is interpreted cautiously.

Materials And Methods

Study design and setting

This was a prospective, randomized, open-label, parallel-group trial with 1:1 allocation, conducted in the Department of Neurology at Dhaka Medical College Hospital, a tertiary referral center in Dhaka, Bangladesh. Participants were recruited from the epilepsy clinic, the outpatient department, and the inpatient wards of the departments of neurology and medicine between November 2022 and October 2023. The trial is reported in accordance with the CONSORT 2010 statement and its extension for noninferiority and equivalence trials [20,21].

Participants

Adults older than 18 years of either sex with focal epilepsy who were starting antiseizure monotherapy were eligible. Three groups were included: patients with newly diagnosed focal epilepsy, with or without evolution to bilateral tonic-clonic seizures; patients whose seizures had relapsed after withdrawal of an antiseizure medication; and patients in whom a previous antiseizure medication other than lamotrigine or carbamazepine had failed. The latter two groups were included because they make up a substantial proportion of patients who start one of these two drugs as monotherapy in our clinic, and the trial aimed to reflect that population. Prior treatment status was recorded on the case record form at enrollment; it was not used for stratification, and its balance between groups relied on randomization. Seizure type was classified using the operational criteria of the International League Against Epilepsy, and epilepsy was defined using the practical clinical definition of the same body [22,23]. Patients were excluded if they had generalized or unknown-onset seizures, known hypersensitivity to either study drug, a history of substance abuse, or serious concurrent illness, including cardiovascular disease, hepatic failure, renal failure, or malignancy. Each participant underwent a detailed history, general and neurological examination, and routine investigations, including complete blood count, random blood sugar, serum electrolytes, creatinine,

calcium and magnesium, electroencephalography, and computed tomography or magnetic resonance imaging of the brain.

Randomization and masking

Participants were enrolled consecutively and allocated in a 1:1 ratio by lottery. Allocation was organized in blocks of six participants so that the two groups would be equal in size at the end of every block, and 17 blocks were prepared to cover the planned sample of 100. Within each block, a lottery was drawn for the first, third, and fifth participants, and the second, fourth, and sixth participants each received the drug not allocated to the participant immediately before them. The procedure was then repeated for the next block. Each block therefore contained three participants on each drug, but allocation was effectively balanced in consecutive pairs, so the allocation of every second participant could be anticipated. The lottery was conducted by the investigators at the time of enrollment, and no independent mechanism for allocation concealment, such as sequentially numbered, sealed, opaque envelopes, was used. Because the two regimens differed in dosing frequency and tablet appearance, the trial was open-label, and neither participants nor investigators were masked.

Interventions

Lamotrigine was started at 25 mg once daily for two weeks and increased to 50 mg once daily for the next two weeks. Carbamazepine was started at 100 mg twice daily for two weeks and increased to 200 mg twice daily for the next two weeks. Each participant received the allocated drug as monotherapy. Thereafter, the dose was increased at follow-up until seizures were controlled or adverse effects appeared, to a maximum of 500 mg/day for lamotrigine and 1,600 mg/day for carbamazepine. No fixed increment schedule was prespecified; the size and timing of each dose change were decided by the treating neurologist according to seizure control and tolerability. The prescribed strength and dosage were recorded on the case record form at each visit, but individual doses were not entered in the analysis database, so achieved doses could not be summarized. Participants with continuing seizures or intolerable adverse effects were managed by the treating neurologist, remained in follow-up, and were analyzed in the group to which they had been randomized. Screening, randomization, and the first dose all occurred on day 1, which was taken as baseline.

Outcomes and follow-up

Participants were reviewed at one, three, and six months in the epilepsy clinic or outpatient department, and by telephone when attendance was not possible. Each participant kept a diary recording the date, time, and duration of every seizure, together with any adverse effect.

The primary outcome was seizure freedom at month 6, defined as the absence of any seizure recorded in the seizure diary or reported at the visit during the interval between the month 3 and month 6 visits. Seizure freedom at months 1 and 3 was defined in the same way for the intervals from day 1 to the month 1 visit and from the month 1 visit to the month 3 visit. Seizure freedom at a visit therefore refers to the preceding interval only, and a participant who had a seizure in an earlier interval could be seizure free in a later one. Seizure recurrence was defined as the first seizure of any type after the first dose of the study drug, and continuous freedom from seizure recurrence was defined as the absence of any seizure from day 1 to the month 6 visit. Because seizures were reviewed at scheduled visits, the time to first recurrence was assigned to the visit at which the seizure was first recorded. Status epilepticus was defined according to the criteria of the International League Against Epilepsy, namely, a tonic-clonic seizure lasting five minutes or longer or a focal seizure with impaired awareness lasting 10 minutes or longer [24]. Hospital admission was defined as any inpatient admission for any cause during the preceding interval, and death was defined as death from any cause. The trial registry listed these clinical outcomes without designating a primary outcome. Seizure freedom at month 6 was designated as the primary outcome because the sample size had been calculated for it, using the six-month seizure freedom rate with carbamazepine reported by Nieto Barrera and colleagues [25]. Seizure freedom at months 1 and 3, time to first recurrence, and all other outcomes were secondary outcomes, and their comparisons are regarded as exploratory.

The safety outcome was the occurrence of any of 10 prespecified adverse events, namely, dizziness, fatigue, headache, sedation, nausea, anorexia, ataxia, abdominal pain, diarrhea, and insomnia. At each visit, an event was recorded if it had occurred at any time during the preceding interval, as documented in the diary or elicited by structured questioning. The proportion of participants with an event at a visit is therefore an interval prevalence for that visit, and the cumulative incidence over six months was calculated separately as the proportion of participants who reported at least one event at any visit. The investigator reviewed serious adverse events, discontinuation because of adverse events, laboratory data, and drug hypersensitivity on an ongoing basis. Severity was not graded with a standardized scale, and no formal causality algorithm was applied, so all events were recorded regardless of their presumed relation to the study drug. Nonserious events such as headache, dizziness, nausea, anorexia, and abdominal pain were managed conservatively, and any skin rash was managed by immediate withdrawal of the study drug.

Adherence and direct drug cost

Adherence was assessed at the month 1, month 3, and month 6 visits using the four-item self-reported scale

of Morisky, Green, and Levine [26], which asks whether the patient ever forgets to take the medicine, is careless at times about taking it, stops taking it when feeling better, and stops taking it when feeling that it is not effective. Each "yes" answer scores one point, giving a total score of 0 to 4. The original scale classifies a score of 0 as high adherence, 1 to 2 as medium adherence, and 3 to 4 as low adherence [26]. We classified a score of 0 as good adherence and a score of 1 or more as poor adherence. This merges the medium and low categories of the original scale and is therefore a strict definition of good adherence.

Direct drug cost was defined as the cost of the study drug alone over six months, from the patient perspective, because patients in Bangladesh usually buy antiseizure medicines from retail pharmacies at their own expense. For each participant, the cost was calculated by the investigators using the strength and dosage of the study drug prescribed at each visit, as recorded on the case record form, and the local retail price. These costs were summed over six months and expressed in Bangladeshi taka. Consultation, investigation, travel, hospital, and productivity costs were not included, so this outcome describes drug expenditure and is not a cost-effectiveness analysis.

Sample size calculation

The sample size was calculated for a noninferiority comparison of lamotrigine (test treatment) with carbamazepine (reference treatment) in terms of seizure freedom at 6 months. The sample size for two independent proportions was estimated using the following formula:

\(n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^{2} \times \left[p_{1}\left(1-p_{1}\right) + p_{2}\left(1-p_{2}\right)\right]}{\left(p_{2} - p_{1} + \delta\right)^{2}}\)

where (p1) represents the expected proportion of seizure freedom in the reference group, (p2) represents the expected proportion in the test group, and (δ) represents the prespecified noninferiority margin [27]. Based on a previous randomized comparison of lamotrigine and carbamazepine among patients with newly diagnosed partial epilepsy, the six-month seizure-freedom rate with carbamazepine was 73% [25]. Therefore, the expected proportions were assumed to be equal in both groups, with (p1 = 0.73) and (p2 = 0.73). Considering a two-sided significance level of 5% ($\left(Z_{1-\alpha/2} = 1.96\right)$), 80% power ($\left(Z_{1-\beta} = 0.84\right)$), and a noninferiority margin of 0.30, the required sample size was calculated as follows:

$$n = \frac{(1.96 + 0.84)^2 \times [(0.73)(1 - 0.73) + (0.73)(1 - 0.73)]}{(0.73 - 0.73 + 0.30)^2}$$

$$n = \frac{(1.96 + 0.84)^2 \times (0.1971 + 0.1971)}{0.30^2} = 34.34$$

Thus, the minimum required sample size was approximately 35 participants in each group. To compensate for possible loss to follow-up and participant withdrawal, the final sample size was increased to 50 participants per group, resulting in a total sample size of 100 participants. The noninferiority margin of 30% points was prespecified in the study protocol as the maximum allowable difference between the two treatments. However, this margin was selected by the investigators without formal derivation from previous randomized trials, as generally recommended for noninferiority studies [21]. Because the selected margin was relatively wide, the noninferiority findings were interpreted cautiously. Accordingly, noninferiority was assessed using the prespecified margin, while the between-group treatment effect and its 95% CI were given particular importance in the interpretation of efficacy.

Participant flow and analyzed population

The flow of participants is shown in Figure *1*. One hundred adults with focal epilepsy were randomized, 50 to lamotrigine and 50 to carbamazepine, and all received the allocated drug. Two participants allocated to lamotrigine and two allocated to carbamazepine were lost to follow-up after randomization and provided no seizure outcome data. One further participant allocated to carbamazepine withdrew after two doses because of a generalized rash with itching. The rash resolved after the drug was stopped and hydrocortisone, an antihistamine, intravenous fluids, and oxygen were administered. The participant was subsequently switched to levetiracetam. Ninety-five participants, 48 in the lamotrigine group and 47 in the carbamazepine group, were followed through the month 6 assessment and formed the per-protocol population.

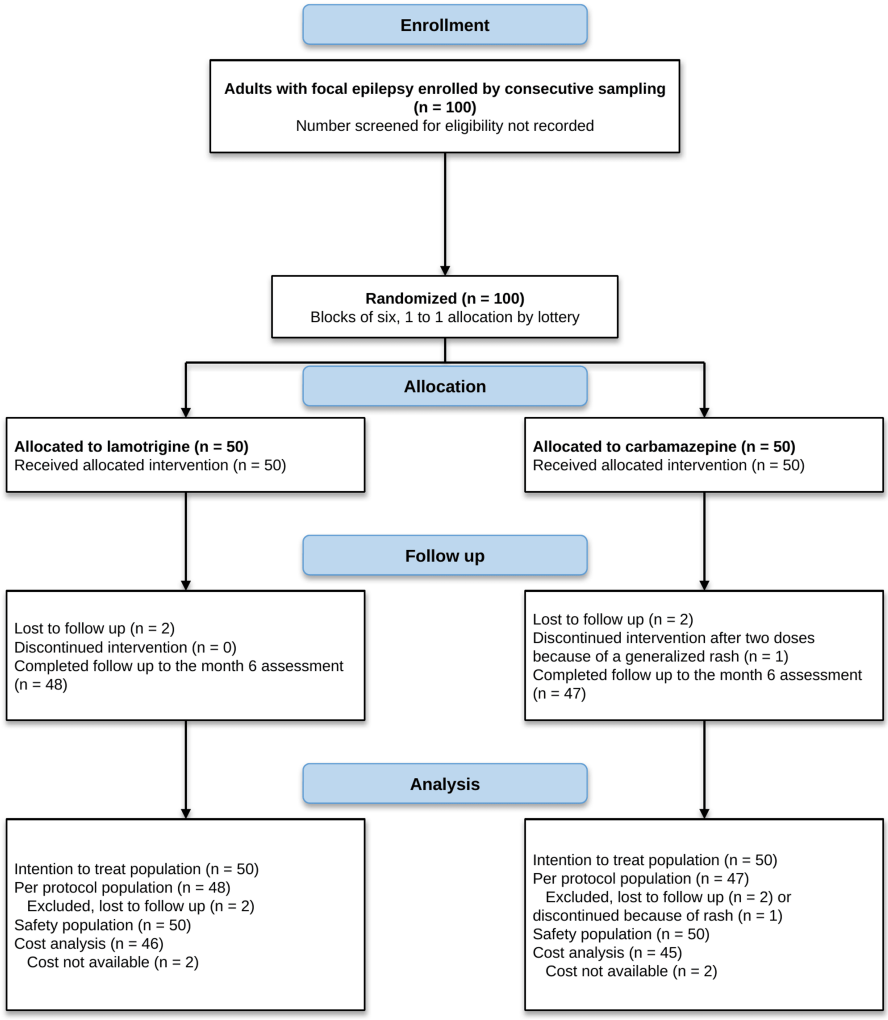


FIGURE 1: CONSORT flow diagram showing enrollment, allocation, follow-up, and the trial analysis populations

Statistical analysis

Data were analyzed with SPSS version 26 (IBM Corporation, Armonk, NY, USA), and Python version 3.10 was used to calculate risk differences, the Hodges-Lehmann estimate, and the grouped-time survival model. Seizure freedom was analyzed in two populations. The intention-to-treat population included all 100 randomized participants, with missing outcomes counted as treatment failures, and the second population included the 95 participants who completed follow-up through month 6. All other outcomes were analyzed among these 95 participants, and adverse events were also reported for all participants who took at least one dose. Age was expressed as mean ± standard deviation and compared using the independent-samples t-test. Skewed variables, namely baseline seizure frequency and drug cost, were expressed as medians with interquartile ranges and compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. Risk differences with Newcombe 95% CIs and risk ratios were calculated. Noninferiority was to be concluded if the lower confidence limit for seizure freedom at month 6 exceeded -30% points. Time to first recurrence was analyzed using the Kaplan-Meier method and the log-rank test, and a grouped-time model was used to account for interval censoring. Zero drug costs were treated as missing. No adjustment was made for multiple comparisons, and $p < 0.05$ was considered statistically significant.

Ethical consideration

The study protocol was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh (approval number ERC-DMC/ECC/2022/330). The trial was registered at ClinicalTrials.gov (NCT05748236) after enrollment had begun and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from every participant or a legal attendant before enrollment.

Results

Baseline characteristics of the per-protocol population are shown in Table 1. The mean age was 31.10±10.51 years in the lamotrigine group and 32.94±10.56 years in the carbamazepine group (median 29.5 and 29.0 years, Mann-Whitney p = 0.335), and most participants in both groups were aged 18 to 30 years (27 (56.2%) and 27 (57.4%)). Males accounted for 29 (60.4%) and 27 (57.4%) of the two groups, respectively, and 31 (64.6%) and 27 (57.4%) came from rural areas. Focal to bilateral tonic-clonic seizure was the predominant seizure type (26 (54.2%) and 23 (48.9%)), and the median baseline seizure frequency was 4 per month in each group. The groups were descriptively similar in most characteristics. Small differences were seen in the proportion of day laborers (8 (16.7%) and 2 (4.3%)) and in smoking status, which we did not consider likely to influence seizure outcomes.

Variables	Lamotrigine (n = 48), n (%)	Carbamazepine (n = 47), n (%)	p-value
Age (years)			
Mean ± SD	31.10 ± 10.51	32.94 ± 10.56	0.399[a]
Age group (years)			
18-30	27 (56.2)	27 (57.4)	
31-40	11 (22.9)	11 (23.4)	1.000[c]
41-50	7 (14.6)	6 (12.8)	
≥51	3 (6.2)	3 (6.4)	
Sex			
Male	29 (60.4)	27 (57.4)	0.769[b]
Female	19 (39.6)	20 (42.6)	
Residence			
Rural	31 (64.6)	27 (57.4)	0.476[b]
Urban	17 (35.4)	20 (42.6)	
Education level			
Illiterate	8 (16.7)	8 (17.0)	
Primary	22 (45.8)	16 (34.0)	0.794[c]
Secondary	11 (22.9)	14 (29.8)	
Higher secondary	5 (10.4)	7 (14.9)	
Graduate and above	2 (4.2)	2 (4.3)	
Occupation			
Student	11 (22.9)	13 (27.7)	
Homemaker	12 (25.0)	12 (25.5)	
Service holder	6 (12.5)	5 (10.6)	0.466[c]
Business	2 (4.2)	4 (8.5)	
Day laborer or rickshaw puller	8 (16.7)	2 (4.3)	
Unemployed	9 (18.8)	11 (23.4)	
Smoking			
Non-smoker	33 (68.8)	32 (68.1)	0.188[b]
Current smoker	10 (20.8)	5 (10.6)	
Ex-smoker	5 (10.4)	10 (21.3)	
Comorbidity			

Hypertension	7 (14.6)	7 (14.9)	0.966[b]
Diabetes mellitus	5 (10.4)	6 (12.8)	0.720[b]
Bronchial asthma	0 (0.0)	1 (2.1)	0.495[c]
Dyslipidemia	2 (4.2)	1 (2.1)	1.000[c]
Hypothyroidism	1 (2.1)	2 (4.3)	0.617[c]
Family history of epilepsy			
Yes	5 (10.4)	3 (6.4)	0.714[c]
No	43 (89.6)	44 (93.6)	
History of febrile seizure			
Yes	6 (12.5)	8 (17.0)	0.534[b]
No	42 (87.5)	39 (83.0)	
History of past illness			
Head injury	4 (8.3)	2 (4.3)	0.677[c]
Meningitis	1 (2.1)	1 (2.1)	1.000[c]
Encephalitis	3 (6.2)	3 (6.4)	1.000[c]
Stroke	3 (6.2)	5 (10.6)	0.486[c]
Central nervous system tuberculosis	0 (0.0)	1 (2.1)	0.495[c]
Seizure type			
Focal aware seizure	5 (10.4)	4 (8.5)	0.789[c]
Focal impaired awareness seizure	17 (35.4)	20 (42.6)	
Focal to bilateral tonic-clonic seizure	26 (54.2)	23 (48.9)	
Aura			
Yes	14 (29.2)	10 (21.3)	0.376[b]
No	34 (70.8)	37 (78.7)	
Automatism			
Yes	4 (8.3)	4 (8.5)	1.000[c]
No	44 (91.7)	43 (91.5)	
Baseline seizure frequency (per month)			
Median (IQR)	4 (3 to 6)	4 (3 to 6)	0.715[d]

TABLE 1: General characteristics of participants who completed follow-up

[a]t-test; [b]chi-square test; [c]Fisher's exact test, used when any expected count was below five; [d]Mann-Whitney U test.

p-values are descriptive only.

SD, standard deviation; IQR, interquartile range

Seizure control is presented in Table 2. Among participants who completed follow-up, seizure freedom during the first month was achieved by 28 (58.3%) participants on lamotrigine and 30 (63.8%) on carbamazepine (risk difference -5.5% points, 95% CI -24.1 to 13.7), during months 2 and 3 by 31 (64.6%) and 32 (68.1%) participants (-3.5, 95% CI -21.7 to 15.1), and during months 4 to 6, the primary outcome, by 33 (68.8%) and 35 (74.5%) participants (-5.7, 95% CI -23.2 to 12.3; risk ratio 0.92, 95% CI 0.72 to 1.19; p = 0.537).

In the intention-to-treat population, seizure freedom at month 6 was achieved by 33 of 50 (66.0%) and 35 of 50 (70.0%) participants (-4.0, 95% CI -21.6 to 14.0; p = 0.668), and the results at months 1 and 3 were similar.

Variables	Lamotrigine, n (%)	Carbamazepine, n (%)	Risk difference, percentage points (95% CI)	Risk ratio (95% CI)	p-value
Seizure freedom, participants who completed follow-up (lamotrigine, n = 48; carbamazepine, n = 47)					
Month 1 (day 1 to month 1)	28 (58.3)	30 (63.8)	-5.5 (-24.1 to 13.7)	0.91 (0.66 to 1.26)	0.583[b]
Month 3 (month 1 to month 3)	31 (64.6)	32 (68.1)	-3.5 (-21.7 to 15.1)	0.95 (0.71 to 1.26)	0.718[b]
Month 6 (month 3 to month 6), primary outcome	33 (68.8)	35 (74.5)	-5.7 (-23.2 to 12.3)	0.92 (0.72 to 1.19)	0.537[b]
Seizure freedom, intention-to-treat population (n = 50 per group)[a]					
Month 1	28 (56.0)	30 (60.0)	-4.0 (-22.5 to 14.9)	0.93 (0.67 to 1.30)	0.685[b]
Month 3	31 (62.0)	32 (64.0)	-2.0 (-20.2 to 16.4)	0.97 (0.72 to 1.31)	0.836[b]
Month 6, primary outcome	33 (66.0)	35 (70.0)	-4.0 (-21.6 to 14.0)	0.94 (0.72 to 1.23)	0.668[b]
Continuous freedom from seizure recurrence, participants who completed follow-up					
Day 1 to month 6[c]	24 (50.0)	26 (55.3)	-5.3 (-24.3 to 14.3)	HR 1.14 (0.63 to 2.04)[d]	0.597[e]

TABLE 2: Seizure control during six months of follow-up among participants who completed follow-up and in the intention-to-treat population

Risk difference is lamotrigine minus carbamazepine.

[a]Missing outcomes were counted as not seizure-free; [b]Chi-square test; [c]Kaplan-Meier estimate; [d]Based on observed and expected events; [e]Log-rank test.

CI, confidence interval; HR, hazard ratio

The Kaplan-Meier curves for time to first seizure recurrence are shown in Figure *2*. Among participants who completed follow-up, recurrence was first recorded at the month 1 visit in 20 participants on lamotrigine and 17 on carbamazepine, and at the month 3 visit in four participants in each group, giving 24 events among 48 participants and 21 among 47; no first recurrence was recorded at the month 6 visit. The numbers remaining at risk after the month 1 and month 3 visits were 28 and 24 with lamotrigine and 30 and 26 with carbamazepine, and these 24 and 26 participants were censored at month 6. Continuous freedom from recurrence through six months was therefore 24 (50.0%) with lamotrigine and 26 (55.3%) with carbamazepine (HR 1.14, 95% CI 0.63 to 2.04, log-rank p = 0.597).

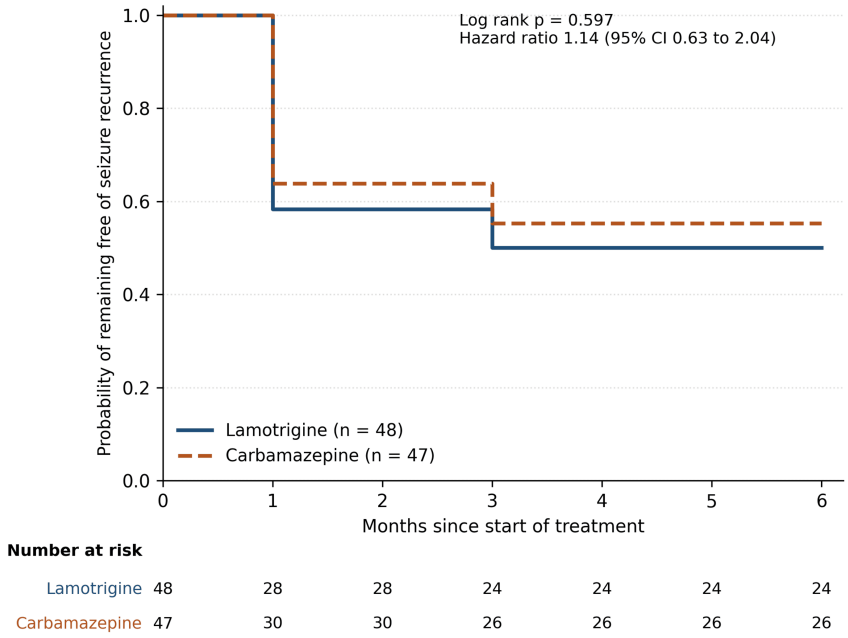


FIGURE 2: Kaplan-Meier curves for time to first documented seizure recurrence among participants receiving lamotrigine or carbamazepine. Recurrence was assigned to the scheduled visit at which it was first recorded, and participants without recurrence were censored at six months

The numbers below the horizontal axis indicate the number of participants remaining at risk.

Status epilepticus, hospital admission, and death are presented in Table 3. Over six months, status epilepticus occurred in 1 (2.1%) participant on lamotrigine and 3 (6.4%) on carbamazepine (p = 0.362). All episodes began in the first month, and one participant on carbamazepine had status epilepticus in each of the three intervals and is therefore counted at every visit in Table 3. Hospital admission was needed by 2 (4.2%) and 3 (6.4%) participants, respectively (p = 0.677). Both admissions in the lamotrigine group occurred in the first month, whereas on carbamazepine, two participants were admitted in both the first and second intervals and a third participant in both the first and third intervals. Two participants on carbamazepine died (2 (4.3%) versus none, p = 0.242; p = 0.495 in the safety population of 50 per group), and both had been admitted to hospital in the first and second intervals.

Variables	Lamotrigine (n = 48), n (%)	Carbamazepine (n = 47), n (%)	p-value
Status epilepticus			
Month 1	1 (2.1)	3 (6.4)	0.362
Month 3	0 (0.0)	1 (2.1)	0.495
Month 6	0 (0.0)	1 (2.1)	0.495
Any episode during six months[a]	1 (2.1)	3 (6.4)	0.362
Hospital admission			
Month 1	2 (4.2)	3 (6.4)	0.677
Month 3	0 (0.0)	2 (4.3)	0.237
Month 6	0 (0.0)	1 (2.1)	0.495
Any admission during six months[a]	2 (4.2)	3 (6.4)	0.677
All-cause mortality			
During six months, participants who completed follow-up	0 (0.0)	2 (4.3)	0.242
During six months, safety population (n = 50 per group)	0 (0.0)	2 (4.0)	0.495

TABLE 3: Status epilepticus, hospital admissions, and mortality during six months of follow-up

Participants with an event during the interval ending at each visit; The small number of events does not allow equivalence in safety to be inferred.

[a]Any event during follow-up; all comparisons were performed using Fisher's exact test.

Adverse events are presented in Table 4. Each visit-specific figure is the proportion of participants who reported an event during the preceding interval. At least one adverse event was reported by 17 (35.4%) participants on lamotrigine and 33 (70.2%) on carbamazepine during the first month (risk difference -34.8% points, 95% CI -51.2 to -14.8), by 10 (20.8%) and 28 (59.6%) during months 2 and 3, and by 6 (12.5%) and 23 (48.9%) during months 4 to 6 (all $p < 0.001$). Every participant who reported an event at month 3 or month 6 had also reported one at month 1, so the cumulative incidence over six months was the same as at month 1, 17 (35.4%) versus 33 (70.2%). Sedation (2 (4.2%) vs. 10 (21.3%) at month 1, $p = 0.012$; 0 vs. 9 (19.1%) at month 3, $p = 0.001$; 0 vs. 7 (14.9%) at month 6, $p = 0.006$) and fatigue at month 1 (3 (6.2%) vs. 10 (21.3%), $p = 0.033$) differed between the groups. The remaining events were infrequent and did not differ significantly, and none of these comparisons were adjusted for multiplicity. In the safety population, which also includes the five participants without follow-up after the first month, at least one adverse event in the first month was reported by 17 of 50 (34.0%) participants on lamotrigine and 36 of 50 (72.0%) on carbamazepine ($p < 0.001$).

Variables	Lamotrigine (n = 48), n (%)	Carbamazepine (n = 47), n (%)	p-value
Any adverse event			
Month 1	17 (35.4)	33 (70.2)	<0.001*[b]
Month 3	10 (20.8)	28 (59.6)	<0.001*[b]
Month 6	6 (12.5)	23 (48.9)	<0.001*[b]
Any visit, cumulative incidence[a]	17 (35.4)	33 (70.2)	<0.001*[b]
Sedation			
Month 1	2 (4.2)	10 (21.3)	0.012*[b]
Month 3	0 (0.0)	9 (19.1)	0.001*[c]
Month 6	0 (0.0)	7 (14.9)	0.006*[c]

Fatigue			
Month 1	3 (6.2)	10 (21.3)	0.033*[b]
Month 3	3 (6.2)	9 (19.1)	0.058[b]
Month 6	2 (4.2)	7 (14.9)	0.091[c]
Dizziness			
Month 1	5 (10.4)	10 (21.3)	0.147[b]
Month 3	4 (8.3)	8 (17.0)	0.203[b]
Month 6	3 (6.2)	7 (14.9)	0.199[c]
Nausea			
Month 1	4 (8.3)	7 (14.9)	0.318[b]
Month 3	4 (8.3)	7 (14.9)	0.318[b]
Month 6	1 (2.1)	4 (8.5)	0.204[c]
Headache			
Month 1	2 (4.2)	3 (6.4)	0.677[c]
Month 3	1 (2.1)	2 (4.3)	0.617[c]
Month 6	0 (0.0)	2 (4.3)	0.242[c]
Anorexia			
Month 1	4 (8.3)	2 (4.3)	0.677[c]
Month 3	2 (4.2)	1 (2.1)	1.000[c]
Month 6	1 (2.1)	0 (0.0)	1.000[c]
Ataxia			
Month 1	1 (2.1)	3 (6.4)	0.362[c]
Month 3	0 (0.0)	1 (2.1)	0.495[c]
Month 6	0 (0.0)	0 (0.0)	NA
Abdominal pain			
Month 1	1 (2.1)	3 (6.4)	0.362[c]
Month 3	0 (0.0)	1 (2.1)	0.495[c]
Month 6	0 (0.0)	0 (0.0)	NA
Diarrhea			
Month 1	2 (4.2)	2 (4.3)	1.000[c]
Month 3	1 (2.1)	2 (4.3)	0.617[c]
Month 6	0 (0.0)	0 (0.0)	NA
Insomnia			
Month 1	1 (2.1)	0 (0.0)	1.000[c]
Month 3	0 (0.0)	0 (0.0)	NA
Month 6	0 (0.0)	0 (0.0)	NA
Adverse event leading to discontinuation, safety population (n = 50 per group)			

During six months	0 (0.0)	1 (2.0)	1.000[c]

TABLE 4: Adverse events during six months of follow-up

Participants reporting the event during the interval ending at each visit (interval prevalence). Comparisons of individual events are exploratory and unadjusted. The last row includes all 100 participants who took at least one dose.

[a]Any event at any visit; [b]Chi-square test; [c]Fisher's exact test. *p < 0.05. NA, no event in either group.

Adherence and direct drug costs are presented in Table 5. Adherence was assessed in all 48 participants on lamotrigine and all 47 on carbamazepine at each of the three visits, so the same participants contributed at every visit. Good adherence was reported by 45 (93.8%) and 46 (97.9%) participants at month 1, 43 (89.6%) and 43 (91.5%) at month 3, and 41 (85.4%) and 40 (85.1%) at month 6, with no significant difference at any visit. Cost data were available for 46 participants on lamotrigine and 45 on carbamazepine. The median direct drug cost over six months was 6480 taka (IQR 6480 to 9720) with lamotrigine and 3510 taka (IQR 3067 to 5040) with carbamazepine (p < 0.001). The Hodges-Lehmann estimate of the difference was 3413 taka (95% CI 2970 to 4680), whereas the simple difference between the two medians was 2970 taka. The direct drug cost of lamotrigine was therefore close to twice that of carbamazepine.

Variables	Lamotrigine (n = 48), n (%)	Carbamazepine (n = 47), n (%)	p-value
Adherence at month 1			
Good	45 (93.8)	46 (97.9)	0.617[c]
Poor	3 (6.2)	1 (2.1)	
Adherence at month 3			
Good	43 (89.6)	43 (91.5)	1.000[c]
Poor	5 (10.4)	4 (8.5)	
Adherence at month 6			
Good	41 (85.4)	40 (85.1)	0.966[b]
Poor	7 (14.6)	7 (14.9)	
Direct drug cost over six months (Taka)			
Participants with cost data, n	46	45	
Median (IQR)	6480 (6480 to 9720)	3510 (3067 to 5040)	<0.001*[d]
Difference, Hodges-Lehmann estimate (95% CI)	3413 (2970 to 4680)		

TABLE 5: Treatment adherence and direct drug costs

Adherence was assessed in all participants at every visit, and good adherence is [a]Morisky score of 0. [b]Chi-square test; [c]Fisher's exact test; [d]Mann-Whitney U test. *p < 0.05.

Zero costs (two per group) were treated as missing. The difference is the Hodges-Lehmann estimate.

IQR, interquartile range; CI, confidence interval

Discussion

In this randomized, open-label trial in adults with focal epilepsy, seizure freedom over six months did not differ significantly between lamotrigine and carbamazepine, fewer adverse events were reported with lamotrigine, and the direct drug cost of carbamazepine was about half that of lamotrigine. The observed differences in seizure freedom were small, at most 6% points, but the CIs were wide and were compatible with anything from a loss of about 23% points to a gain of about 14% points with lamotrigine. Although the prespecified margin of 30% points was formally met, this margin is permissive, and the results do not establish therapeutic equivalence or noninferiority by conventional standards.

Our efficacy findings are broadly consistent with earlier evidence, although the endpoints differ. The individual participant data review found no clear difference between the two drugs in time to six- or 12-month remission, while lamotrigine was associated with a longer time to treatment withdrawal [11]. The network meta-analysis placed both drugs close together for treatment failure and remission in focal epilepsy [19], and the SANAD trial found lamotrigine better than carbamazepine for time to treatment failure and noninferior for time to 12-month remission [14]. A community-based comparison of generic carbamazepine, lamotrigine, and levetiracetam over 24 months reported comparable effectiveness [28], as did a real-world cohort of newly diagnosed focal epilepsy [29]. These endpoints describe remission, treatment failure, and retention over one or more years, and they are related to, but not interchangeable with, the visit-based seizure freedom over six months reported here. Our seizure freedom proportions were higher than those of some Western cohorts. Possible explanations include the short follow-up, the interval-based definition of seizure freedom, and the exclusion of participants without follow-up from the main analysis, but our data cannot establish the reason.

Tolerability differed more clearly. Sedation and fatigue were the events that separated the groups, and both are consistent with the pharmacology of carbamazepine and with the sedative and cognitive burden described in reviews of antiseizure medication adverse effects [10]. The size of the difference should nevertheless be interpreted with caution. Adverse events were self-reported in an open-label trial without standardized severity grading or blinded assessment, so reporting bias cannot be excluded, and differences in titration speed and in the dose reached relative to the usual range of each drug may have contributed. The decline in adverse events over time in both groups suggests dose-related and partly transient effects, yet the burden with carbamazepine remained substantial at six months. One participant receiving carbamazepine developed a generalized rash after two doses, but this single event cannot establish a difference between the drugs in the incidence of serious cutaneous reactions. That question rests on the broader pharmacogenetic evidence, which links carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis to HLA-B*15:02, an allele whose frequency varies across Asian populations, and which supports pretreatment genotyping where it is available and affordable [12,13].

Cost pointed the other way. The direct drug cost over six months was close to twice as high with lamotrigine, a difference of about 3,400 taka that must usually be met from household income in a health system dominated by out-of-pocket payment. Analyses across Asia have shown that newer antiseizure medicines are unaffordable for a large share of patients in the region, and studies from comparable settings have found affordability and supply to be stronger predictors of adherence than patient beliefs [4,17,30]. Our cost analysis was, however, limited to the price of the study drug. It excluded consultations, laboratory monitoring, management of adverse events, hospital care, travel, productivity losses, and later treatment switching, so it cannot show which drug is economically preferable overall. Self-reported adherence was high and similar in both groups, but participants were followed in a structured trial setting with counseling, and self-report may overestimate actual medication use. The trial therefore cannot show whether the higher cost of lamotrigine affects adherence under routine care.

Taken together, these findings support individualized treatment selection rather than a single preferred drug. In addition to tolerability and affordability, the choice should take account of seizure type, comorbidities, interacting medicines, reproductive considerations, hypersensitivity risk, and the feasibility of dose titration and monitoring [7]. At the level of health services, reducing the epilepsy treatment gap is likely to require affordable access to a range of appropriate antiseizure medicines, continuity of supply, counseling, pharmacovigilance, and individualized prescribing, rather than better access to any single drug [3,5].

This trial has several limitations. Follow-up lasted only six months, which is shorter than the 12-month remission window used in most monotherapy comparisons and too short to capture long-term retention, delayed adverse effects, or the premature mortality that is well documented in epilepsy. The trial was open-label, single-center, and small, so the findings may not transfer to primary care or community settings, and the trial cannot reliably detect differences in rare serious adverse events, mortality, long-term remission, or treatment retention. Allocation within each block was, in effect, balanced in consecutive pairs and was not concealed by an independent mechanism, so the allocation of every second participant could be anticipated, which may have introduced selection bias. The trial was registered after enrollment had begun, the number of patients screened was not recorded, and duration of epilepsy, prior treatment category, previous status epilepticus, and previous hospital admission were recorded on the case record form but not entered in the analysis database, so baseline comparability for these variables could not be shown. The causes of the two deaths were not documented. The noninferiority margin of 30% points was not derived from earlier trials and is permissive, so noninferiority by conventional standards could not be established. Five randomized participants without follow-up data were excluded from the main analysis. The intention-to-treat analysis, which counted them as treatment failures, gave similar results, but the handling of missing data can influence a noninferiority comparison. Recurrence was detected only at scheduled visits, so event times were interval-censored, although a model that accounts for this gave a similar estimate. Titration followed clinical judgment; achieved doses were not compared, and plasma drug concentrations were not measured, so the comparison reflects usual practice rather than matched exposure. Adverse events were self-reported without a validated tolerability instrument, severity grading, or blinded assessment, and no adjustment was made for multiple comparisons. Finally, the economic outcome covered only the price of the study drug and

excluded other direct and indirect costs, and switching or discontinuation beyond six months was not recorded.

Conclusions

In adults with focal epilepsy in Bangladesh, seizure freedom over six months did not differ significantly between lamotrigine and carbamazepine. The CIs were wide, and although the prespecified margin was met, the trial does not establish equivalence or noninferiority by conventional standards. At each visit, a smaller proportion of participants reported at least one adverse event with lamotrigine, mainly because of less sedation and fatigue, whereas the direct cost of the study drug over six months was about half as much with carbamazepine. This cost comparison does not establish the overall cost-effectiveness of either drug, and this small, single-center trial cannot establish differences in rare serious adverse events or mortality. Treatment choice should therefore be individualized. Larger multicenter trials with longer follow-up, a clinically justified noninferiority margin, a prespecified primary endpoint, intention-to-treat and completer analyses, standardized safety assessments, and a comprehensive economic evaluation are needed.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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