ORIGINAL RESEARCH ARTICLE

Effectiveness at 24 Months of Single-Source Generic Carbamazepine, Lamotrigine, or Levetiracetam in Newly Diagnosed Focal Epilepsy

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ABSTRACT

Background: Kaiser Permanente advocates using single-source generics for brand-name drugs. We compared the effectiveness of 3 different-generation generic antiepileptic drugs (AEDs) in patients with focal epilepsies.

Objective: To compare the effectiveness of the 3 most commonly used AEDs (carbamazepine [CBZ], lamotrigine [LTG], and levetiracetam [LEV]) after 24-month monotherapy.

Methods: This is a retrospective data analysis of 646 consecutive AED-naive patients aged 1-88 years treated with CBZ, LTG, or LEV between 2006 and 2012 with dosing adjustments permitted during the first 6 months. Chi-squared test with $p < 0.05$ was used to calculate seizure-freedom and tolerability rates.

Results: At the end of the 24-month study period, 65.69% patients in the CBZ group continued to remain seizure free, 25.98% were drug failures, and 8.33% dropped out due to adverse events, with the corresponding numbers being 66.49%, 23.94%, and 9.57% in the LTG group and 72.44%, 12.99%, and 14.57% in the LEV group. Rash was the most common adverse event for CBZ (3.43%) and LTG (6.38%), and mood changes were the most commen adverse event for LEV (7.87%). Among the 3 groups ($n = 646$), AED tolerance rates and AED retention rates showed no significant difference ($p = 0.08$ and $p = 0.23$, respectively). Seizure-freedom rate difference among the 3 groups ($n = 574$) was significant ($p = 0.003$), and seizure-freedom rate for LEV was superior to CBZ ($p = 0.001$) and to LTG ($p = 0.006$).

Conclusion: At the end of the 24-month study period, in a head-to-head comparison of single-source bioequivalent generic formulations, superior seizure-freedom rate and comparable tolerability and retention rates for LEV were observed when compared with CBZ and LTG.

INTRODUCTION

Kaiser Permanente promotes the use of single-source bioequivalent generics for brand-name drugs throughout its health care programs. The Food and Drug Administration (FDA) holds generic drugs to the same strict standards they use for brand-name medications, and the FDA testing processes assure that the generics work as well as the brand-name medications. Using generic drugs helps Kaiser Permanente provide quality health care at affordable prices. There had been a concern that generic drugs with narrow therapeutic index, which include antiepileptic drugs (AEDs), might not work as well as the original brand-name product. A systemic review and metaanalysis of generic versus brand-name AEDs in 2010 showed little evidence-based rationale to challenge the implementation of generic substitution for AEDs.[1,2] Carbamazepine was originally approved by the FDA on March 11, 1968. The FDA has approved therapeutic equivalents produced by 5 different manufacturers. Lamotrigine was originally approved by the FDA on December 27, 1994. The FDA has now approved therapeutic equivalents produced by 13 different manufacturers. Levetiracetam was originally approved by the FDA on November 30, 1999. The FDA has now approved therapeutic equivalents produced by 21 different manufacturers.

Prior to the approval of many second-generation AEDs in the 1990s, carbamazepine (CBZ) was the preferred AED for focal epilepsy. Among the second-generation AEDs, lamotrigine (LTG) and levetiracetam (LEV) have broad-spectrum mechanisms of action and therefore have been used as initial monotherapies for focal and generalized epilepsies. The SANAD trial concluded that LTG was the drug of first choice for focal epilepsy.[3] The LaLiMo trial found no significant difference regarding efficacy of LTG and LEV in the management of newly diagnosed focal and generalized epilepsy.[4]

Epilepsy is a chronic condition that negatively affects a person's social, psychological, and neurocognitive status, and the side effects of AEDs can worsen them. It is therefore imperative to try to minimize adverse effects of AEDs while pursuing the goal of seizure freedom. Approximately 50% of patients fail their first AED monotherapy due to either inadequate seizure control or poor tolerability.[5] In randomized controlled trials (RCTs), new AEDs are introduced as an add-on pharmacotherapy in patients with drug-resistant epilepsy, with relatively short-term treatment evaluation (usually < 4 months). Head-to-head long-term comparison trials for the newer AEDs used as initial monotherapy for focal epilepsy are rare.[6]

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American Epilepsy Society concluded that newer-generation AEDs were equivalent in seizure control, and a few may have favorable adverse effect profiles and minimal pharmacokinetic interactions when compared with the first-generation AEDS.[7]

Retention rate (effectiveness) of an AED is a composite measure that is quantified as the percentage of patients who, after starting an AED, continued taking it for a given period while maintaining seizure freedom (efficacy) and tolerability.[8]

Our study compares effectiveness (seizure-freedom rate and tolerability rate) among generic formulations of 3 most commonly used different-generation antiepilepsy medications (CBZ, LTG, and LEV) after a 24-month study period after initiating AED as a monotherapy for the treatment of AED-naive patients with newly diagnosed focal epilepsy.

METHODS

This was a longitudinal cohort retrospective data analysis study of 646 consecutive patients aged 1-88 years in whom diagnosis of new-onset focal epilepsy with and without impaired awareness and with and without progression to convulsive seizures was established and in whom treatment with CBZ, LTG, or LEV was initiated. This retrospective study of existing medical record data was reviewed and approved by the Kaiser Permanente Southern California (KPSC) Institutional Review Board. Patients were treated at the KPSC Epilepsy Center in Orange County, California, between January 2006 and December 2012. All patients were managed by the epileptologists for a minimum of 24 months. Most patients were referred by primary care providers, and the remainder were referred from urgent care or emergency department or following their discharge from the hospital. AED-naive patients who were on AED other than CBZ, LTG, or LEV for more than 30 days prior to being switched to any of the 3 study AEDs were not included in the study. All data, including demographic and clinical, was collected from a review of Kaiser Permanente electronic medical records. Scalp EEG results were studied to delineate focal interictal epileptiform discharges that might support the diagnosis and classification of the epilepsy. Results of magnetic resonace imaging and/or computed tomography of the brain were reviewed to rule out medical diagnoses that may interfere with the outcome of epilepsy treatment and to investigate for underlying neuro-structural abnormalities that might contribute to the generation of seizures. Patients with a history of substance abuse, alcohol abuse, noncompliance with epilepsy medication regimen, nonepileptic seizures, severe psychiatric disorders, progressive neurological disorders, and other serious medical conditions that may interfere with the outcome of treatment of epilepsy were excluded from the study.

Epilepsy was diagnosed if there was a history of 2 unprovoked seizures with stereotypic focal semiology or of a single focal seizure with focal abnormality noted on EEG or if there was clinical history or neuroimaging studies that suggest increased risk of seizure recurrence without intervention with AEDs after the first seizure. To allow for a slow titration rate needed to minimize the risk of life-threatening events such as Stevens Johnson syndrome and toxic epidermal necrolysis during LTG therapy initiation, AED dosing regimen adjustments were permitted during the first 6 months, during which AED was incrementally increased to achieve seizure freedom with tolerable side effects. These patients were treated with the original AED monotherapy for at least 24 months as measured from day 1 of treatment unless the drug failed to control the seizures or caused unacceptable side effects.

Chi-squared test with p value at < 0.05 was used to calculate effectiveness, efficacy, and tolerability of the AED regimen with CBZ, LTG, and LEV.

RESULTS

A total of 646 AED-naive patients with newly diagnosed focal epilepsy who fulfilled the inclusion criteria were identified during the study period, of which 328 (50.77%) were male. Baseline data characteristics of the patients are described in Table 1.

A total of 204 patients were started on CBZ, 188 on LTG, and 254 on LEV. Adverse events in 72 (11.15%) patients necessitated discontinuation of AED during the next 24-month period, of which 17 (8.33%) were in the CBZ group, 18 (9.57%) in the LTG group, and 37 (14.57%) in the LEV group. Rash was the most common adverse event in 7 (3.43%) patients in the CBZ group and in 12 (6.38%) patients in the LTG group. In the LEV group, mood change was the most prominent adverse event and was reported in 20 (7.87%) patients, including 10 patients with mood swings, 7 with aggressive behavior, and 3 with anxiety (Table 1). Comparison of AED dropout rates among the 3 groups showed no significant difference at $p < 0.05$ ($p = 0.13$). There were no reported fatalities or hospital admissions due to adverse events during the study. Groupwise AED adverse event rates are described in Table 2.

The remaining 574 patients (187 in the CBZ group, 170 in the LTG group, and 217 in the LEV group) continued the original AED regimen with seizure freedom (AED efficacy) at 24 months maintained in 443 (77.18%), with individual AED group efficacy rates being 134 (71.66%) for CBZ, 125 (73.53%) for LTG, and 184 (84.79%) for LEV. Groupwise AED efficacy rates after 24 months are described in Table 2. Post hoc analysis showed that

Table 1. Baseline characteristics and outcome and adverse event distribution requiring anti-pilepsy drug substitution in the study patients during the 24-mo study period by treatment group

	Carbamazepine	Lamotrigine	Levetiracetam
Total (N = 646)	204	188	254
Male	105	75	148
Female	99	113	106
Age 1-18 y	105	63	70
Age > 18 y	99	125	184
Average age at onset			
1-18 y	9.3 ± 3.6	9.6 ± 4.8	9.7 ± 4.5
18+ y	43.9 ± 16.0	40.9 ± 18.8	50.1 ± 18.0
Outcome at 24 mo			
Seizure free	134	125	184
Not seizure free	53	45	33
Total adverse events	17	18	37
Rash	7	12	0
Dizziness	0	3	3
Lethargy	5	1	7
Mood change	3	2	20
Slow thinking	1	0	4
Depression	0	0	2
Headache	0	0	1
Abnormal alanine aminotransferase	1	0	0

Table 2. Adverse event rates and seizure-freedom rates at 24-mo study period after initiating pharmacotherapy with carbamazepine, lamotrigine, or levetiracetam

		AED discontinued due to adverse events		Seizure-freedom at the end of 24- mo study period	
	At baseline	Yes	No	Yes	No
CBZ	204	17	187	134	53
LTG	188	18	170	125	45
LEV	254	37	217	184	33
Total	646	72	574	443	131
Combined 3 AEDs		p = 0.08; not significant		p = 0.003; significant	
CBZ vs LTG				p = 0.69; not significant	
LTG vs LEV				p = 0.006; significant	
LEV vs CBZ				p = 0.001; significant	

AED = anti-epilepsy drug; CBZ = carbamazepine; LEV = levetiracetam; LTG = lamotrigine.

differences in the seizure-freedom rates among the 3 groups were significant (p = 0.003) and that the seizure-freedom rate for LEV was superior to that of CBZ (p = 0.001) and of LTG (p = 0.006).

Retention rates (seizure freedom and tolerability) at 24 months for the CBZ group, the LTG group, and the LEV group were 134 (65.68%), 125 (66.49%), and 184 (72.44%), respectively. Comparison of AED retention rates among the 3 groups showed no significant difference at p < 0.05 (p = 0.23) (Figure 1).

DISCUSSION

In 1984 the FDA approved the use of generic drugs that have bioequivalent pharmacokinetics comparable to their brand-name versions. The FDA Abbreviated New Drug Application guidelines require that the generic version of a drug must deliver the same amount of active ingredients into the patient's bloodstream in the same amount of time as its brand-name drug. The same Abbreviated New Drug Application guidelines apply to generic-to-generic drug substitution as well.[1,2] A systematic review and metaanalysis

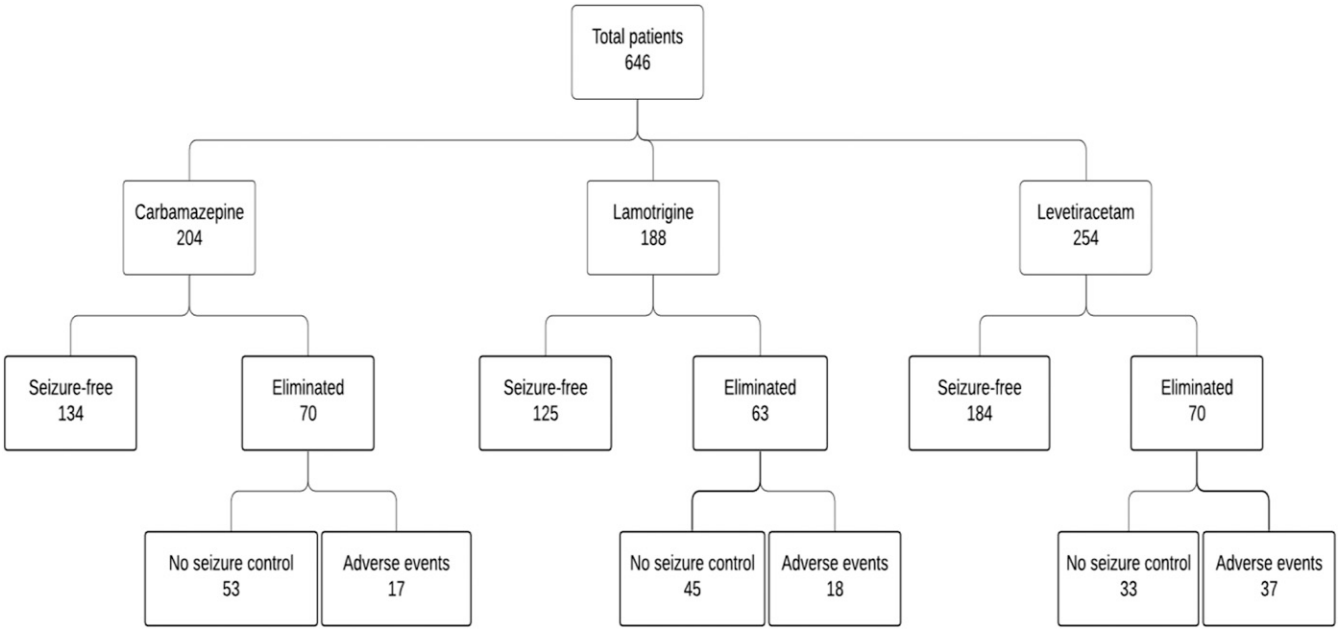

Figure 1. Flow of 646 patients through the study period.

of seizure outcomes following use of generic vs brand-name AEDs concluded that there was little evidence-based rationale to challenge the implementation of generic substitution for brand-name AEDs.[1] However, most RCTs in that study were of short-term evaluations. A 30-year longitudinal cohort epilepsy management study concluded that, among the patients who remained seizure free for at least the previous 12 months, 72% achieved seizure freedom with the first AED regimen.[9] An AED comparison RCT study in elderly patients with new-onset focal epilepsy showed equivalent efficacy among CBZ, LTG, and LEV after a 52-week maintenance phase and provided evidence supporting the use of LEV as first-line treatment and of LTG as an alternative to LEV when compared with CBZ.[10]

Effectiveness (retention rate) of an AED is a composite measure that is quantified as the percentage of patients who, after starting an AED, continue taking it for a given study period while maintaining efficacy (seizure freedom) and tolerability (no major side effects).[8]

After reviewing the literature, we believe that ours is the first longitudinal cohort study that compares effectiveness, efficacy, and tolerability rates among single-source bioequivalent generic-for-brand-name formulations of the 3 most commonly used different generation antiepilepsy medications (CBZ, LTG, and LEV) after a 24-month study period after initiating AED pharmacotherapy as a monotherapy in AED-naive patients with focal epilepsy who were treated by epileptologists at a single community-based epilepsy center.

In our study, out of 646 patients at the start of the study, adverse events necessitating AED withdrawal by the end of the 24-month study period occurred in 17 (8.33%) patients in the CBZ group, 18 (9.57%) in the LTG group, and 37 (14.57%) in the LEV group. Rash was the most common adverse event in 7 (3.43%) patients in the CBZ group and in 12 (6.38%) patients in the LTG group. In the LEV group, mood changes were the most prominent adverse event in 20 (7.87%) patients, which included 10 patients with mood swings, 7 with aggressive behavior, and 3 with anxiety (Table 1). Tolerability rates among the 3 AED groups were comparable (combined 3 AEDs p value = 0.08; not significant at $p < 0.05$). There were no fatalities or hospital admissions due to adverse events noted during the study period. In the LaLiMo trial, which included patients with newly diagnosed focal and generalized epilepsies, at 6 weeks after randomization adverse events requiring discontinuation of AED occurred in 4% of subjects taking LTG and in 8.3% taking LEV.[4] The LaLiMo trial also reported no significant differences in tolerability rates between the LTG and the LEV groups. Another RCT for focal epilepsy reported a comparable incidence of adverse reaction between the CBZ and the LEV monotherapy groups.[11]

LTG should be used with caution in patients with history of a suspected immune-mediated hypersensitivity from other medications, and LEV should be used with caution in patients with psychiatric disorders. In our study, rash was noted during the early phase of LTG slow titration and was rare after reaching the dose of 50 mg twice daily. In the LEV group, mood changes were the most common adverse

events that occurred at the low dosing regimen of 500 mg twice daily and continued if LEV was not stopped. In a study comparing the effects on mood changes in patients with focal epilepsy, LTG and LEV were used as adjunctive therapy. At the end of a 20-week study period, moods improved significantly in the LTG group when compared with the LEV group.[12]

The remaining 574 patients continued the original AED. The overall seizure-freedom rate for the 3 study drugs at the end of the 24-month study period was 77.18% (443/574), with individual seizure-freedom rates being 71.66% (134/187) for CBZ, 75.53% for LTG (125/179), and 84.79% (184/217) for LEV. Post hoc analysis (Table 2) showed that the difference in the seizure-freedom rate among the 3 groups was significant (p = 0.003) and that the seizure-freedom rate for LEV was superior to CBZ (p = 0.001) and to LTG (p = 0.006). Seizure-freedom rates in our study were not inferior to those reported in the literature for brand-name AEDs.[1-6] In the LaLiMo RCT trial, at 6 weeks after randomization 64% patients in the LTG group and 67.5% in the LEV group were seizure free. They reported no significant differences in seizure control rates between the LTG and LEV groups.[4] In an RCT in young adults with new-onset focal epilepsy, 78.57% in the LEV group and 20 71.42% in the CBZ group were seizure free for at least 6 months.[11] Another study of 117 elderly (65-92 years) patients with newly diagnosed focal epilepsy reported comparable 12-month seizure-freedom rates of 67% for CBZ (slow-release formulation) and 63% for LTG.[13] Among 10 AEDs used in a 30-year longitudinal study in 332 teenage patients, comparable efficacy rate for different monotherapies was reported in the cohort of newly diagnosed epilepsies, with seizure-freedom rates for at least 12 months being 72% for CBZ, 75% for LTG, and 73% for LEV.[14]

In our longitudinal cohort study of 646 patients, which included patients from all the age groups, the retention rates at the end of the 24-month study period were 65.69% for CBZ, 66.49% for LTG, and 72.44% for LEV (combined 3 AEDs p = 0.23; not significant); these results were not inferior to those reported in the literature for their brand-name versions.[1-6] In a new-onset focal epilepsy AED monotherapy effectiveness RCT in elderly patients, the retention rates at the end of a 52-week study period were 45.8% for CBZ, 55.6% for LTG, and 61.5% for LEV.[10] Logistic regression analysis in that study suggested that the concomitant diseases in elderly patients had a major negative influence on the retention rate. Retention rates of 67% for CBZ and 73% for LTG were noted in a multicenter RCT comparing a CBZ sustained-release formulation and LTG in elderly patients with newly diagnosed epilepsy.[15]

The seizure-freedom rates for the 3 AED groups in our study were relatively high compared with those reported in literature. In most RCTs, new AEDs are introduced as add-on pharmacotherapy in patients with long-term drug-resistant epilepsies. Also, AED allocation is randomized, titration rate and maximum dose of AED are fixed per study protocol, and treatment evaluation period is short (usually < 4 months). However, in our community-based practice, the decision regarding choice of AED is that of the patients and is guided, but not controlled, by the treating epileptologist. Also, titration rate and maximum dose of AED can be modified depending on the clinical scenario and tolerability of the patient. Both these factors may have contributed to the higher efficacy rates in our study. Pharmacokinetics and pharmacodynamics of AEDs between younger and older generations are different. Logistic regression analysis in an AED trial suggested that the concomitant diseases in elderly patients had a major negative influence on the retention rate.[10] The age spectrum of the patients in our study was broad, which also may have positively affected tolerability and in turn seizure-freedom rates.

In conclusion, in our study, at the end of a 24-month study period in a head-to-head comparison of single-source bioequivalent generic formulations in AED-naive patients with focal epilepsy, when compared with CBZ and LTG, comparable tolerability and retention rates but a superior seizure-freedom rate for LEV were observed.

Not being a randomized control trial is a major limitation of this study.

All the patients were diagnosed and managed by an epileptologist. This was a community-based study where the decision regarding choice of AED was that of the patients and was guided by the treating epileptologist, who was also able to manage titration rate to help minimize side effects. These factors added strength to this study.

This paper used data collected from Kaiser Permanente SCPMG Institutional Review Board approved studies 5386 and 6655. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Authors' Contributions

Suresh Gurbani, MD, PhD, participated in the study design, data collection, data analysis, and manuscript preparation and submission. Sirichai Chayasirisobhon, MD, participated in study design, data collection, and data analysis. Aditya Gurbani, BA, participated in data analysis and in drafting the manuscript, figure, and tables. Stephanie Tovar, MS, participated in study design and data analysis. Erika Pietzsch, MD, participated in data collection. Benjamin Spurgeon, DO, participated in data collection.

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