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Clinical experience with generic levetiracetam in people with epilepsy

Siresha Chaluvadi[*], **Sharon Chiang**[†], **Larry Tran**[*], **Corey E. Goldsmith**[*], and **David E. Friedman**[*]

[*]Department of Neurology, Baylor College of Medicine, Houston, Texas, U.S.A.

[†]Baylor College of Medicine, Houston, Texas, U.S.A.

SUMMARY

Purpose—To describe the clinical outcomes of a compulsory switch from branded to generic levetiracetam (LEV) among people with epilepsy (PWE) in an outpatient setting.

Methods—We conducted a retrospective chart review of 760 unduplicated consecutive adult patients attending a tertiary care epilepsy clinic at Ben Taub General Hospital. On November 1, 2008 hospital policy required all patients receiving branded LEV to be automatically switched to generic LEV. We calculated the proportion of patients switching back to branded LEV and reasons for the switch back.

Key Findings—Of the 260 patients (34%) being prescribed LEV (generic and brand name) during the study period, 105 (42.9%) were switched back to brand name LEV by their treating physicians. Reasons for switch back included increase in seizure frequency (19.6% vs. 1.6%; $p < 0.0001$) and adverse effects (AEs) (3.3%). AEs included headache, fatigue, and aggression. Patient age was associated with switchback when controlling for gender, epilepsy classification, and treatment characteristics [relative risk (RR) 2.44; 95% confidence interval (CI) 2.09–2.84; $p < 0.05$)]. An increase in seizure frequency subsequent to generic substitution was associated with polytherapy compared to monotherapy (3.225; 1.512–6.880; $p < 0.05$).

Significance—A significant proportion of patients in our cohort on generic LEV required switch back to the branded drug. Careful monitoring is imperative because a compulsory switch from branded to generic LEV may lead to poor clinical outcomes, with risk of AEs and increased seizure frequency.

Keywords

Keppra; Levetiracetam; AED; Adverse effects

Until the present day, U.S. health care systems have adopted various measures to maximize cost savings. It has been well known to encourage or have mandatory requirements to use

Address correspondence to Siresha Chaluvadi, M.D., Department of Neurology, Baylor College of Medicine, One Baylor Plaza, NB 302, Houston, TX 77030, U.S.A. chaluvad@bcm.edu.

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cheaper, generic drugs instead of their branded counterparts (Andermann et al., 2007). The U.S. Food and Drug Administration (FDA) has allowed generic medications that have shown short-term bioequivalence to be granted product license. However, bioavailability may be different from branded counterparts because of the use of other chemicals that are used to make generic medications (Borgheini, 2003). Generic medications must have the same dose and form as the brand name and must have been studied and determined to have equivalent bioavailability of the brand name (Andermann et al., 2007). Notwithstanding, variation of generic antiepileptic drugs (AEDs) versus name brand AEDs can be highly problematic among people with epilepsy (PWE). This has led to a debate on the appropriateness of generic substitution of AEDs to generic compounds. Because of the potential for poor clinical outcomes with generic AEDs, several agencies (UK National Institute for Health and Clinical Excellence (Andermann et al., 2007) and the American Academy of Neurology (AAN) (Borgheini, 2003) have instituted policies to discourage the substitution of generic AEDs from brand name due to the potentially negative consequences such as increased monitoring costs and loss of seizure control. Other countries have implemented stricter guidelines in dealing with generic AEDs. In Sweden the Medical Products Agency instituted a policy that certain AEDs (lamotrigine, carbamazepine, phenytoin, valproic acid, gabapentin) cannot be switched from brand name to generic (Borgheini, 2003; Andermann et al., 2007). The Italian Chapter of the International League Against Epilepsy instituted a policy that patients who are in seizure remission or with well-controlled seizure activity on a brand name AED, should not be switched from branded to generic medication (Perucca et al., 2006).

Confirmatory observations lend support to the concerns involving generic AEDs. Recent studies have noted high switch back rates, loss of seizure control, increased toxicity, and increased health care utilization costs associated with generic AEDs (Andermann et al., 2007; LeLorier et al., 2008; Kesselheim 2010; Labiner et al., 2010; Sethi et al., 2010). Given these findings of poor outcomes, the AAN has instituted guidelines in 2006 opposing generic substitution of AEDs without attending/physician approval (Liow et al., 2007). Nevertheless, other organizations such as the FDA promote interchangeability with generic and branded AEDs.

To our knowledge, none of the recent studies specifically investigated the potential consequences associated with Keppra or generic levetiracetam (LEV). The purpose of our study is to measure the proportion of PWE who switch back from generic to branded LEV required due to poor clinical outcomes directly associated with the generic compound.

Methods

Standard protocol approvals

The institutional review boards at both Baylor College of Medicine and Harris County Hospital District approved the use of a retrospective analysis of human subjects for this study.

Data source

Medical records for all adult patients attending the epilepsy clinic at Ben Taub General Hospital (BTGH) were reviewed. The following data were collected: patient demographic and clinical information (Table 1), duration of drug therapy, dose, dosage form, and whether the patient was on monotherapy versus polytherapy. In addition pharmacy data were gathered to verify drug dispensation, dispensation date, and whether the drug was generic or branded.

Study population

BTGH is the flagship hospital of the Harris County Hospital District (HCHD). Harris County is the nation's third largest county with an estimated population of 3.9 million according to 2008 estimates by the U.S. Census Bureau. The study population comprising patients using branded LEV preceding the compulsory switch to the generic LEV on November 1, 2008, had their prescriptions dispensed through the HCHD pharmacy after the generic start date, had continuous health care follow-up in the epilepsy clinic. The study population was further stratified into monotherapy versus polytherapy. Monotherapy was defined as the patient taking only LEV for seizure control 90 days prior to the compulsory switch and polytherapy are those using at least one other AED at the same time as LEV.

Study design

A retrospective study where we sought to quantify the switchback rate from generic to branded LEV after the compulsory switch date on November 1, 2008, the reasons for the switch back, and the risks associated with necessitation for switchback. “LEV variations since Nov 1, 2008 included oral formulations (250, 500, 750 mg tablets) from Mylan Pharmaceuticals Inc (Morgantown, WV, U.S.A.) and from Torrent Pharmaceuticals Limited (Ahmadabad, Gujarat, India) a 500 mg tablet.”

Statistical analysis

All statistical analyses were performed using R version 2.9.2 (R Foundation, Vienna, Austria). Associations were evaluated at the $\alpha = 0.05$ significance level.

Switchback rates—Switchback rates were estimated using the Kaplan-Meier method, which is a conditional probability approach based on the patients who were on the generic drug at the beginning of the time interval. The Kaplan-Meier estimate of the switchback rate is calculated as the cumulative probability of a patient switching back to branded LEV (Keppra), given that he was on generic LEV at the beginning of the time interval. Because no patients were lost to follow-up, the cumulative probability in our case is equivalent to the simple proportion, which was used.

Variables associated with switchback—The associations of gender, seizure type, treatment characteristics, and increased seizures and AEs with switchback occurrences were estimated using relative risk. A slightly amended estimator corresponding to adding one half to each cell count was used in cases with a zero in the denominator. Associations of continuous variables (i.e., age) with switch-back were estimated using a generalized logistic

model that controlled simultaneously for age, gender, seizure type, and treatment characteristics.

Variables associated with increased adverse effects on generic LEV—The associations of gender, seizure type, treatment characteristics, switchback, increased adverse effects (AEs) on brand LEV, and increased seizures with increased AEs on generic LEV were estimated using relative risk. A slightly amended estimator corresponding to adding one half to each cell count was used in cases with a 0 in the denominator. Associations of continuous variables (i.e., age) with increased adverse effects on generic LEV were estimated using a generalized logistic model that controlled simultaneously for age, gender, seizure type, and treatment characteristics.

Variables associated with increased seizures on generic LEV—The associations of gender, seizure type, treatment characteristics, switchback, and increased adverse effects with increased seizures on generic LEV were estimated using relative risk. A slightly amended estimator corresponding to adding one half to each cell count was used in cases with a 0 in the denominator. Associations of continuous variables (i.e., age) with increased seizures on generic LEV were estimated using a generalized logistic model that controlled simultaneously for age, gender, seizure type, and treatment characteristics.

Seizure rates on generic versus brand LEV—The hypothesis that the proportion of patients experiencing increased seizures on generic LEV was greater than the proportion experiencing increased seizures on branded LEV was tested using a McNemar's test with continuity correction for dependent proportions, with statistical significance evaluated at the $\alpha = 0.05$ level. With significantly large number of discordants (n = 52), the test statistic was compared to a χ_1^2 distribution.

Mean seizure frequency—The mean (and median) seizure frequency for (1) baseline (on brand), (2) on generic, (3) when switched back to brand were calculated.

Paired sign test—Examination of the difference of medians.

Results

A total of 760 patients received care at the Ben Taub epilepsy clinic during the study period. Of these patients, 260 patients (34%) were prescribed LEV (generic or brand name) and these charts were reviewed retrospectively. Fifteen patients were not included in the mandatory switch on November 1, 2008, and remained on branded LEV, leaving a total of 245 PWE prescribed generic LEV at the start of the study period.

Switchback rates

The estimated switchback rate for the total population was 42.9%. Table 1 provides characteristics of the study population such as demographics and clinical characteristics. Table 2 lists additional switchback rates for subpopulations of demographic and clinical interest. Reasons for switchback included an increase in seizure frequency on the generic

formulation (19.6%) and adverse effects that were not experienced on the branded LEV (3.3%).

The switchback rate for patients who experienced AEs on the generic formulation that had not been experienced on the branded LEV was 100% (Table 2). AEs included complaints of blurred vision (four patients), headache (three patients), depression (two patients), memory loss (two patients), aggression (one patient), and mood swings (one patient), where several of these AEs were experienced in conjunction with each other.

Variables associated with switchback

Age was found to be significantly associated with switch-back when gender, seizure type, and treatment characteristics were simultaneously controlled for ($p < 0.05$, Tables 3 and 4). No other clinical variables were associated with poor outcomes on generic LEV.

Switchback rates were higher among those who experienced increased AEs on generic LEV (100% vs. 40.927%; RR 2.443; CI 2.094–2.843; $p < 0.05$). Patients who had experienced increased AEs on brand LEV were also more likely than those who had not experienced increased AEs on brand LEV to switch back to brand (100% vs. 41.176%; RR 2.41118; CI 2.079–2.812; $p < 0.05$). Patients who had experienced increased seizures on generic LEV were also more likely than those who had not experienced increased seizures on generic LEV to switch back to generic (100% vs. 28.934%; RR 3.456; CI 2.776–4.302; $p < 0.05$). When specifically assessing individual poor outcomes associated with switchback separately (increase in seizure frequency and AEs), polytherapy was significantly associated with an increase in seizure frequency when using generic LEV compared to those on monotherapy (RR 3.225; CI 1.512–6.880; $p < 0.05$).

Variables associated with increased AEs on generic LEV

Age, gender, seizure type, and mono-/polytherapy were not significantly associated with experiencing increased AEs on generic LEV. Patients who eventually switched back to branded LEV were more likely than patients who did not switch back to branded LEV to have experienced increased AEs on generic LEV (8.019% vs. 0.355%; RR 22.613; CI 1.320–387.456; $p < 0.05$). Patients who experienced increased AEs on branded LEV were more likely than patients who did not experience increased AEs on branded LEV to have experienced increased AEs on generic LEV (71.429% vs. 1.261%; RR 56.667; CI 16.761–191.588; $p < 0.05$). Patients who had experienced increased seizures on generic LEV were also more likely than patients who had not experienced increased seizures on generic LEV to experience increased AEs on generic LEV (12.500% vs. 1.015%; RR 12.313; CI 2.564–59.118; $p < 0.05$).

Variables associated with increased seizures on generic LEV

When specifically assessing individual poor outcomes associated with switchback separately (increase in seizure frequency and AEs), polytherapy was significantly associated with an increase in seizure frequency when using generic LEV compared to those on monotherapy (RR 3.225; CI 1.512–6.880; $p < 0.05$).

Patients who eventually switched back to branded LEV were also more likely than patients who did not switch back to branded LEV to have experienced increased seizures on generic LEV (45.755% vs. 0.355%; RR 129.028; CI 8.047–2068.802; $p < 0.05$). Patients who experienced increased AEs on generic LEV were also more likely than patients who had not experienced increased AEs on generic LEV to have experienced increased seizures on generic LEV (75.000% vs. 17.722%; RR 4.232; CI 2.605–6.874; $p < 0.05$). Patients who experienced increased AEs on branded LEV were also more likely than patients who had not experienced increased AEs on branded LEV to have experienced increased seizures on generic LEV (57.143% vs. 18.487%; RR 3.091; CI 1.543–6.192, $p < 0.05$).

Seizure rates on generic versus brand LEV

The proportion of patients experiencing increased seizures on generic LEV was significantly greater than the proportion experiencing increased seizures on branded LEV during the study period (19.6% vs. 1.6%; $p < 0.0001$).

Mean seizure frequency

For the cohort who eventually switched back to brand (n = 105): The baseline mean seizure frequency was 3.78 per month (median 0.5). The mean seizure frequency on generic was 2.64 per month (median 1). The mean seizure frequency when switched back to brand was 2.52 per month (median 0.33). Among these 105 patients, there were two patients with nonepileptic seizures, one patient who died of HIV/AIDS–related sepsis, and one patient who had a temporal lobectomy and is now seizure free. These patients were left out of the analysis (so that the above measures were calculated with n = 101). The mean time between visits was 3.0 months, and any change in seizure frequency was determined at subsequent clinic visits.

Paired-sign test

The difference in median seizure frequency between original brand and generic was significant at the 0.05 level of significance (p-value 1.17×10^{-4}). (The median seizure frequency on generic was significantly greater than the median seizure frequency on original brand.)

The difference in median seizure frequency between generic and switchback brand was significant at the 0.05 level of significance (p-value 6.42×10^{-10}). (The median seizure frequency on switchback brand was significantly less than the median seizure frequency on generic.)

Discussion

We report a retrospective chart review study over a 1-year period after compulsory switch from branded to generic LEV, noting a switchback rate of 42.9%. To the best of our knowledge, LEV has not been studied in this manner and it is our intention that this study be added to the growing chorus of physicians, patients, and pharmacists advocating against compulsory substitution of AEDs in PWE. Even our largest professional society, the American Academy of Neurology, has issued two position papers stating concern with

generic AED substitution and discourages switching between branded and generic formulation unless medically necessary. (AAN 1990; Liow et al., 2007).

In 2007, a large claims database study published from Ontario, Canada noted higher rates of switchback for generic AEDs when compared to generic antihyperlipemics and antidepressants. Like our study, the switch to generic AEDs was compulsory and a letter of necessity was required for switchback to branded AEDs. The switchback rates reported were 12.9% for generic lamotrigine and 20.9% for generic valproate. In contrast, generic antihyperlipemics and antidepressants had switchback rates of 1.5–2.9%. The Ontario study also reported in the instance of switching from branded to generic lamotrigine a significant increase in average daily doses and increased use of concomitant medications (Andermann et al., 2007).

Researchers working with medical and pharmacy claims data in Quebec, Canada spanning over 8 years noted higher switchback rates than the Ontario study. Of 851 patients receiving generic carbamazepine 20.8% switched back to the branded form. Switchback rates were higher for lamotrigine (27.5%), gabapentin (30.9%), and clobazam (44.1%). The study noted Quebec's greater permissiveness in allowing switching between generic and branded AEDs as a reason for the higher rates when compared to Ontario. Significantly higher rates of physician visits and hospitalizations were also noted from switched lamotrigine (LeLorier et al., 2008).

The low side effect profile and risk of toxicity of LEV lends to the increase use of LEV in the treatment of PWE. Since its introduction into the market in 2000, LEV is attractive in its pharmacokinetic properties including rapid and almost complete absorption, minimal binding to plasma proteins, absence of enzyme induction, minimal interactions with other drugs, partial metabolism outside the liver, availability of an intravenous preparation, and suggestion of safety in pregnancy (Grosso et al., 2005; Lagae et al., 2005; Specchio et al., 2006; Abou-Khalil, 2008). Early clinic trials noted AEs in adults to be somnolence, aggressive or hostile behavior, and headaches, which corresponded to our study results. Nevertheless, generic LEV was associated with higher switchback rates in our study compared to other AEDs in previous studies. This rate of switchback is higher in our patient population than in other studies concerning generic AEDs. It is, however, notable that this was more common in patients who had previously experienced either seizure exacerbation or adverse effects on branded Keppra. Perhaps these patients are more sensitive to minor fluctuations in effective dosing with levetiracetam.

Our finding of a 42.9% switchback rate after compulsory switch to generic LEV is above or at the level of other AEDs reported in the Canadian studies. One major difference between our study and the Canadian study is that our study involved evaluation over a shorter time period (1.5 years), when compared to >4 and 8 years of the Ontario and Quebec studies, respectively. The high proportion of patients experiencing poor outcomes when being switched to generic LEV despite the relatively short study period is important, and may suggest that generic LEV in fact leads to clinical consequences. However, it should be noted that the ability for switchback in the Harris County Hospital District is with fewer regulations than those encountered in Canada (LeLorier et al., 2008), requiring written

consent of the prescribing physician, and thus the relative freedom in switching to the branded compound may be solely responsible for the discrepancies in switchback rates compared to other studies.

In our study we found that age was significantly associated with switchback when gender, seizure type, and treatment characteristics were simultaneously controlled for ($p < 0.05$, Table 3).

To our knowledge, there have not been other generic switchback studies assessing this issue. Reasons for this significant finding may be due to increased age correlating with more comorbidities and more medications prescribed.

We also found that when assessing individual poor outcomes associated with switchback separately (increase in seizure frequency and AEs), polytherapy was significantly associated with an increase in seizure frequency when using generic LEV compared to those on monotherapy (RR 3.225; CI 1.512–6.880; $p < 0.05$). A possible reason for this finding may be due to the fact that PWE requiring polytherapy often experience more severe forms of epilepsy, and may be sensitive to slight variations in drug bioavailability that occur with generic compounds.

There are several limitations to our study. First, the data is retrospective and based on medical chart review, which may be lending itself to ascertainment bias. However, because switchback to branded compound requires a note delineating the reason for medication change, the rates and reasons for switchback were well documented. Furthermore, because this was a retrospective review, no differences in screening for AEs occurred during follow-up clinic visits (patients were not queried more closely following generic substitution). In addition, our study was restricted to a specific time period and did not allow for long-term follow-up. A future study investigating the perennial ramifications of generic and branded LEV may be indicated. Previous studies evaluating clinical consequences of generic AEDs included larger patient populations. Ours investigated outcomes in a relatively small cohort that consisted of predominantly referral patients, and thus may not be representative of epilepsy populations as a whole. Finally, our study, like many others, is observational. A previous meta-analysis noted that although most studies have found significant findings, they are observational in nature. However, randomized controlled trials have not shown an association between poor outcomes and generic substitution of at least three types of AEDs (Kesselheim et al., 2010).

Although our data and previous medical claims database analysis are consistent in our concern of the current practice of switching to generic AEDs, there is a continued call for either a double-blinded placebo-controlled trial or a prospective observational study of sufficient breadth to determine therapeutic equivalence and assess clinical changes in seizure frequency, adverse events, and economic impact. This study could improve our understanding of the role of generic AED in the daily care of our PWE. Until then physicians are asked to be aware of the potential consequences of switching to generic AED therapy and be stewards in ensuring unnecessary changes in the care of PWE.

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Table 1

Patient disposition and baseline characteristics

	Study population
Generic entry time	11/01/2008
No. of patients	245
No. of censored patients, n (%)[a]	140 (57.2)
Discontinued treatment (≥1.5 years), n (%)	0 (0)
Did not switch back, n (%)	140 (57.2)
Switched back, n (%)	105 (42.8)
Mean age in years, y (SD)	42.9 (13.8)
Female, n (%)	131 (53.4)
Mean seizure frequency, per month (SD)	5.952 (58.57)
Mean seizure frequency on brand LEV, per month (SD)	2.473 (8.743)
Idiopathic epilepsy, n (%)	6 (2.4)
Symptomatic epilepsy, n (%)	109 (44.5)
Cryptogenic epilepsy, n (%)	130 (53.1)
Polytherapy, n (%)	158 (64.5)
Experienced increased adverse effects on generic LEV, n (%)	8 (3.3)
Experienced increased seizures on generic LEV (rel to brand), n (%)	48 (19.6)
Experienced decreased seizures on generic LEV (rel to brand), n (%)	4 (1.6)

[a]Defined as discontinued treatment (≥1.5 years) or May 3, 2010, whichever ends first.

Table 2

Switchback rates

Patient characteristic	Switchback rate (%)
Total	42.9
Gender	
Male	41.2
Female	44.3
Monotherapy versus polytherapy	
Monotherapy	39.1
Polytherapy	44.9
Seizure type	
Idiopathic	33.3
Symptomatic	52.3
Cryptogenic	35.4
Increased adverse effects on generic LEV	
No increased adverse effects on generic	40.9
Increased adverse effects on generic	100
Increased adverse effects on brand LEV	
No increased adverse effects on brand	41.2
Increased adverse effects on brand	100
Increased seizures on generic LEV (rel to brand)	
No increased seizures on generic (decreased or no change)	28.9
Increased seizures on generic	100

Table 3

Factors associated with switchback

Variable	Estimate (SE)	p-Value
Demographics		
Age (continuous variable)	−0.024 (0.010)	<0.05
Female (ref: male)	0.205 (0.272)	0.451
Epilepsy classifications		
Symptomatic (ref: idiopathic)	1.019 (0.927)	0.272
Cryptogenic (ref: idiopathic)	0.183 (0.924)	0.843
Treatment characteristics		
Polytherapy (ref: monotherapy)	0.364 (0.288)	0.207

Table 4

Factors associated with increased seizures on generic LEV

Variable	Estimate (SE)	p-Value
Demographics		
Age (continuous variable)	0.004 (0.013)	0.728
Female (ref: male)	0.190 (0.339)	0.575
Seizure type		
Symptomatic (ref: idiopathic)	15.200 (941.029)	0.987
Cryptogenic (ref: idiopathic)	14.395 (941.029)	0.988
Treatment characteristics		
Polytherapy (ref: monotherapy)	1.462 (0.445)	<0.05